26 March 2026
EMADOC-1700519818-2933962
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Feraccru

International non-proprietary name: Ferric maltol

Procedure No. EMA/VR/0000268118

Note

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Table of contents

List of abbreviations

AI	Anaemia of inflammation
ANOVA	Analysis of variance
AUC	Area under the plasma concentration curve
AUC_{0-6}	Area under the plasma concentration curve from time 0 to 6 hours
AUC_{0-t} / AUC_{last}	Area under the plasma concentration-time curve from pre-dose (time 0) to the last quantifiable plasma concentration
AUC_{inf}	Area under the plasma concentration-time curve from time 0 to infinity
BID	Twice daily (administration)
BQL	Below the quantifiable limit
$C_{ave[0-6h]}$	Average steady state plasma concentration from time 0 to 6 hours
CI	Confidence interval
CL/F	Apparent systemic clearance
CSR	Clinical study report
C_{trough}	minimum plasma concentration
C_{max}	Maximum plasma concentration
ECG	Electrocardiogram
FAS	Full Analysis Set
GM	Geometric mean
Hb	Haemoglobin
IBD	Inflammatory bowel disease
ID	Iron deficiency
IDA	Iron deficiency anaemia
ITT	Intent-to-Treat (population)
IV	Intravenous
LS	Least squares
MCV	Mean corpuscular volume
mITT	Modified Intent-to-Treat (population)
MMRM	Mixed model for repeated measures
PD	Pharmacodynamics
PI	Product Information
PK	Pharmacokinetics
PPK	Population PK
RMP	Risk Management Plan
SAE	Serious adverse event
SD	Standard deviation
SmPC	Summary of Product Characteristics
$t_{½}$	Half-life
TEAE	Treatment-emergent adverse events
TIBC	Total iron binding capacity
T_{max}	Time to maximum plasma concentration
TSAT	Transferrin saturation
UIBC	Unsaturated iron binding capacity
V_z/F	apparent volume of distribution
WHO	World Health Organization

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Norgine B.V. submitted to the European Medicines Agency on 25 April 2025 an application for a variation.

The following changes were proposed:

Variation(s) requested		**Type**
C.I.6.a	C.I.6.a Addition of a new therapeutic indication or modification of an approved one	Variation type II

Extension of indication to include treatment of paediatric population (adolescents aged 12 years and above) for FERACCRU, based on results from phase 1 study ST10-01-103, phase 3 study ST10-01-305 and a supportive phase 1 study ST10-01-104. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 9.1 of the RMP has also been submitted. In addition, the marketing authorisation holder (MAH) took the opportunity to update the list of local representatives in the Package Leaflet and to implement editorial changes to the PI. Furthermore, the PI is brought in line with the latest QRD template version 10.4.

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

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0503/2023 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0503/2023 was completed.

The PDCO issued an opinion on compliance for the PIP P/0503/2023.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Antonio Gomez-Outes Co-Rapporteur:N/A

Timetable	Actual dates
Submission date	4 June 2025
Start of procedure:	21 June 2025
PRAC assessment report circulated on:	30 July 2025
CHMP Rapporteur's preliminary assessment report circulated on:	14 Aug 2025
PRAC outcome	4 September 2025
Joint Rapporteur's updated assessment report circulated on:	12 September 2025
Request for supplementary information	18 September 2025
Re-Start date	29 December 2029

Timetable	Actual dates
CHMP Rapporteur AR	26 January 2026
PRAC Rapporteur AR	30 January 2026
PRAC outcome	12 February 2026
Updated CHMP Rapporteur AR	19 February 2026
Request for supplementary information	26 February 2026
CHMP Rapporteur AR	11 March 2026
Updated CHMP Rapporteur AR	20 March 2026
CHMP opinion	26 March 2026

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Claimed therapeutic indication

The MAH seeks approval to extend the currently authorized indication "treatment of iron deficiency" in adults, to adolescents aged 12 years and older.

Epidemiology

Iron deficiency (ID) is manifested as iron deficiency anaemia (IDA). IDA is the most prevalent nutritional disorder and dietary iron deficiency and represents the leading cause of all-age anaemia, constituting 66.2% of total anaemia cases, with 825 million women and 444 million men affected globally in 2021 (GBD, 2023).

The prevalence of ID varies greatly according to factors such as age, gender, physiological, pathological, environmental, and socio-economic conditions (WHO, 2001). The prevalence of IDA also exhibits variations across geographic regions, races, genders, and age groups, affecting two billion individuals globally, with a significant majority residing in non-industrialized countries (WHO, 2001). The World Health Organization (WHO) estimates global prevalence of anaemia to be 40% in children 6-59 months of age, 37% in pregnant women, and 30% in women 15-49 years (WHO, 2023). In line with all-cause anaemia, ID and IDA are most common in preschool-age children (0-4 years) and women of reproductive age (15-49 years), and overall ID is most common in low-income settings where dietary iron content and availability are low and parasitic infections are highly prevalent (WHO, 2020).

Aetiology and pathogenesis

During childhood, IDA has two peaks of incidence in infancy and adolescence, when there is a discrepancy between food intake and the elevated need of iron depending on the growth speed. IDA is particularly prevalent and impactful in the paediatric population, with children under 2 years of age being at a higher risk due to the high iron requirements needed for rapid growth and development, often coupled with inadequate dietary iron intake. Though children over 2 years of age generally have a lower prevalence of anaemia than the youngest children, as a group, children aged under 5 years bear the largest burden of anaemia globally (WHO, 2017). During adolescence, other contributing causes can compromise iron supply: low intake with the (often inadequate) diet, consumption of food products that reduce absorption, malnutrition, obesity, ID associated with sport, and, for females, the loss of iron during the menstrual cycle. In adolescents, the prevalence of IDA can be as high as 25-30% in countries with a low to medium social development index.

ID may result from physiological, environmental, pathological, drug-related, genetic or iron-restricted erythropoietic causes. ID may be caused by inadequate iron intake, excess iron loss (i.e., haemorrhage), or excess iron utilization. In low-income settings, other important causes include chronic blood loss from hookworm and schistosomiasis (WHO, 2020). In developing countries, IDA is nutritional, resulting from reduced intake of bioavailable iron, while in developed countries iron depletion mainly results from chronic bleeding and/or reduced iron absorption, making it essential to identify the underlying cause for an adequate management.

In children, the causes of ID can vary depending on the age. In infants up to 6 months of age, ID may be due to low maternal iron status, low birth weight, prematurity and lack of iron supplementation. For older infants, the causes for ID can include exclusive breastfeeding, introduction of cow's milk before 12 months of age, and excessive cow's milk intake (>500 ml/day). After 12 months of age, ID is more likely to be related to low socio-economic status, low iron in the diet, overweight/obesity, and bleeding. In adolescence, it may also be caused by participation in endurance sports/running. Absolute ID results from insufficient dietary iron intake, impaired iron absorption, or blood loss, while functional ID occurs during inappropriate prolonged tissue iron sequestration, as during chronic inflammation. Moreover, deficiencies in vitamins, copper and magnesium can also lead to anaemia due to their specific roles in haemoglobin and red blood cell production. ID has three stages, progressing from depletion of iron stores (mild iron deficiency) to iron deficiency erythropoiesis (erythrocyte production), and finally to IDA. With ID erythropoiesis (also known as marginal ID), iron stores are depleted and transferrin saturation declines, but haemoglobin levels are usually within the normal range (WHO, 2020; NIH, 2024). IDA occurs when the body lacks sufficient iron to produce adequate amounts of haemoglobin, resulting in a drop of blood haemoglobin concentrations below the normal range and decreases in haematocrit and mean corpuscular volume (WHO, 2020; NIH, 2024).

Clinical presentation, diagnosis and stage/prognosis

In paediatric population, mild to moderate ID not associated with anaemia can be asymptomatic or lead to fatigue and/or poor tolerance to exercise. Typical clinical presentation of moderate to severe ID includes the usual signs of anaemia, such as pallor and fatigue.

Non-haematological findings of ID include growth delay, neurological manifestations (restlessness, decreased mental, memory and motor functions, decreased production of neurotransmitters sleep disturbances, breath-holding spells, restless legs syndrome), gastrointestinal disturbances (anorexia, glossitis, angular cheilitis, oesophageal web or stricture, gastric atrophy, damage of microvilli, enteropathy, pica), and integumentary system problems (spoon nails, easy breakage of nails and hair, hair loss) (WHO, 2001).

Untreated ID in infants and young children may cause irreversible consequences in this critical period, such as permanent neurocognitive impairments, reduced learning capacity, and altered motor ability.

Management

The diagnostic assessment of ID and IDA in children involves the combination of medical history, physical examination, and laboratory tests (Kulik-Rechberger and Dubel, 2024). Serum ferritin (ferritin) is considered to be the most efficient and cost-effective single indicator of iron status and is also the most widely used, giving a good indication of the size of the iron stores in the absence of infection and inflammation, thus helping to differentiate between IDA and anaemia of inflammation (AI). Ferritin can even be used for diagnosing even mild iron deficiencies (Rolic et al., 2024; Domellöf and Sjöberg, 2024; Kulik-Rechberger and Dubel, 2024).

On the other hand, the basic criterion for diagnosing anaemia is a decrease in haemoglobin (Hb) concentration below the norm for age and gender, even though haematocrit and red blood cell count can also be used to define and diagnose anaemia (Kulik-Rechberger and Dubel, 2024; Badireddy and Baradhi, 2023). WHO defines anaemia as a haemoglobin concentration <110 g/L (at sea level) in children aged under 5 years and pregnant women, and a haemoglobin concentration <120 g/L in non-pregnant women (WHO NLiS, 2024; WHO, 2024). For males, anaemia is defined as a haemoglobin concentration <130 g/L; however, these thresholds are subject to debate due to

ethnic differences (Rolic et al., 2024). The threshold for haemoglobin concentration to define anaemia in children should be determined by age. According to the WHO, this it determined to be below 11 g/dL in children aged 6 months to 6 years, and below 12 g/dL in children 6–14 years old (WHO, 2001).

Typical haematological features of IDA are decreased Hb levels, decreased mean corpuscular Hb concentration, decreased mean corpuscular volume (MCV), significant anisocytosis on a peripheral blood smear, elevated red cell distribution width, as well as decreased reticulocyte Hb concentration and reticulocyte count (Kulik-Rechberger and Dubel, 2024).

Regarding treatment of ID, it normally begins with simple dietary replacement (i.e., fortified cereals and breads, red meat). When diet alone is inadequate to restore iron stores and haemoglobin to normal levels, or when anaemia is moderate or severe, treatment with exogenous iron supplements should be implemented (WHO, 1968). In case that these dietary measures were not enough, there are available iron preparations based on iron salts include ferrous iron salts (sulphate, gluconate, fumarate, acetate, ascorbate), and ferric iron salts (citrate) (Mantadakis et al., 2020).

2.1.2. About the product

Feraccru (ferric maltol) is an iron-containing product, currently used for the treatment of iron deficiency in adults. It was granted a Marketing Authorisation in the EU on 18 February 2016. The current variation seeks to extend the therapeutic indication of Feraccru, by expanding its use in adolescents aged 12 years and above, with iron deficiency.

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). The complex dissociates on uptake from the gastro-intestinal tract and the complex itself does not enter the systemic circulation.

This preparation contains a non-salt oral iron formulation composed of stable ferric iron complexed with a sugar derivative, tri-maltol. Maltol reduces the formation of free iron by maintaining the unabsorbed fraction of iron chelated in a redox-inert form and facilitating iron transport across the enterocytes. This increases the bioavailability of iron such that lower doses of elemental iron are required to treat IDA compared with the ferrous iron preparations. Furthermore, ferric maltol has been shown to have less of an effect on the gut microbiome (Kumar et al., 2022; Pantopoulos, 2024). In contrast to the traditional oral ferrous iron products, if the iron in ferric maltol is not absorbed, the iron remains in the chelated form and is inhibited from participating in the oxidation-reduction reaction. As a result, ferric maltol has less gastrointestinal irritation and better taste, so that it can be taken under the fasting condition without gastrointestinal irritation (Cai et al., 2023).

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

This type II variation application seeks to extend the indication to include adolescents aged 12 years and older, based on the results of clinical studies conducted in accordance with the agreed Paediatric Investigation Plan (PIP). The proposed variation is supported by the results from 2 clinical studies: a Phase 1 study (ST10-01- 103) which assessed the pharmacokinetic, pharmacodynamics and safety of ferric maltol capsules in children aged 10 to <18 years with ID, and a Phase 3 study (ST10-01-305) which assessed the pharmacokinetics, and clinical efficacy and safety of ferric maltol oral suspension in children aged 2 to <18 years with IDA. Furthermore, an

additional, supportive Phase 1 study was also carried out to compare the therapeutic equivalence between the ferric maltol oral suspension and the existing ferric maltol capsules in adult healthy volunteers under fed and fasted states.

Studies ST10-01-103 and Study ST10-01-305 were part of agreed paediatric investigation plan (PIP) EMEA-001195-PIP01-11-M07. On 29 December 2023 the PDCO agreed on a paediatric investigation plan (PIP) with a waiver and a deferral for ferric citrate coordination complex (FCCC) for children from 6 months of age to less than 18 years of age in the condition of treatment of anaemia due to chronic kidney disorders.

The company carried out paediatric clinical studies with an oral suspension as specified in the agreed PIP but opted not to apply for a paediatric indication for this formulation. Instead, the applicant sought an extension of the indication for the hard capsules in adolescents and proposed inclusion of all paediatric studies in the product information.

2.1.4. General comments on compliance with GCP

All studies were conducted in full compliance with GCP as declared by the MAH. All studies were closely monitored by the sponsor for compliance with the protocol, Norgine Standard Operating Procedures (SOPs), and applicable regulatory guidance.

2.2. Non-clinical aspects

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

2.2.1. Ecotoxicity/environmental risk assessment

A justification for the absence of a complete environmental risk assessment was provided according to the current ERA guideline (CPMP/SWP/4447/00). Although the indication is being broadened for use in adolescents, it will still be administered to replace iron in iron-deficient patients and therefore impact on environmental risk is not foreseen.

2.2.2. Discussion on non-clinical aspects

ERA studies are not required as both components of this medicinal product (the active moiety iron and maltol)are unlikely to result in significant risk to the environment. Maltol is a simple sugar and a dehydration product of glucose.

2.2.3. Conclusion on the non-clinical aspects

Considering the above data, ferric maltol is not expected to pose a risk to the environment.

2.3. Clinical aspects

2.3.1. Introduction

The proposed variation to extend the use of Feraccru in adolescents aged 12 years and above is supported by the results from 2 clinical studies: a Phase 1 study (ST10-01-103) which assessed the pharmacokinetic (PK), pharmacodynamics and safety of ferric maltol capsules in children aged 10 to <18 years with ID, and a Phase 3 study (ST10-01-305) which assessed the

pharmacokinetics, and clinical efficacy and safety of ferric maltol oral suspension in children aged 2 to <18 years with IDA.

An additional supportive Phase 1 (Study ST10-01-104) study was also carried out to compare the therapeutic equivalence between the ferric maltol oral suspension and the existing ferric maltol capsules in adult healthy volunteers (age 18 to 55 years) under fed and fasted states. This study was intended to evaluate the PK of a single 30 mg dose of ferric maltol administered as a capsule or oral suspension and the assessment of safety and tolerability of the two ferric maltol formulations.

Based on the results of studies ST10-01-103 and ST10-01-305, supported by the results of study ST10-01-104, the existing formulation (30 mg capsules) is proposed for both adult and adolescent patients.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH. The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- **Tabular overview of clinical studies**

Table 1. Overview of clinical studies.

Study ID	Study Objectives	Study Design; Endpoints	Test Product(s); Dosage Regimen; Route of Administration	Study population	Treatment duration	Subjects treated
ST10-01-103	*Primary* • To assess the PK and iron uptake of 3 doses of ferric maltol in children and adolescents *Secondary* • To assess the effects of 3 doses of ferric maltol in children and adolescents • To assess the safety and tolerability of ferric maltol in children and adolescents	Phase 1, randomized, open-label, parallel group, multicentre, paediatric, PK study.	Ferric maltol, 7.8 mg, 16.6 mg, 30 mg. Capsules, BID, oral on Days 1 to 9 Single dose, oral on Day 10.	Male and female paediatric subjects, aged 10 to <18 years old, with iron deficiency.	10 days	Dosed: 37 7.8 mg group: 12 16.6 mg group: 13 30 mg group: 12 Completed: 35 7.8 mg group: 12 16.6 mg group: 11 30 mg group: 12
ST10-01-104	*Primary* • To evaluate the PK of iron absorption, after a single 30 mg dose of ferric maltol, administered as a capsule or oral suspension (under fasted and fed conditions) based on primary parameters *Secondary* • To evaluate the PK after a single 30 mg dose of ferric maltol, administered as a capsule or oral suspension, (under fasted and fed conditions), based on TSAT, TIBC, UIBC and plasma maltol and maltol glucuronide	Phase 1, randomized, open-label, single dose, 4-way crossover study	*Treatment* Ferric maltol: • Capsules: 30 mg • Oral suspension: 30 mg (5mL) Single dose, oral,	Healthy adult subjects, 18 to 55 years of age	8 days Telephone FU: 3-7 days post last treatment	Randomized and completed: 32

Study ID	Study Objectives	Study Design; Endpoints	Test Product(s); Dosage Regimen; Route of Administration	Study population	Treatment duration	Subjects treated
	• To assess the safety and tolerability of ferric maltol following a single 30 mg dose, administered as a capsule or oral suspension (under fasted and fed conditions)					
ST10-01-305	*Primary* • To compare the safety and gastrointestinal tolerability of ferric maltol oral suspension and ferrous sulphate oral liquid in children and adolescents (2 to <18 years) and assess the safety and tolerability of ferric maltol oral suspension in children (1 month to <2 years), in the treatment of iron deficiency anaemia • To assess the effect on haemoglobin in children and adolescents (1 month to <18 years) *Secondary* • To assess the PK in children and adolescents (2 to <18 years) after a single dose of ferric maltol oral suspension, and after BID administration for at least 6 days, after a single morning dose • To assess the effect on iron markers in children and adolescents (1 month to <18	Phase 3, randomized, open-label, active controlled, multicentre, comparative study.	*Treatment* Ferric maltol, oral suspension, BID 1 month to < 2 years: 0.6 mg/kg/dose 2-11 years: 15 mg/dose 12-17 years: 30 mg/dose *Comparator* Ferrous sulphate (125 mg/ml), oral liquid 3 mg/kg/dose, BID	Male and female paediatric subjects, aged 1 month to <18 years, with iron deficiency anaemia	Treatment: 12 weeks Follow-up visit: 10-14 days after completion of treatment	Randomized: Ferric maltol: 31 Ferric maltol assigned [1]: 4 Ferrous sulphate: 30 **Total: 65** Completed: Ferric maltol: 28 Ferric maltol assigned [1]: 3 Ferrous sulphate: 25 **Total: 56**

Study ID	Study Objectives	Study Design; Endpoints	Test Product(s); Dosage Regimen; Route of Administration	Study population	Treatment duration	Subjects treated
	years) after BID administration of ferric maltol oral suspension • To assess the PK, in children (1 month to <2 years) after a single dose of ferric maltol oral suspension and after BID administration for at least 6 days, after a single morning dose • To assess the effect, in children (1 month to <2 years) after BID administration for at least 6 days, after a single morning dose • To assess the effect, in children (2 to <18 years) after a single dose of ferric maltol suspension, and after BID administration for at least 6 days, after a single morning dose • To compare the palatability from age-appropriate scoring system of ferric maltol oral suspension and ferrous sulphate oral liquid					

Abbreviations: **AUC_{0-6h}** = plasma concentration curve from time 0 to 6 hours; **AUC_{0-inf}** = plasma concentration curve from time 0 to infinity; **BID** = twice daily (administration); **b.w.** = body weight; **$C_{ave[0-6h]}$** = average steady state plasma concentration from time 0 to 6 hours; **$C_{L/F}$** = apparent systemic clearance; **C_{max}** = maximum plasma concentration; **ECG** = electrocardiogram; **NTBI** = Non-transferrin bound iron; **PK** = pharmacokinetics; **$t_{1/2}$** = half-life; **TEAEs** = treatment-emergent adverse events; **TESAEs** = treatment-emergent serious adverse events; **TIBC** = total iron binding capacity; **T_{max}** = time to maximum plasma concentration; **TSAT** = transferrin saturation; **UIBC** = unsaturated iron binding capacity; **V_z/F** = apparent volume of distribution.

[1] Ferric maltol assigned group included only infants 1 month to <2 years of age. There is no ferrous sulphate comparison for this age group.

2.3.2. Pharmacokinetics

Two prospective PK studies have been conducted in paediatric subjects and in healthy adult volunteers (ST10-01-103 and ST10-01-104, respectively). Additional PK evaluations in children aged 1 month to <2 years and children and adolescents aged 2 to <18 years were also carried out in study ST10-01-305.

A population PK (PPK) modelling approach was also used in study ST10-01-103 to describe the serum iron concentrations in the paediatric population and to determine the significance of possible covariates which may contribute to the differences in iron PK estimates among individuals.

In studies ST10-01-103 and ST10-01-104, the Full Analysis Set (FAS) included all subjects who took at least 1 dose of study drug and had at least 1 evaluable post-dose PK sample and was used in the PK analysis. In study ST10-01-103, this population was also called the Intent-to-Treat (ITT) Population and was also used in the PPK analysis.

In both studies, the Safety Population included all subjects who took at least 1 dose of study drug and had 1 subsequent contact with the investigator and was used to summarize all safety data.

In study ST10-01-305, the PK analysis was carried out on the PK Population which was defined as all randomized/assigned subjects who had at least 1 dose of study drug and who had at least 1 evaluable post-dose PK sample (applicable only for the ferric maltol group).

Analytical methods

Blood samples were obtained from studies ST10-01-103, ST10-01-104 and ST10-01-305. Depending on the study, different analytes were measured. Among them: total iron, maltol, maltol glucuronide, iron markers and non-transferrin bound iron.

Method validation

Total iron

Quantification of total iron in serum was carried out bichromatically on the Beckman Coulter Chemistry Analyzers (AU5800) following method "Iron on the Beckman Coulter Chemistry Analyzers". A validation summary was submitted, including results from intra and inter-run precision and accuracy, a validated range from 10 to 1000 µg/mL with a 10-fold dilution capability, long term stability of up to 1 year at −20 °C and -70ºC, and interference testing against bilirubin, lipemia, and haemoglobin. This method was submitted in previous regulatory procedures.

Maltol glucuronide

Quantification of maltol glucuronide was carried out in human plasma samples (lithium heparin as anticoagulant) using a LC-MS/MS method (study number V/MG/HP/A), developed and validated in ABS Laboratories Ltd (UK). The linearity range used was 0.050-10.00 µg/mL (range truncated and validated in previous procedures). This method was already submitted in previous procedures.

In the present procedure, the MAH submitted a new validation report (study number V/MG/HP/A2) to extended long-term stability (LTS) of study samples for maltol and maltol glucuronide analysis. This partial validation was carried out in ABS Laboratories Ltd (UK). QC stability samples were prepared in two different dates and analysed long term storage at -20ºC to validate a new LTS. The mean concentration at each QC level was within acceptable limits of the nominal concentration for maltol glucuronide after the storage period. For maltol, the mean concentration at each QC level was also within ±15% of the nominal concentration. Additionally, stock solution stability of maltol and maltol glucuronide primary stock, in the most concentrated and diluted mixed standard solution in water at 4ºC was evaluated. Stock solution stability of internal standard (IS) primary stock and in the mixed IS spiking solution in water at 4°C was also determined. These stabilities were also extended.

Sample analysis

Total iron – Studies ST10-01-103 and ST10-01-104

Bioanalytical report ST10-01-103 (Medpace Reference Laboratories, Leuven, Belgium) applied the method "Iron on the Beckman Coulter Chemistry Analyzers" on AU5400/AU2700 instruments using three QC levels (MultiQual MQ1–MQ3) within a 10–1000 µg/mL range. The assay showed consistent performance, with intra- and inter-assay within acceptable limits. All samples complied with stability criteria, and no interferences were detected.

Bioanalytical report ST10-01-104 (Medpace Reference Laboratories, Cincinnati, US) used the same method on the AU5800 platform and the same QC scheme and range. Precision parameters were similarly acceptable. All samples met stability requirements, and no analytical interferences were observed.

Maltol glucuronide – Study ST10-01-103

Maltol glucuronide concentrations were analysed in 212 samples from Study ST10-01-103 at ABS Laboratories Ltd (UK) between 20 June 2017 and 24 May 2018. The maximum storage time was 209 days at -20ºC and the validated stability of maltol glucuronide for method V/MG/HP/A is 263 days at -20 °C.

Sample analysis was carried out in 11 accepted runs. Two calibration curves and 6 QCs (2 of each level) were included in every run. Accuracy and precision of the accepted run were within ±15% of the nominal value (±20% at the LLOQ).

Overall, no pre-dose samples produced results within the range of quantitation. No reanalysis was carried out. The storage of various samples was outside the acceptable range before being received at ABS Laboratories.

Incurred sample reanalysis was performed in 22 samples and the percentage difference in more than 67% of the samples was within ±20%.

Absorption

Bioequivalence and influence of food

ST10-01-104: Randomized, open-label, single dose, 4-way crossover, phase 1 study to compare the pharmacokinetics (PK) of ferric maltol capsules and oral suspension under fasted and fed conditions in adult healthy volunteers.

Objectives

The primary objective was to evaluate the PK of iron absorption after a single 30 mg dose of ferric maltol administered as a capsule or oral suspension (fasted and fed conditions) via C_{max} and AUC_{last}. The secondary objectives were to evaluate the PK through measurements of transferrin saturation (TSAT), baseline corrected serum iron, transferrin, total iron binding capacity (TIBC), unsaturated iron binding capacity (UIBC), and plasma maltol and maltol glucuronide; and to assess the safety and tolerability of ferric maltol.

Design

This was a phase 1, randomized, open-label, single dose, 4-way crossover study with a treatment period of 4 days with at least a 48-hour washout period between each dose administration. Subjects were randomized in a 1:1:1:1 ratio to receive one of the treatment sequences (make up with 4 period: 30 mg ferric maltol capsule in fed, 30 mg (5 mL) ferric maltol suspension in fed, 30

mg ferric maltol capsule in fasted and 30 mg (5 mL) ferric maltol suspension in fasted). A schematic of the study design is presented in Figure 1.

Figure 1. Design of study ST10-01-104

The day of the first dose of study drug was Day 1, and the day immediately before Day 1 was Day -1. There was no Day 0.

Further information is listed below:

Protocol approval date	15 July 2020 (Version 2.0)
IEC approval of protocol	14 August 2020
Period clinical study	16 September 2020 – 13 November 2020
Principal Investigator	Leela Vrishabhendra, MD
Clinical facility	Medpace Clinical Pharmacology Unit (5355 Medpace Way, Cincinnati, OH 45227, USA)
Bioanalytical facility	Medpace Reference Laboratories (5365 Medpace Way, Cincinnati, Ohio, United States)

Dosing dates were different regarding each subject and ranged from 30 September 2020 to 10 November 2020.

The total wash-out period was at least 48 hours.

PK samples were collected pre-dose and up to 24 hours post-dose during each period (11 times – 15min, 30min, 45min, 1h, 1.5h, 2h, 3h, 4h, 6h, 10h and 24h) for the measurements of serum iron, TSAT, TIBC, UIBC, transferrin, and plasma maltol and maltol glucuronide.

For the determination of total iron and related iron markers, samples were collected in 2.5 mL Serum Separator Tube/SST (Red and Yellow Top) tubes. After collection, samples were mixed gently by inverting the tubes 5-10 times and then the tubes were placed in upright position for 30 minutes at ambient temperature in order to allow the blood to clot. Within 60 minutes of collection, samples were centrifuged at approximately 1800 g for 15 minutes. Two serum aliquots were transferred into 3.5mL Freestanding CryoSure vials. One aliquot was shipped refrigerated on the day of collection, and the second aliquot was kept frozen at -20ºC ± 5ºC.

Test and reference products

Test product: A single oral dose of 30 mg ferric maltol was administered as 5 mL oral suspension.

- Batch number: SHI/20/0660.
- Retest date: January 2021.
- Measured content (% label claim): 101.9%.
- Batch size: 30 l.

Reference product: A single oral dose of 30 mg ferric maltol was administered as one 30 mg capsule.

- Batch number: SHI/20/0661.
- Retest date: February 2021.

- Measured content (% of label claim): 101.7%.
- Batch size: 7781 capsules.

Certificates of analysis were provided for test and reference formulation.

Method of administration

In fasted conditions, capsules were taken with 240 mL potable tap water, must have been swallowed whole, and must not have been chewed, divided, or crushed. Suspension could have been taken with 240 mL potable tap water, if needed. No food was also allowed for at least 4 hours post-dose.

In fed conditions, subjects had their baseline blood samples taken and received the test meal 30 minutes prior to administration of ferric maltol. Subjects finished their meal in 30 minutes or less; however, ferric maltol was administered 30 minutes after start of the meal. Capsules were taken with 240 mL potable tap water. Suspension was taken with 240 mL potable tap water if needed. No food was also allowed for at least 4 hours post-dose.
The test meal consisted of 164, 192, and 576 calories from protein, carbohydrates, and fat, respectively.

Population studied

A total of 32 healthy subjects were randomised with a mean age ranged in each treatment sequence from 33.6 to 40.5 (6.44 to 11.05) years, mean weight ranged from 72.61 and 88.57 kg, mean height ranged from 165.68 and 175.56 cm, and mean body mass index ranged from 23.51 to 28.55 kg/m^2.

The main inclusion criteria were:
- Healthy, adult subjects aged between 18 and 55 years (inclusive) at the time of informed consent.
- The subject must have had a body mass index of 18 to 32 kg/m2, inclusive, and been willing and able to comply with study requirements.

All 32 subjects completed the study according to protocol and were therefore included in the statistical analysis.

Analytical methods

Bioanalytical report of total iron quantification was not provided. For further details, refer to section on Analytical methods.

Pharmacokinetic variables

The following PK parameters of iron and baseline corrected serum iron were derived by non-compartmental analysis of the serum concentration-time profiles: C_{max}, T_{max}, apparent terminal elimination rate constant (λ_z), apparent terminal elimination half-life ($t_{1/2}$), AUC_{last} and AUC_{inf}.

The actual collection times were used for the calculation of PK parameters. The Linear Up Log Down method (equivalent to the Linear Up/Log Down option in WinNonlin Professional) was used in the computation of area under the plasma concentration curve (AUC), if applicable.

Statistical analysis

SAS software, version 9.4 was used for the statistical analysis and the reporting of clinical and PK data.

An analysis of variance (ANOVA) model was performed on the ln-transformed PK parameters (C_{max}, AUC_{last}, and AUC_{inf}) of the 2 formulations including terms for sequence (treatment sequence),

treatment (formulation/condition), period as fixed effects, and subjects nested within a sequence as a random effect. The estimates were back-transformed into original scale. The point estimates for ratios and the corresponding 90% CIs are provided.

Results

Considering that serum iron is an endogenous compound and subjects had baseline values, the results provided below are of those of baseline corrected serum iron comparative analysis. Negative values were incorporated into AUC calculations to determine AUC above and below baseline value; net AUC was calculated as AUC above – AUC below. Because of the incorporation of negative AUC values, a nonparametric approach was utilized for AUC the median of differences in place of the planned ANOVA.

Tmax was observed in the first sampling point (pre-dose) in various patients for both formulations mainly in fed conditions.

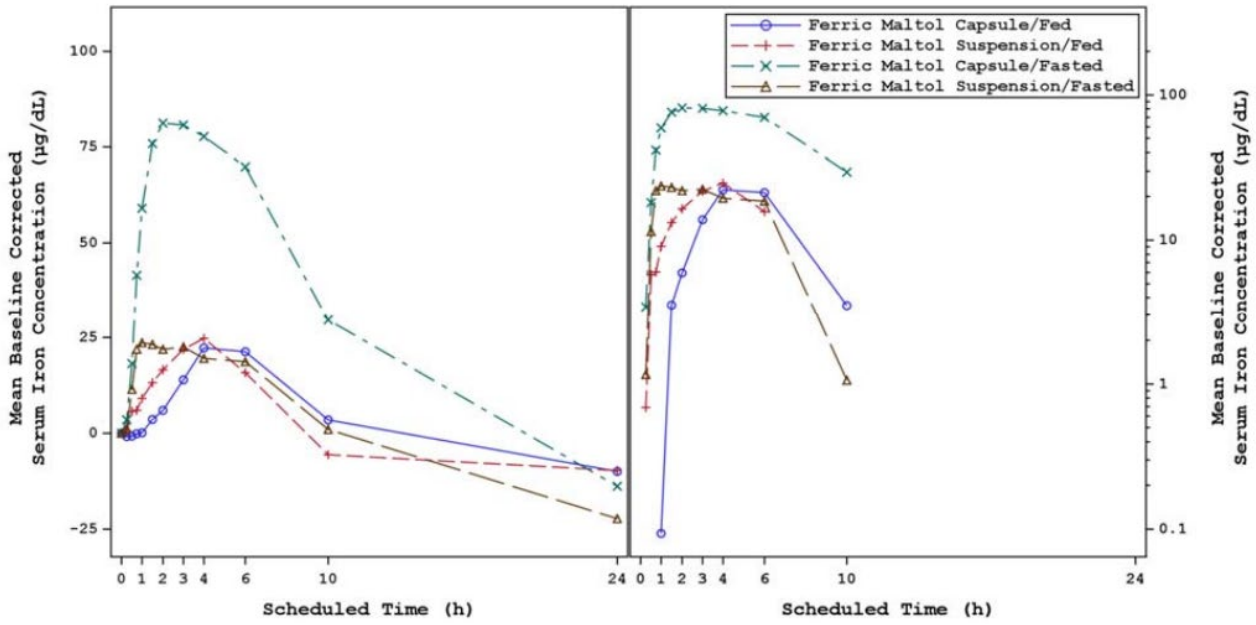
Summary of the main pharmacokinetic parameters for baseline corrected serum iron are shown in Table 2.

Table 2. Summary of PK parameters for baseline corrected serum iron

Formulation/Condition Statistic	C_{max} (ng/mL)	T_{max} (h)	AUC_{last} Above Baseline (h*ng/mL)	AUC_{last} Below Baseline (h*ng/mL)	AUC_{last} Net (h*ng/mL)
Ferric maltol capsule/fed					
n	32	32	32	32	32
Mean	44.469	7.398	372.434	316.284	56.150
SD	73.0572	9.1629	714.8305	442.3182	964.9572
Median	12.000	3.500	90.140	92.024	16.478
Minimum	0.00	0.00	0.00	0.00	-1630.63
Maximum	294.00	24.00	3015.52	1630.63	3014.69
Geometric mean	23.568	5.444	95.588	83.884	277.905
Geometric CV%	277.0	177.1	2198.6	1144.3	311.9
Ferric maltol suspension/fed					
n	32	32	32	32	32
Mean	40.219	5.461	342.700	340.197	2.503
SD	52.9715	7.4920	582.2122	480.5673	889.0745
Median	21.000	3.500	91.797	102.320	-48.998
Minimum	0.00	0.00	0.00	0.00	-1808.55
Maximum	225.00	24.00	2450.64	1808.55	2446.53
Geometric mean	24.170	3.512	96.398	164.466	408.765
Geometric CV%	225.0	173.7	1365.5	374.2	408.9
Ferric maltol capsule/fasted					
n	32	32	32	32	32
Mean	89.938	3.726	834.344	142.952	691.392
SD	50.9927	4.0687	634.1700	259.9277	791.8671
Median	79.000	2.000	711.958	39.437	666.514
Minimum	18.00	1.00	36.70	0.00	-967.51
Maximum	202.00	24.00	2488.17	1190.03	2480.06
Geometric mean	75.407	2.868	578.593	46.918	694.206
Geometric CV%	70.7	71.5	128.7	569.7	114.8
Ferric maltol suspension/fasted					
n	32	32	32	32	32
Mean	33.250	3.211	301.905	311.342	-9.436
SD	23.0637	2.7534	330.3642	467.2600	693.2830
Median	27.000	2.000	143.782	114.808	66.665
Minimum	0.00	0.00	0.00	0.00	-2296.38
Maximum	83.00	10.00	1244.42	2296.38	1244.33
Geometric mean	27.069	2.326	149.131	116.369	300.328
Geometric CV%	86.4	108.3	302.2	2102.5	148.2

The mean plasma baseline corrected serum iron concentration-time curves by formulation/condition group on linear scale and semi-log scale concentration-time curves are shown in Figure 2.

Figure 2. Plot of mean baseline corrected serum iron concentration (µg/dl) by formulation/condition group on linear scale and semi-log scale



Values of 0 or below for baseline corrected serum iron were excluded from this analysis.

Bioequivalence evaluation

Table 3. Analysis of pk parameters for baseline corrected serum iron in fasted condition

Parameter Statistic	Ferric Maltol Capsule/Fasted (N=32)	Ferric Maltol Suspension/Fasted (N=32)
C_{max} (ng/mL)		
n	32	32
Geometric LS mean	75.41	26.19
Treatment comparison [1] ferric maltol suspension/fasted vs capsule/fasted		
Ratio of geometric LS mean (%)		34.73
90% CI for ratio (%)		(24.71, 48.83)
AUC_{last} net (h*ng/mL)		
n	32	32
Median	666.51	66.67
Q1, Q3	176.07, 1234.28	-531.17, 501.64
Treatment comparison [2] ferric maltol suspension/fasted vs capsule/fasted		
Median of differences		-644.75
90% CI (%)		(-945.69, -374.04)

Values of 0 or below for baseline corrected serum iron were excluded from this analysis.

1. An ANOVA model was performed on the ln-transformed PK parameters (C_{max}) of the 2 formulations including terms for sequence (treatment sequence), treatment (formulation/condition), and period as fixed effects, and subjects nested within a sequence as a random effect. The estimates were back-transformed into original scale. Ratio was defined as C_{max}(suspension)/C_{max}(capsule).
2. Median of differences and 90% CI statistics were from the nonparametric Hodges-Lehman estimation method with treatment (formulation/condition) as the class variable. Difference was defined as AUC_{last}(suspension) – AUC_{last}(capsule).

ANOVA = analysis of variance; AUC_{last} = area under the plasma concentration curve from 0 up to the last measurable concentration (non-below) quantification limit after dosing; CI = confidence interval; C_{max} = maximum plasma concentration; FAS = Full Analysis Set; ln = natural logarithm; LS = least squares; PK = pharmacokinetic(s); Q1 = quartile 1; Q3 = quartile 3; vs = versus.

Table 4. Analysis of additional Parameters for Baseline Corrected Serum Iron in Fasted Condition Full Analysis Set Population

Parameter Statistic	Ferric Maltol Capsule/Fasted (N=32)	Ferric Maltol Suspension/Fasted (N=32)
AUC0-last (h*ug/dL)		
n	32	31
Geometric LS Mean	480.49	119.15
Treatment Comparison		
Ferric Maltol Suspension/Fasted vs Capsule/Fasted		
Ratio of Geometric LS Mean (%)		24.80
90% CI for Ratio (%)		(13.57, 45.30)
AUC0-inf (h*ug/dL)		
n	13	7
Geometric LS Mean	752.01	243.07
Treatment Comparison		
Ferric Maltol Suspension/Fasted vs Capsule/Fasted		
Ratio of Geometric LS Mean (%)		32.32
90% CI for Ratio (%)		(13.16, 79.41)

An ANOVA model was performed on the ln-transformed PK parameters (AUC0-last and AUC0-inf) of the two formulations including terms for sequence (treatment sequence), treatment (formulation/condition), and period as fixed effects, and subjects nested within a sequence as a random effect. The estimates were back-transformed into original scale.

Ratios are defined as AUC0-last(suspension)/ AUC0-last(capsule), AUC0-inf(suspension)/ AUC0-inf(capsule) in fasted condition.

Table 5. Analysis of pk parameters for baseline corrected serum iron in fed condition

Parameter Statistic	Ferric Maltol Capsule/Fed (N=32)	Ferric Maltol Suspension/Fed (N=32)
C_{max} (ng/mL)		
n	32	32
Geometric LS mean	20.82	23.23
Treatment comparison [1] ferric maltol suspension/fed vs capsule/fed		
Ratio of geometric LS mean (%)		111.55
90% CI for ratio (%)		(76.01, 163.71)
AUC_{last} net (h*ng/mL)		
n	32	32
Median	16.48	-49.00
Q1, Q3	-496.38, 328.38	-539.01, 483.79
Treatment comparison [2] ferric maltol suspension/fed vs capsule/fed		
Median of differences		-15.78
90% CI (%)		(-288.29, 326.47)

Values of 0 or below for baseline corrected serum iron were excluded from this analysis.

1. An ANOVA model was performed on the ln-transformed PK parameters (C_{max}) of the 2 formulations including terms for sequence (treatment sequence), treatment (formulation/condition), and period as fixed effects, and subjects nested within a sequence as a random effect. The estimates were back-transformed into original scale. Ratio was defined as C_{max}(suspension)/C_{max}(capsule).
2. Median of differences and 90% CI statistics were from the nonparametric Hodges-Lehman estimation method with treatment (formulation/condition) as the class variable. Difference was defined as AUC_{last}(suspension) – AUC_{last}(capsule).

ANOVA = analysis of variance; AUC_{last} = area under the plasma concentration curve from 0 up to the last measurable concentration (non-below) quantification limit after dosing; CI = confidence interval; C_{max} = maximum plasma concentration; FAS = Full Analysis Set; ln = natural logarithm; LS = least squares; PK = pharmacokinetic(s); Q1 = quartile 1; Q3 = quartile 3; vs = versus.

Source: Post-text Table 14.2.2.3

Table 6. Analysis of additional PK Parameters for Baseline Corrected Serum Iron in Fed Condition Full Analysis Set Population

Parameter Statistic	Ferric Maltol Capsule/Fed (N=32)	Ferric Maltol Suspension/Fed (N=32)
AUC0-last (h*ug/dL)		
n	25	27
Geometric LS Mean	82.42	85.90
Treatment Comparison		
Ferric Maltol Suspension/Fed vs Capsule/Fed		
Ratio of Geometric LS Mean (%)		104.23
90% CI for Ratio (%)		(52.93, 205.23)
AUC0-inf (h*ug/dL)		
n	3	6
Geometric LS Mean	226.41	270.27
Treatment Comparison		
Ferric Maltol Suspension/Fed vs Capsule/Fed		
Ratio of Geometric LS Mean (%)		119.37
90% CI for Ratio (%)		(33.24, 428.75)

An ANOVA model was performed on the ln-transformed PK parameters (AUC0-last and AUC0-inf) of the two formulations including terms for sequence (treatment sequence), treatment (formulation/condition), and period as fixed effects, and subjects nested within a sequence as a random effect. The estimates were back-transformed into original scale.

Ratios are defined as AUC0-last(suspension)/ AUC0-last(capsule), AUC0-inf(suspension)/ AUC0-inf(capsule) in fed condition.

Food-effect evaluation

Table 7. Analysis of PK parameters for baseline corrected serum iron for fasted vs fed condition by formulation

Formulation Parameter Statistic	Ferric Maltol Fed (N=32)	Ferric Maltol Fasted (N=32)
Capsule		
C_{max} (ng/mL)		
n	32	32
Geometric LS mean	20.82	75.41
Treatment comparison [1] ferric maltol fasted vs fed		
Ratio of geometric LS mean (%)		362.18
90% CI for ratio (%)		(251.15, 522.28)
AUC_{last} net (h*ng/mL)		
n	32	32
Median	16.48	666.51
Q1, Q3	-496.38, 328.38	176.07, 1234.28
Treatment comparison [2] ferric maltol fasted vs fed		
Median of differences		719.30
90% CI		(386.52, 1043.59)
Suspension		
C_{max} (ng/mL)		
n	32	32
Geometric LS mean	23.23	26.19
Treatment comparison [1] ferric maltol fasted vs fed		
Ratio of geometric LS mean (%)		112.77
90% CI for ratio (%)		(78.65, 161.69)
AUC_{last} net (h*ng/mL)		
n	32	32
Median	-49.00	66.67
Q1, Q3	-539.01, 483.79	-531.17, 501.64
Treatment comparison [2] ferric maltol fasted vs fed		
Median of differences		57.22
90% CI		(-262.14, 352.72)

Values of 0 or below for baseline corrected serum iron were excluded from this analysis.

1. An ANOVA model was performed on the ln-transformed PK parameters (C_{max}) of the 2 formulations including terms for sequence (treatment sequence), treatment (formulation/condition), and period as fixed effects, and subjects nested within a sequence as a random effect. The estimates were back-transformed into original scale. Ratio was defined as C_{max}(fasted)/C_{max}(fed).
2. Median of differences and 90% CI statistics were from the nonparametric Hodges-Lehman estimation method with treatment (formulation/condition) as the class variable. Difference was defined as AUC_{last}(fasted) – AUC_{last}(fed).

ANOVA = analysis of variance; AUC_{last} = area under the plasma concentration curve from 0 up to the last measurable concentration (non-below) quantification limit after dosing; CI = confidence interval; C_{max} = maximum plasma concentration; FAS = Full Analysis Set; ln = natural logarithm; LS = least squares; PK = pharmacokinetic(s); Q1 = quartile 1; Q3 = quartile 3; vs = versus.

Table 8. Analysis of additional PK Parameters for Baseline Corrected Serum Iron for Fasted versus Fed Condition by Formulation Full Analysis Set Population

Parameter Statistic	Ferric Maltol Fed (N=32)	Ferric Maltol Fasted (N=32)
Capsule		
AUC0-last (h*ug/dL)		
n	25	32
Geometric LS Mean	82.42	480.49
Treatment Comparison		
Ferric Maltol Fasted vs Fed		
Ratio of Geometric LS Mean (%)		582.96
90% CI for Ratio (%)		(305.29, 1113.20)
AUC0-inf (h*ug/dL)		
n	3	13
Geometric LS Mean	226.41	752.01
Treatment Comparison		
Ferric Maltol Fasted vs Fed		
Ratio of Geometric LS Mean (%)		332.14
90% CI for Ratio (%)		(96.34, 1145.15)

An ANOVA model was performed on the ln-transformed PK parameters (AUC0-last and AUC0-inf) of the two formulations including terms for sequence (treatment sequence), treatment (formulation/condition), and period as fixed effects, and subjects nested within a sequence as a random effect. The estimates were back-transformed into original scale.

Ratios are defined as AUC0-last (fasted) / AUC0-last(fed), AUC0-inf(fasted)/ AUC0-inf(fed).

Parameter Statistic	Ferric Maltol Fed (N=32)	Ferric Maltol Fasted (N=32)
Suspension		
AUC0-last (h*ug/dL)		
n	27	31
Geometric LS Mean	85.90	119.15
Treatment Comparison		
Ferric Maltol Fasted vs Fed		
Ratio of Geometric LS Mean (%)		138.70
90% CI for Ratio (%)		(73.36, 262.23)
AUC0-inf (h*ug/dL)		
n	6	7
Geometric LS Mean	270.27	243.07
Treatment Comparison		
Ferric Maltol Fasted vs Fed		
Ratio of Geometric LS Mean (%)		89.93
90% CI for Ratio (%)		(36.62, 220.87)

An ANOVA model was performed on the ln-transformed PK parameters (AUC0-last and AUC0-inf) of the two formulations including terms for sequence (treatment sequence), treatment (formulation/condition), and period as fixed effects, and subjects nested within a sequence as a random effect. The estimates were back-transformed into original scale.

Ratios are defined as AUC0-last (fasted) / AUC0-last(fed), AUC0-inf(fasted)/ AUC0-inf(fed).

Safety

During the study, 8 subjects (25%) experienced treatment-emergent adverse events (TEAEs): 3 subjects in the ferric maltol suspension/fed period, 3 subjects in the ferric maltol suspension/fasted period and 2 subjects in the ferric maltol capsule/fasted period. These TEAEs were mild in severity: headache (3), vessel puncture site pain (2), hypoesthesia oral (1), rhinalgia (1) and pruritus (1).

Those TEAEs were not considered to be study-drug related. No deaths, other SAEs, or other significant AEs occurred during this study.

Protocol deviations

Protocol deviations by treatment sequence for the randomized population can be seen in Table 9. A total of 5 (15.6%) subjects had a protocol deviation: 1 subject had a major protocol deviation for not consuming the entire test meal prior to dosing in the ferric maltol suspension/fed condition, and 4 subjects had minor protocol deviations for PK or clinical laboratory draws being conducted outside of windows, in error, or not per protocol.

Table 9. Protocol deviations

Category Deviation Category	Ferric Maltol Sequence A (N=8) n (%)	Ferric Maltol Sequence B (N=8) n (%)	Ferric Maltol Sequence C (N=8) n (%)	Ferric Maltol Sequence D (N=8) n (%)	Total (N=32) n (%)
Randomized Population	8	8	8	8	32
Any protocol deviation [1]	0 (0.0)	2 (25.0)	1 (12.5)	2 (25.0)	5 (15.6)
Any major protocol deviation [1]	0 (0.0)	0 (0.0)	1 (12.5)	0 (0.0)	1 (3.1)
Investigational product	0 (0.0)	0 (0.0)	1 (12.5)	0 (0.0)	1 (3.1)
Any minor protocol deviation [1]	0 (0.0)	2 (25.0)	0 (0.0)	2 (25.0)	4 (12.5)
Study procedures	0 (0.0)	2 (25.0)	0 (0.0)	2 (25.0)	4 (12.5)

Sequence A: Period 1 capsule-fed; Period 2 suspension-fed; Period 3 capsule-fasted; Period 4 suspension-fasted.
Sequence B: Period 1 suspension-fasted; Period 2 capsule-fed; Period 3 suspension-fed; Period 4 capsule-fasted.
Sequence C: Period 1 capsule-fasted; Period 2 suspension-fasted; Period 3 capsule-fed; Period 4 suspension-fed.
Sequence D: Period 1 suspension-fed; Period 2 capsule-fasted; Period 3 suspension-fasted; Period 4 capsule-fed.
1. The denominators for calculating percentages were based on the number of subjects in the Randomized Population for each treatment sequence group and overall.

Concomitant medication

Two (6.3%) subjects took progestogens as concomitant medications for birth control.

Dose proportionality and time dependencies

The dose proportionality was assessed using a power model for predicted maltol glucuronide and predicted serum iron on Day 1 and on Day 10 iron the FAS/ITT Population. The 7.8 mg, 16.6 mg, and 30 mg doses of ferric maltol contain 52.39 mg, 111.497 mg, and 201.5 mg of maltol, respectively

For predicted maltol glucuronide on Day 1, the 90% CIs for AUCs and Cmax contained 1, indicating that dose proportionality of maltol glucuronide existed over the maltol dose range tested. Table 10 summarises the power model analysis of dose proportionality.

Table 10. Power Model Analysis of Dose Proportionality for Predicted Maltol Glucuronide (mg/L) on Day 1– FAS/ITT Population

PK Parameter (Unit)	Statistic	Maltol Dose Level			Dose Proportionality
		52.39 mg (N=12)	111.497 mg (N=13)	201.5 mg (N=12)	
$AUC_{0\text{-}6h}$ (h·mg/L)	n	12	13	12	
	Geo. mean (CV%)	2.58 (3.7)	5.57 (13.4)	10.57 (32.3)	
Dose proportionality for $AUC_{0\text{-}6h}$	n				37
	Slope estimate (SE)				1.04 (0.059)
	90% CI				(0.94, 1.14)
$AUC_{0\text{-}12h}$ (h·mg/L)	n	12	13	12	
	Geo. mean (CV%)	4.50 (3.1)	9.61 (10.8)	17.93 (21.9)	
Dose proportionality for $AUC_{0\text{-}12h}$	n				37
	Slope estimate (SE)				1.02 (0.042)
	90% CI				(0.95, 1.10)
$AUC_{0\text{-}inf}$ (h·mg/L)	n	12	13	12	
	Geo. mean (CV%)	8.59 (2.3)	17.84 (5.1)	34.12 (12.5)	
Dose proportionality for $AUC_{0\text{-}inf}$	n				37
	Slope estimate (SE)				1.02 (0.024)
	90% CI				(0.98, 1.06)
C_{max} (mg/L)	n	12	13	12	
	Geo. mean (CV%)	0.53 (4.1)	1.15 (15.7)	2.24 (43.9)	
Dose proportionality for C_{max}	n				37
	Slope estimate (SE)				1.07 (0.077)
	90% CI				(0.94, 1.20)

Ferric maltol 7.8 mg, 16.6 mg, and 30 mg includes 52.39 mg, 111.497 mg, and 201.5 mg of maltol, respectively.
The power model for dose proportionality was fitted by regressing the logarithm-transformed PK parameter on logarithm-transformed dose with logarithm-transformed dose as a covariate.
$AUC_{0\text{-}6h}$ = area under the plasma concentration versus time curve from time 0 to 6 hours post-dose; $AUC_{0\text{-}12h}$ = area under the plasma concentration versus time curve from time 0 to 12 hours post-dose; $AUC_{0\text{-}inf}$ = area under the plasma concentration versus time curve from time 0 to infinity; CI = confidence interval; C_{max} = maximum observed plasma concentration; CV = coefficient of variation; Geo. = geometric; PK = pharmacokinetic; SE = standard error.
Source: Post-text Table 14.2.6

For predicted maltol glucuronide on Day 10, the 90% CIs for AUC0-Tau and Ctrough contained 1, indicating that dose proportionality of maltol glucuronide existed for AUC0-Tau and Ctrough over the maltol dose range tested. The Cmax were shown to be slightly deviated from dose proportionality as its 90% CI was close to 1. Table 11 summarises the power model analysis of dose proportionality.

Table 11. Power Model Analysis of Dose Proportionality for Predicted Maltol Glucuronide (mg/L) on Day 10 – FAS/ITT Population

PK Parameter (Unit)	Statistic	Maltol Dose Level			Dose Proportionality
		52.39 mg (N=12)	111.497 mg (N=13)	201.5 mg (N=12)	
$AUC_{0\text{-}Tau}$ (h·mg/L)	n	12	13	12	
	Geo. mean (CV%)	8.59 (2.3)	17.84 (5.1)	34.12 (12.5)	
Dose proportionality for $AUC_{0\text{-}Tau}$	n				37
	Slope estimate (SE)				1.02 (0.024)
	90% CI				(0.98, 1.06)
C_{max} (mg/L)	n	12	13	12	
	Geo. mean (CV%)	0.99 (2.3)	2.10 (6.4)	4.18 (16.0)	
Dose proportionality for C_{max}	n				37
	Slope estimate (SE)				1.06 (0.031)
	90% CI				(1.01, 1.12)
C_{trough} (mg/L)	n	12	13	12	
	Geo. mean (CV%)	0.48 (3.3)	0.97 (10.2)	1.70 (51.9)	
Dose proportionality for C_{trough}	n				37
	Slope estimate (SE)				0.94 (0.085)
	90% CI				(0.79, 1.08)

Ferric maltol 7.8 mg, 16.6 mg, and 30 mg includes 52.39 mg, 111.497 mg, and 201.5 mg of maltol, respectively.
The power model for dose proportionality was fitted by regressing the logarithm-transformed PK parameter on logarithm-transformed dose with logarithm-transformed dose as a covariate.
Tau = 12 hours.
$AUC_{0\text{-}Tau}$ = area under the plasma concentration versus time curve from time 0 to Tau; CI = confidence interval; C_{max} = maximum observed plasma concentration; C_{trough} = minimum concentration between dose time and dose time + Tau; CV = coefficient of variation; Geo. = geometric; PK = pharmacokinetic; SE = standard error.
Source: Post-text Table 14.2.7

For predicted serum iron on Day 1, the exposure of iron increased with dosage, but the 90% CIs for AUCs and Cmax did not contain 1, indicating that dose proportionality of plasma iron did not exist over the 7.8 to 30 mg dose range tested. Table 12 summarises the power model analysis of dose proportionality.

Table 12. Power Model Analysis of Dose Proportionality for Predicted Serum Iron (mg/L) on Day 1 FAS/ITT Population

PK Parameter (Unit)	Statistic	Ferric Maltol Dose Level			Dose Proportionality
		7.8 mg (N=12)	16.6 mg (N=13)	30 mg (N=12)	
$AUC_{0\text{-}6h}$ (h·mg/L)	n	12	13	12	
	Geo. Mean (CV%)	3.79 (28.2)	5.72 (31.6)	6.31 (37.4)	
Dose proportionality for $AUC_{0\text{-}6h}$	n				37
	Slope estimate (SE)				0.39 (0.096)
	90% CI				0.22, 0.55
$AUC_{0\text{-}12h}$ (h·mg/L)	n	12	13	12	
	Geo. mean (CV%)	7.35 (27.7)	10.71 (31.2)	11.61 (36.6)	
Dose proportionality for $AUC_{0\text{-}12h}$	n				37
	Slope estimate (SE)				0.35 (0.095)
	90% CI				0.19, 0.51
$AUC_{0\text{-}inf}$ (h·mg/L)	n	12	13	12	
	Geo. mean (CV%)	27.03 (55.8)	27.22 (41.4)	25.75 (58.0)	
Dose proportionality for $AUC_{0\text{-}inf}$	n				37
	Slope estimate (SE)				-0.03 (0.145)
	90% CI				-0.28, 0.21
C_{max} (mg/L)	n	12	13	12	
	Geo. mean (CV%)	0.68 (28.0)	1.03 (30.8)	1.16 (37.0)	
Dose proportionality for C_{max}	n				37
	Slope estimate (SE)				0.40 (0.095)
	90% CI				0.24, 0.56

The power model for dose proportionality was fitted by regressing the logarithm-transformed PK parameter on logarithm-transformed dose with logarithm-transformed dose as a covariate.
$AUC_{0\text{-}6h}$ = area under the serum concentration versus time curve from time 0 to 6 hours post-dose; $AUC_{0\text{-}12h}$ = area under the serum concentration versus time curve from time 0 to 12 hours post-dose; $AUC_{0\text{-}inf}$ = area under the serum concentration versus time curve from time 0 to infinity; CI = confidence interval; C_{max} = maximum observed serum concentration; CV = coefficient of variation; Geo. = geometric; PK = pharmacokinetic; SE = standard error.
Source: Post-text Table 14.2.12

For predicted serum iron on Day 10, the exposure of iron seems to be comparable across the 3 dose groups, and the 90% CIs for AUC0-Tau, Cmax, and Ctrough did not contain 1, indicating that dose proportionality of iron did not exist for AUC0-Tau, Cmax, and Ctrough over the 7.8 to 30 mg dose range. Table 13 summarises the power model analysis of dose proportionality.

Table 13. Power Model Analysis of Dose Proportionality for Predicted Serum Iron (mg/L) on Day 10 – FAS/ITT Population

PK Parameter (Unit)	Statistic	Ferric Maltol Dose Level			Dose Proportionality
		7.8 mg (N=11)	16.6 mg (N=11)	30 mg (N=12)	
$AUC_{0\text{-}Tau}$ (h·mg/L)	n	11	11	12	
	Geo. Mean (CV%)	10.35 (41.7)	10.03 (36.5)	10.99 (66.5)	
Dose proportionality for $AUC_{0\text{-}Tau}$	n				34
	Slope Estimate (SE)				0.04 (0.144)
	90% CI				-0.20, 0.29
C_{max} (mg/L)	n	11	11	12	
	Geo. Mean (CV%)	0.97 (37.5)	1.00 (34.4)	1.14 (61.0)	
Dose proportionality for C_{max}	n				34
	Slope Estimate (SE)				0.12 (0.133)
	90% CI				-0.11, 0.34
C_{trough} (mg/L)	n	11	11	12	
	Geo. Mean (CV%)	0.73 (48.9)	0.65 (36.8)	0.62 (75.8)	
Dose proportionality for C_{trough}	n				34
	Slope Estimate (SE)				-0.13 (0.159)
	90% CI				-0.40, 0.14

The power model for dose proportionality was fitted by regressing the logarithm-transformed PK parameter on logarithm-transformed dose with logarithm-transformed dose as a covariate.
Tau = 12 hours.
$AUC_{0\text{-}Tau}$ = area under the serum concentration versus time curve from time 0 to Tau; CI = confidence interval;
C_{max} = maximum observed serum concentration; C_{trough} = minimum concentration between dose time and dose time + Tau;
CV = coefficient of variation; Geo. = geometric; PK = pharmacokinetic; SE = standard error.
Source: Post-text Table 14.2.13

Special populations

Study ST10-01-103

Methodology

Study ST10-01-103 was a Phase 1 randomized, open-label, parallel group, paediatric PK study which assessed the pharmacokinetic, pharmacodynamics and safety of ferric maltol capsules in children aged 10 to <18 years with ID.

A total of 38 eligible subjects aged 10 to 17 years were randomized at a ratio of 1:1:1 to 1 of 3 doses of ferric maltol (7.8 mg, 16.6 mg, or 30 mg BID) for 9 days (Days 1 to 9); and a final dose was to be administered on the morning of Day 10.

The randomization scheme was stratified by covariates for age (10 to 14 years old and 15 to 17 years old) and sex (male and female). This ensured that a minimum of 25% of each gender and at least 3 children per age group were enrolled in each ferric maltol dose group.

- Group 1: 12 subjects received 30 mg ferric maltol BID for 9 days (Days 1 to 9) plus a final 30 mg dose on the morning of Day 10. Pharmacokinetic study Days 1 and 10.
- Group 2: 13 subjects received 16.6 mg ferric maltol BID for 9 days (Days 1 to 9) plus a final 16.6 mg dose on the morning of Day 10. Pharmacokinetic study Days 1 and 10.

- Group 3: 12 subjects received 7.8 mg ferric maltol BID for 9 days (Days 1 to 9) plus a final 7.8 mg dose on the morning of Day 10. Pharmacokinetic study Days 1 and 10.

Doses chosen for this paediatric PK study were based on the daily elemental iron requirements of the study subjects and the broad range of weights likely to enroll, with an aim of finding a minimum effective dose in this age group. With the 30 mg BID adult dose chosen as the highest exposure, 16.6 mg BID and 7.8 mg BID were chosen as approximately one-half and one-quarter of the adult dose, respectively. The exact doses coincided with full fill of available capsule shell sizes. The lower strength formulations were based on the 30 mg capsule formulation. Fixed dosing with 7.8 mg, 16.6 mg, or 30 mg ferric maltol BID was considered sufficient to meet the objectives of this study for a population PK (PPK) analysis approach.

Subjects were instructed to take ferric maltol on an empty stomach (1 hour before eating or 2 hours after eating) with a glass of water, as the absorption of iron is reduced when taken with food.

Lot numbers for the study drugs used in this study are listed in Table 14.

Table 14. Study Drug

Study Drug	Dose and Mode of Administration	Lot Number
Ferric maltol 30 mg capsule	BID – oral on Days 1 to 9 Single dose – oral on Day10	K00014319T, K00014402L, K00016214P
Ferric maltol 16.6 mg capsule	BID – oral on Days 1 to 9 Single dose on Day10	K00014319T
Ferric maltol 7.8 mg capsule	BID – oral on Days 1 to 9 Single dose on Day10	K00014319T, B16291, K00014851X
BID = twice daily. Source: Certificates of Conformity (Appendix 16.1.6)		

PK Objectives and endpoints

PK was assessed in terms of serum maltol and maltol glucuronide, and serum iron and TSAT (primary endpoints). PK blood sampling sessions were scheduled on Days 1 and 10, pre-dose and post-dose, at the following time collection windows: 0.5 to 1 hour, 1 to 2 hours, 2 to 3 hours, 3 to 4 hours, and 4 to 6 hours.

The primary PK endpoints were:

• PPK analysis of maltol and maltol glucuronide in plasma from PK samples collected on Days 1 (after first morning dose) and 10 (after last morning dose). The following parameters were derived and reported for each ferric maltol dose:

- Cmax, average steady state plasma concentration from time 0 to 6 hours (Cave[0-6h])
- AUC from time 0 to 6 hours (AUC0-6h), AUC from time 0 to infinity (AUC0-inf) on Days 1 and 10, and ratios of Day 10/Day 1 for these parameters
- Tmax and half-life (t1/2)
- Apparent systemic clearance (CL/F) and apparent volume of distribution (Vz/F)

• Descriptive statistics for plasma concentration of maltol and maltol glucuronide by time of collection on Days 1 and 10 were also presented, including minimum plasma concentration (Ctrough)

• Descriptive and PPK analysis of serum iron and TSAT from PK samples collected on Days 1 and 10. The following parameters were derived and reported for each ferric maltol dose:

- Change from pre-dose Ctrough to maximum post-dose Cmax value for serum iron and TSAT
- Cave[0-6h]
- Pre-dose adjusted incremental AUC0-6h on Days 1 and 10 from a population PK (PPK) analysis approach, and percentage change from Days 1 to 10
- CL/F and Vz/F.

Serum iron and TSAT by time of collection on Days 1 and 10 were also presented.

The secondary variables included:

• Transferrin, TIBC, UIBC, and ferritin concentrations from PK samples collected on Days 1 and 10

• Non-transferrin bound iron concentrations from PK samples collected on Days 1 and 10

• Haemoglobin concentration and absolute reticulocyte count from haematology samples collected at Screening and Day 10.

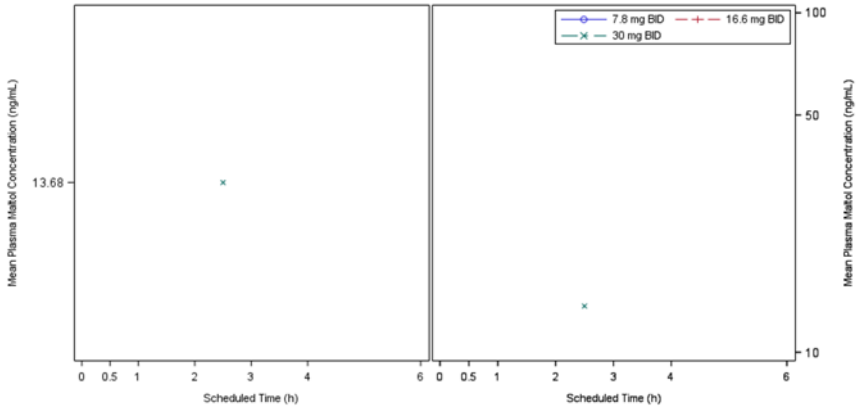
Results

- *Observed Maltol and maltol glucuronide concentration*

Predicted maltol glucuronide concentrations were used to calculate PK parameters, including AUCs and Cmax/minimum plasma concentration (Cmin). The 7.8 mg, 16.6 mg, and 30 mg doses of ferric maltol contain 52.39 mg, 111.497 mg, and 201.5 mg of maltol, respectively.

After the first dose on Day 1, maltol was detected in subjects in the 30 mg group only, after 2-3 hours post-dosing, at a concentration of 13.68 ± 12.671 ng/mL; in the other two groups, maltol was below the quantifiable limit (BQL) at all sampling timepoints (Figure 3).

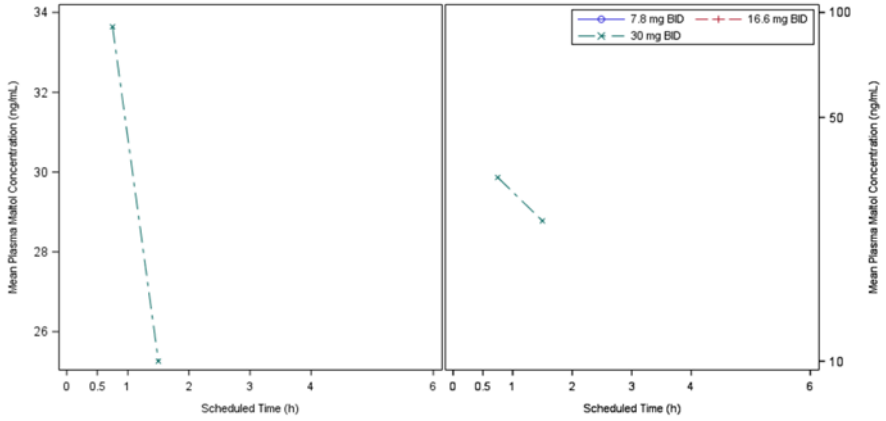
Figure 3. Plot of mean plasma maltol concentrations (ng/mL) by dose group on linear and semi-logarithmic scales on Day 1



The scheduled time was chosen from the intermediate time point of the particular window. For example, pre-dose was deemed as 0 h, and '0.5 - 1 h' was deemed as 0.75 h. When more than half (>50%) of the values at a single time point were BQL or the calculation of the mean was less than the LLOQ, the mean plot was not displayed at this time point.
LLOQ for maltol = 10.0 ng/mL
BID = twice daily; BQL = below the quantifiable limit; LLOQ = lower limit of quantitation.
Source: Post-text Figure 14.2.1.1

After the repeated dosing of ferric maltol, on Day 10, maltol was again detected only in the 30 mg group. The maltol concentration peaked at 0.5-1 hours post-dosing (33.64 ± 38.885 ng/mL) and dropped at 1-2 hours (25.26 ± 22.743 ng/mL), falling BQL after 2 hours (Figure 4).

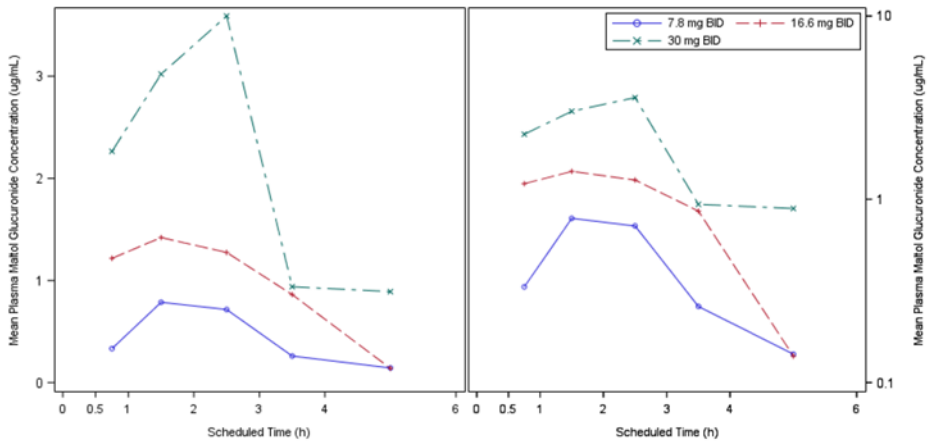
Figure 4. Plot of mean plasma maltol concentrations (ng/mL) by dose group on linear and semi-logarithmic scales on Day 10



The scheduled time was chosen from the intermediate time point of the particular window. For example, pre-dose was deemed as 0 h, and '0.5 - 1 h' was deemed as 0.75 h. When more than half (>50%) of the values at a single time point were BQL or the calculation of the mean was less than the LLOQ, the mean plot was not displayed at this time point.
LLOQ for maltol = 10.0 ng/mL
BID = twice daily; BQL = below the quantifiable limit; LLOQ = lower limit of quantitation.
Source: Post-text Figure 14.2.1.2

After a single dose of ferric maltol on Day 1, maltol glucuronide (a maltol metabolite) was detected as early as 0.5-1 hour post-dosing (Figure 5). The maltol glucuronide concentration peaked at 1-2 hours post-dosing in the 7.8 and 16.6 mg groups (0.78700 ± 0.182266 µg/mL in the 7.8 mg group, 1.42067 ± 0.988814 µg/mL in the 16.6 mg group) and at 2-3 hours in the 30 mg group (3.59000 ± 1.597514 µg/mL), followed by a decrease up to 6 hours post-dosing.

Figure 5. Plot of Mean Plasma Maltol Glucuronide Concentrations (µg/mL) by Dose Group on Linear and Semi-Logarithmic Scales on Day 1 – Full Analysis Set/Intent-to-Treat Population

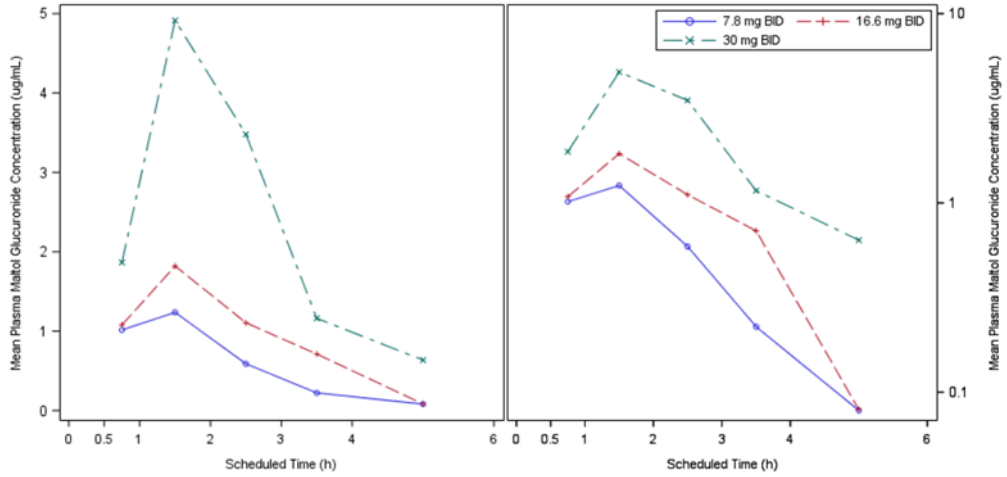


The scheduled time was chosen from the intermediate time point of the particular window. For example, pre-dose was deemed as 0 h, and '0.5 - 1 h' was deemed as 0.75 h. When more than half (>50%) of the values at a single time point were BQL or the calculation of the mean was less than the LLOQ, mean plot was not displayed at this time point.
LLOQ for maltol glucuronide = 0.0500 µg/mL
BID = twice daily; BQL = below the quantifiable limit; LLOQ = lower limit of quantitation.
Source: Post-text Figure 14.2.2.1

After repeated dosing of ferric maltol, on day 10, maltol glucuronide was detected as early as 0.5-1 hour post-dose (Figure 6). Before dosing, the maltol glucuronide concentration was BQL for all 3 dose levels. After dosing, maltol glucuronide concentrations peaked at 1-2 hours post-dosing in all

groups (1.23600 ± 0.887941 µg/mL in the 7.8 mg group, 1.81960 ± 0.710486 µg/mL in the 16.6 mg group, and 4.91429 ± 1.908157 µg/mL in the 30 mg group) followed by a decreasing trend up to 6 hours after dosing.

Figure 6. Plot of Mean Plasma Maltol Glucuronide Concentrations (µg/mL) by Dose Group on Linear and Semi-Logarithmic Scales on Day 10 – Full Analysis Set/Intent-to-Treat Population

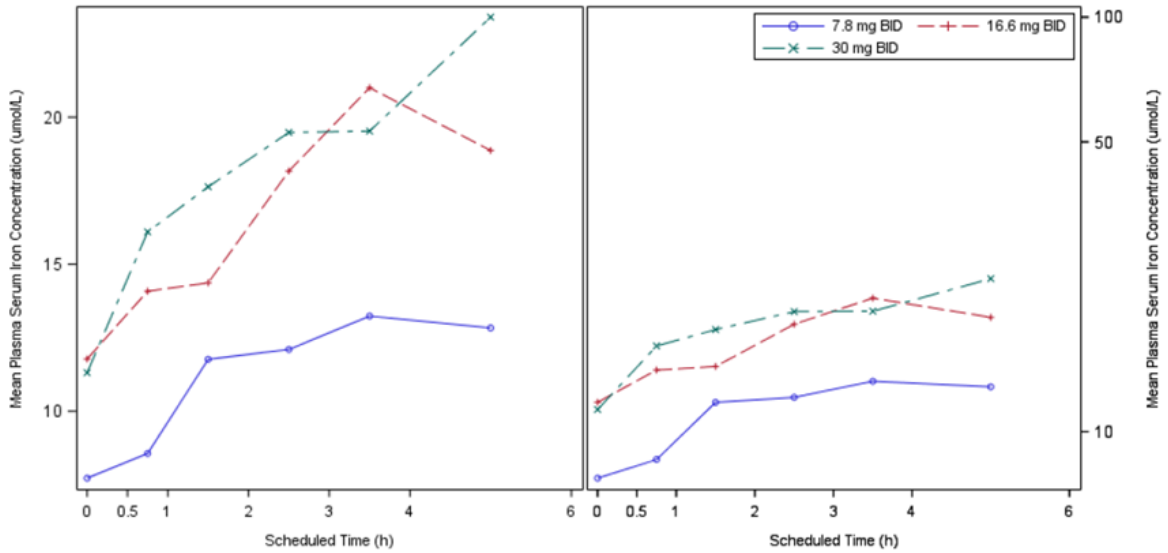


The scheduled time was chosen from the intermediate time point of the particular window. For example, pre-dose was deemed as 0 h, and '0.5 - 1 h' was deemed as 0.75 h. When more than half (>50%) of the values at a single time point were BQL or the calculation of the mean was less than the LLOQ, mean plot was not displayed at this time point.
LLOQ for maltol glucuronide = 0.0500 µg/mL
BID = twice daily; BQL = below the quantifiable limit; LLOQ = lower limit of quantitation.
Source: Post-text Figure 14.2.2.2

- *Serum iron and transferrin saturation:*

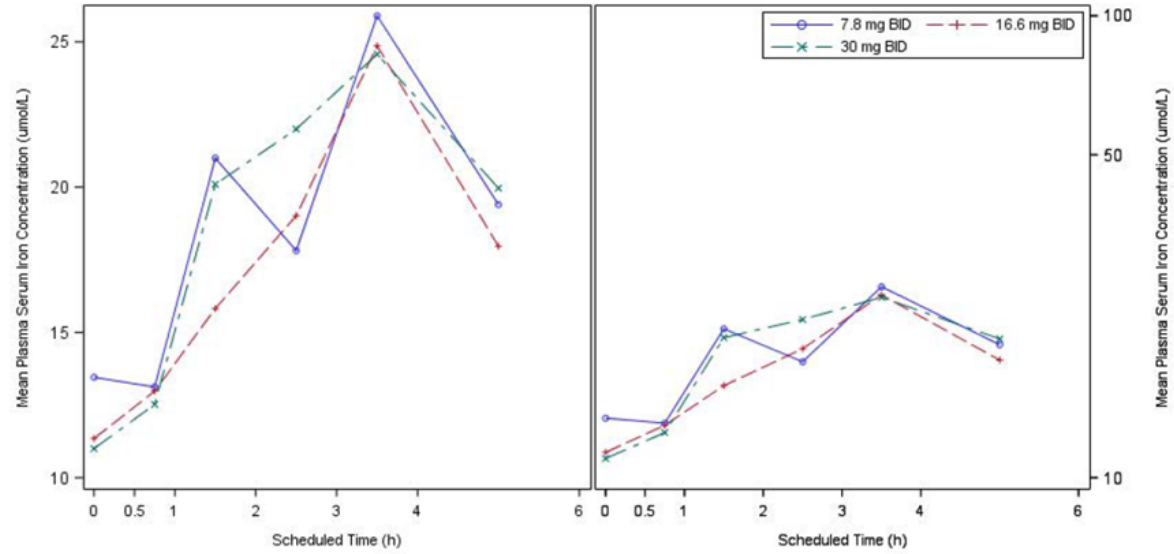
On Day 1, the iron concentration peaked at 3-4 hours post-dosing in the 7.8 and 16.6 mg groups (13.23 ±7.527 µmol/L, and 21.00 ± 4.215 µmol/L, respectively), while in the 30 mg group, the serum iron concentrations peaked at 4-6 hours post-dosing (23.40 ± 19.315 µmol/L) (Figure 7). On Day 10, the serum iron concentrations peaked at 3-4 hours post-dosing in all groups (25.90 ±10.959 µmol/L in the 7.8 mg group; 24.87 ±13.012 µmol/L in the 16.6 mg group; and 24.58 ± 21.014 µmol/L in the 30 mg group) (Figure 8).

Figure 7. Plot of Mean Serum Iron Concentrations (µmol/L) by Dose Group on Linear and Semi-Logarithmic Scales on Day 1 – Full Analysis Set/Intent-to-Treat Population



The scheduled time was chosen from the intermediate time point of the particular window. For example, pre-dose was deemed as 0 h, and '0.5 - 1 h' was deemed as 0.75 h.
Lower limit of quantitation for serum iron = 1.8 µmol/L
BID = twice daily.

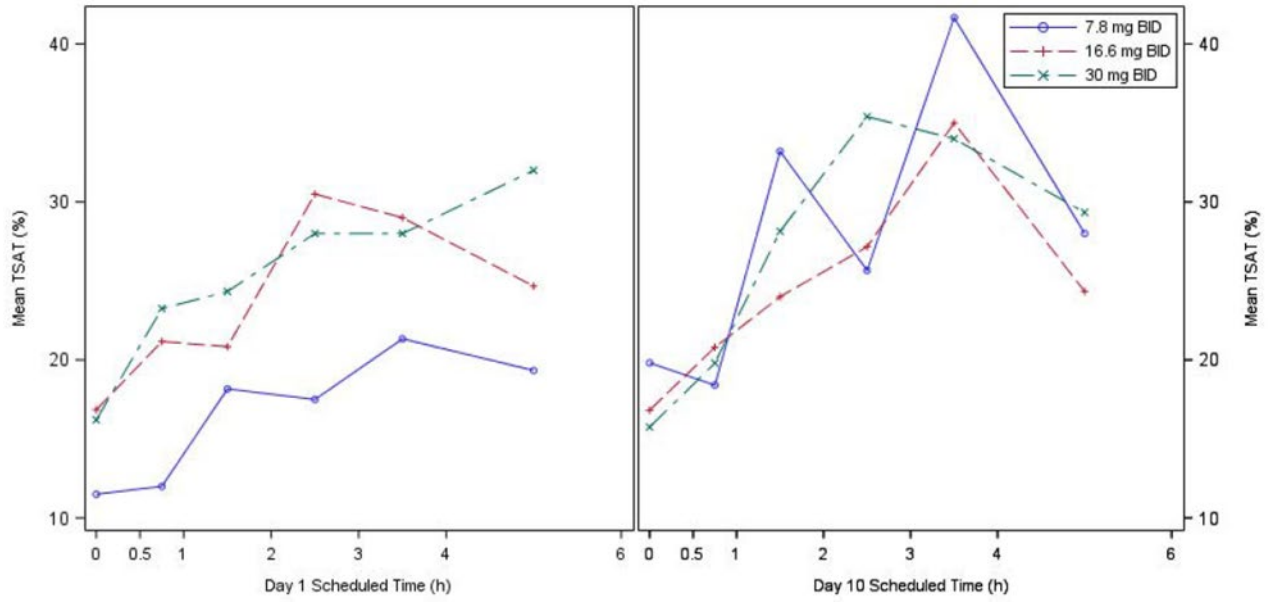
Figure 8. Plot of Mean Serum Iron Concentrations (µmol/L) by Dose Group on Linear and Semi-Logarithmic Scales on Day 10 – Full Analysis Set/Intent-to-Treat Population



The scheduled time was chosen from the intermediate time point of the particular window. For example, pre-dose was deemed as 0 h, and '0.5 - 1 h' was deemed as 0.75 h.
Lower limit of quantitation for serum iron = 1.8 µmol/L
BID = twice daily.

On Day 1, the highest transferrin saturation was recorded at 3-4 hours post-dosing in the 7.8 mg group (21.3 ± 14.47%), at 2-3 hours post-dosing in the 16.6 mg group (30.5 ± 10.13%) and at 2-3 and 3-4 hours post-dosing in the 30 mg group (28.0± 17.20% and 28.0 ± 6.06%). On day 10, the highest transferrin saturation was recorded at 3-4 hours post-dosing in the 7.8 mg and 16.6 mg groups (41.7 ± 21.78% and 35.0 ± 7.81%, respectively), and at 2-3 hours post-dosing in the 30 mg group (35.4 ± 12.12%) (Figure 9).

Figure 9. Plot of Mean Transferrin Saturation (%) by Dose Group on Linear Scale on Days 1 and 10- Full Analysis Set/Intent-to-Treat Population



The scheduled time was chosen from the intermediate time point of the particular window. For example, pre-dose was deemed as 0 h, and '0.5 - 1 h' was deemed as 0.75 h.
BID = twice daily; TSAT = transferrin saturation.

Study ST10-01-305

Methodology:

Study ST10-01-305 was a Phase 3, randomized, open-label, single dose, 4-way crossover study in children with a PK sub-study, which assessed the pharmacokinetics of ferric maltol oral suspension. 20 patients of the ferric maltol group were included in the PK Population. Of these patients, there were:

- 7 patients from 2 to 9 years of age (3 female patients and 4 male patients) who were dosed with 15 mg BID of ferric maltol
- 3 patients (all female patients) from 10-11 years of age who received 15 mg BID of ferric maltol
- 10 patients from 12 to <18 years of age (9 female patients and 1 male patient) who received 30 mg BID of ferric maltol.
- Children aged 1 month to < 2 years were dosed 0.6 mg/kg/dose BID.

Thus, the PK results were further stratified by age, into two groups: 2 to 9 years of age and 10 to <18 years of age sub-groups. Therefore, the 10 to <18 years of age sub-group consisted of 2 dosing groups (15 mg BID and 30 mg BID). Ferric Maltol Group Dosing is shown in Table 15.

Table 15. Ferric Maltol Group Dosing

Age	Treatment	Dose/Frequency	Suspension Equivalent	Administration Route
1 month-<2 years	Ferric maltol oral suspension	0.6 mg/kg/dose, BID	0.1 mL/kg/dose	Oral
2-11 years	Ferric maltol oral suspension	15 mg per dose, BID	2.5 mL per dose	Oral
12-17 years	Ferric maltol oral suspension	30 mg per dose, BID	5 mL per dose	Oral

BID = twice daily.
Source: Protocol (Appendix 16.1.1)

Ferric maltol oral suspension was taken every morning and evening at least 30 minutes after a meal.

PK Objectives and endpoints:

The secondary objectives:

- To assess the pharmacokinetics (PK) in children and adolescents aged 2 to 17 years after a single dose of ferric maltol oral suspension on Visit 2 (PK Day 1), after BID administration for at least 6 days, and on Visit 3 (PK Day 2) after a single morning dose, through measurement of serum iron, corrected serum iron, transferrin saturation (TSAT), and plasma maltol and maltol glucuronide.
- To assess the PK in children aged 1 month to <2 years after a single dose of ferric maltol oral suspension (pre-assignment PK visit), after BID administration for at least 6 days, and on Visit 3 (PK Day 2) after a single morning dose, through measurement of serum iron, corrected serum iron, TSAT (PK Day 2 only), plasma (PK Day 2 only), and urine concentration of maltol and maltol glucuronide. During the pre-assignment PK visit, PK blood samples were collected pre-dosing (0 hour), and at 0.5 to 3 hours, 3 to 6 hours, and 7 to 12 hours post-dose, with samples taken at least 1.0 hour apart. On PK Day 2 (Visit 3), PK blood samples were collected pre-dosing (0 hour), and at 1.0 to 2.0 hours, 3.0 to 4.0 hours, and 10.0 to 12.0 hours. Additionally, urine samples for PK assessment were collected pre-dosing and at 0.5 and 3 hours, 3 to 6 hours, and 7 to 12 hours post-dose.

The following PK parameters in Table 16 were determined for the 2 to 17 years age group using a naïve pooled approach on PK Day 1 and PK Day 2:

Table 16. Pharmacokinetic Analysis of Serum Iron, Corrected Serum Iron, Maltol, and Maltol Glucuronide in the Ferric Maltol Group

Parameters	Description	Precision
C_{max}	Maximum plasma concentration; determined directly from the concentration time profile; if the maximum plasma concentration occurs at more than 1 timepoint, C_{max} is defined as the first maximal value	sig/3
T_{max}	Time to C_{max}; if the maximum value occurs at more than 1 timepoint, T_{max} is defined as the first timepoint with this value	dec/2
AUC_{0-t}	Area under the plasma concentration versus time curve (AUC) from pre-dose (time 0) to the last quantifiable plasma concentration (C_{last})	sig/3
AUC_{inf}	AUC from time 0 to infinity; calculated as ($AUC_{0-t} + C_{last}/\lambda z$)	sig/3
$t_{1/2}$	Apparent first-order terminal elimination half-life; calculated as $\ln(2)/\lambda z$	dec/2

Note: "Precision" is defined as the default type (significant figures "sig" or decimal places "dec") and value displayed in outputs unless specifically defined elsewhere.
Source: Statistical Analysis Plan (Appendix 16.1.9)

The Linear-Log Trapezoidal method (equivalent to the Linear Up/Log Down option in WinNonlin) was used in the computation of all AUC values.

Results:

Blood samples for maltol and maltol glucuronide assessment were collected at the required times on the PK assessment days relative to the time of ferric maltol morning dosing: pre-dose, then 2 further times between 0.5 to 10 hours post-dose in patients 2 to 17 years of age; and pre-dose, then 3 further times between 1 to 12 hours post-dose in patients 1 month to <2 years of age.

Blood samples for iron marker assessment were collected at the required times on the PK assessment days, relative to the time of ferric maltol dosing: pre-dose, then 2 further times between 0.5 to 6 hours post-dose in patients 2 to 17 years of age. The timepoints for iron marker samples were the same timepoints as the timepoints for the maltol/maltol glucuronide samples for each patient.

The majority of samples analyzed for the parent analyte were found to be BLQ. Thus, emphasis was placed on the metabolite (maltol glucuronide) and serum iron for PK analysis.

- *Pharmacokinetic evaluation of maltol glucuronide*:

For the 15 mg BID ferric maltol group, there was a lack of notable increase in Cmax of maltol glucuronide in both age groups when comparing Day 1 and Days 7 to 10. Pre-dose maltol glucuronide levels returned to baseline or close to baseline in all patients in the 15 mg BID ferric maltol group.

For the 30 mg BID ferric maltol group, a moderate increase in Cmax and slightly longer Tmax was noted between Day 1 and Days 7 to 10 in the 10 to 17 years of age population. On Days 7 to 10, the majority of patients had maltol glucuronide levels that were undetectable or approaching undetectable (i.e., <500 ng/mL), indicating a lack of notable accumulation. Overall, Tmax ranged from approximately 1 to 4 hours with a slightly longer Tmax observed in the higher 30 mg BID dose group (Table 17).

Table 17. Summary of PK Parameters for Plasma Maltol Glucuronide – PK Population (Full Analysis Set)

Visit Treatment Group Age Group	C_{max} (ng/mL)	T_{max} (h)	AUC_{0-t} (h×ng/mL)
Day 1			
Ferric maltol 15 mg			
2-9 years (N'=9)	4350	1.00	4670
10-17 years (N'=8)	6810	2.13	12000
Ferric maltol 30 mg			
10-17 years (N'=16)	6420	0.52	14600
Day 7-10			
Ferric maltol 15 mg			
2-9 years (N'=10)	4250	0.98	5900
10-17 years (N'=9)	5940	2.78	8070
Ferric maltol 30 mg			
10-17 years (N'=20)	8160	3.63	16700

15 mg 10 to 17 years age group only contained 10- and 11-year-olds.
30 mg 10 to 17 years age group only contained 12- to 17-year-olds.
Certara Phoenix WinNonlin Version 8.3 was used to validate PK parameters.
AUC_{0-t} = area under the plasma concentration-time curve from pre-dose (time 0) to the time of last quantifiable plasma concentration; C_{max} = maximum plasma concentration; N' = number of measurable concentrations used in pharmacokinetic parameter calculation; PK = pharmacokinetic(s); T_{max} = time to maximum plasma concentration.
Source: Post-text Table 14.2.4.2.2

In addition, patients 1 month to <2 years of age who were assigned to ferric maltol 0.6 mg/kg had a mean urine maltol glucuronide concentration of 153, 28.6, and 3.11 ug/mL at 0.5 to 3 hours, 3 to 6 hours, and 7 to 12 hours post-dose, respectively (Table 18).

Table 18. Summary of Urine Maltol Glucuronide Concentration (ug/mL) PK Population (Full Analysis Set)

Visit Treatment Group Age Group	Scheduled Time Point	N	Geometric Standard Deviation[1]	Geometric Mean	Mean	CV% [2]	Median	Minimum	Maximum
Day 7-10									
Assigned Ferric Maltol 0.6 mg/kg									
1 Month To <2 Years	PRE-DOSE	2	NC	NC	NC	NC	NC	0.00	0.889
	3-6 HOURS	2	2.83	22.3	28.6	88.5	28.6	10.7	46.5
	0.5-3 HOURS	2	1.29	150	153	25.5	153	125	180
	7-12 HOURS	2	2.14	2.71	3.11	69.6	3.11	1.58	4.64

NC = Not Calculable.
15 mg 10-17 years age group only contains 10 and 11 year olds.
30 mg 10-17 years age group only conatins 12 to 17 year olds.
[1] Geometric Mean was calculated with only positive values.
[2] CV = Coefficient of Variation.
Mean concentrations at any individual time point were calculated only if at least half of the subjects had valid values (i.e. quantifiable and not missing) at this time point for each formulation/condition. In cases where a mean value was not calculated, due to the above criterion not being met, the mean value was set to missing for mean plotting purposes and to BLQ for summary table. BLQ was set to zero for the calculation of these mean values.

Patients 1 month to <2 years of age who were assigned to ferric maltol 0.6 mg/kg had a mean urine maltol concentration of 0.527 ug/mL, 0.103 ug/mL, and not calculable at 0.5 to 3 hours, 3 to 6 hours, and 7 to 12 hours post-dose, respectively (Table 19).

Table 19. Summary of Urine Maltol Concentration (ug/mL) PK Population (Full Analysis Set)

Visit Treatment Group Age Group	Scheduled Time Point	N	Geometric Standard Deviation[1]	Geometric Mean	Mean	CV% [2]	Median	Minimum	Maximum
Day 7-10									
Assigned Ferric Maltol 0.6 mg/kg									
1 Month To <2 Years	PRE-DOSE	3	NC	NC	NC	NC	NC	0.00	0.00
	3-6 HOURS	1	NC	0.103	0.103	NC	0.103	0.103	0.103
	0.5-3 HOURS	2	1.53	0.503	0.527	41.5	0.527	0.372	0.681
	7-12 HOURS	1	NC	NC	NC	NC	NC	0.215	0.215

NC = Not Calculable.
15 mg 10-17 years age group only contains 10 and 11 year olds.
30 mg 10-17 years age group only conatins 12 to 17 year olds.
[1] Geometric Mean was calculated with only positive values.
[2] CV = Coefficient of Variation.
Mean concentrations at any individual time point were calculated only if at least half of the subjects had valid values (i.e. quantifiable and not missing) at this time point for each formulation/condition. In cases where a mean value was not calculated, due to the above criterion not being met, the mean value was set to missing for mean plotting purposes and to BLQ for summary table. BLQ was set to zero for the calculation of these mean values.

These data confirm that ferric maltol is metabolized and excreted in urine in infants within this study. Overall, maltol was metabolized to the glucuronide, excreted in urine, and showed no evidence of accumulation.

- Pharmacokinetic evaluation of baseline-corrected serum iron:

For the 15 mg BID ferric maltol group, a slight increase in both Cmax and AUC0-t of baseline-corrected serum iron was observed between Day 1 and Days 7 to 10 for patients in the 2 to 9 years age range. In contrast, for the 10 to 17 years age range, both Cmax and AUC0-t were actually lower on Days 7 to 10 compared to Day 1.

For the 30 mg BID ferric maltol group, a moderate increase in both Cmax and AUC0-t was noted between Day 1 and Days 7 to 10 in the 10 to 17 years of age population. Additionally, a delayed Tmax was observed on Days 7 to 10 compared to Day 1 in the 10 to 17 years age range. Of note, this delayed Tmax trend was not noted for all patients within this treatment group, and the small sample size should be considered when interpreting the clinical implications of these results (Table 20).

Table 20. Summary of PK Parameters for Baseline-Corrected Serum Iron – PK Population (FAS)

Visit Treatment Group Age Group	C_{max} (µg/dL)	T_{max} (h)	AUC_{0-t} (h×µg/dL)
Day 1			
Ferric maltol 15 mg			
2-9 years (N'=18)	87.0	2.37	64.4
10-17 years (N'=12)	40.0	2.13	60.1
Ferric maltol 30 mg			
10-17 years (N'=30)	119	2.00	374
Day 7-10			
Ferric maltol 15 mg			
2-9 years (N'=18)	96.5	2.10	100
10-17 years (N'=12)	21.0	2.78	1.93
Ferric maltol 30 mg			
10-17 years (N'=30)	364	6.63	1180

15 mg 10 to 17 years age group only contained 10- and 11-year-olds.
30 mg 10 to 17 years age group only contained 12- to 17-year-olds.
Certara Phoenix WinNonlin Version 8.3 was used to validate PK parameters.
AUC_{0-t} = area under the plasma concentration-time curve from pre-dose (time 0) to the time of last quantifiable plasma concentration; C_{max} = maximum plasma concentration; N' = number of measurable concentrations used in pharmacokinetic parameter calculation; PK = pharmacokinetic(s); T_{max} = time to maximum plasma concentration.
Source: Post-text Table 14.2.4.2.4

Of note, for the 10 to 17 years, 15 mg BID ferric maltol group, a lower than expected AUC0-t was observed for Day 7; however, this observation may have been driven by multiple negative pre-dose values and the small number of observations and patients.

Population pharmacokinetic analysis:

The serum iron, plasma maltol, plasma maltol glucuronide concentration, and TSAT versus time profiles on Days 1 and 10 were predicted for each subject using the individual PK parameters estimates from the final model.

- *For maltol and maltol glucuronide*

Model development:

The NONMEM data set (STMALTOL10315AUG181130.csv) for maltol and maltol glucuronide PPK analysis contained 422 concentration records from 37 subjects, including 221 concentration records for maltol and 221 concentration records for maltol glucuronide.

Among the total 211 concentration records for maltol, there were only 26 measurable values. Thus, maltol concentration data were not used for the PPK analysis. For the PPK analysis of maltol glucuronide, all BQL concentrations of maltol glucuronide (74 of 211 records) were excluded from the PPK analysis.

The process of base model construction and the assessment data are shown in Table 21.

Table 21. Population Pharmacokinetic Model Construction Process for Maltol Glucuronide (Base Model Construction)

Model No.	Compartment Number	RV	OFV	Comment
105k	Simultaneously model maltol and maltol glucuronide	Mixed	247.232	Condition number >1000
107f	One-compartment linear model using ADVAN6	Mixed	227.985	Condition number >1000
112a	Two-compartment linear model using ADVAN6	Mixed	227.985	95% CIs for Q and V3 estimation contain 0
149	One-compartment nonlinear model using ADVAN6	Mixed	225.123	Condition number >1000
117c	One-compartment linear model using ADVAN2	Mixed	224.827	KA estimate was not reasonable
125M*	One-compartment linear model with lag time using ADVAN2	Mixed	236.843	--
127e	Two-compartment linear model using ADVAN2	Mixed	203.799	Condition number >1000
129b	Two-compartment linear model with lag time using ADVAN2	Mixed	227.457	95% CIs for Q and V3 estimation contain 0

Note: * base model.
CI = confidence interval; KA = absorption constant rate; No. = number; OFV = objective function value; RV = residual variability; Q = distribution clearance for the peripheral compartment; V3 = volume of distribution of the peripheral compartment.
Source: 105k.sum, 107f.sum, 112a.sum, 149.sum, 117c.sum, 125M.sum, 127e.sum, 129b.sum (Appendix 16.2.10)

Review of the minimum objective function value (OFV) and model convergence showed that the one-compartment model with lag time (TLAG) (Run 125M) provided the best fit to the data. The inter-individual variability (IIV) term was implemented using an exponential function to maintain positive PK parameter estimates. Random residual variability (RV) was expressed using the combined additive and proportional model. Parameter estimates for the base model are shown in Table 22.

Table 22. Base Model Parameter Estimates (Run 125M)

	Base Model Parameter Estimates – FOCE Method			
Parameter	Final Estimate	% RSE	95% Bound	Variability
CL/F (L/h)	6.11	34.0%	(2.03, 10.2)	-
V_z/F (L)	94.8	15.1%	(66.8, 123)	-
KA (1/h)	7.89	69.5%	(-2.85, 18.6)	-
TLAG (h)	0.274	14.1%	(0.198, 0.350)	-
CL/F IIV	0.0534	489%	(-0.458, 0.565)	23.1%
V_z/F IIV	0.250	142%	(-0.444, 0.944)	50.0%
KA IIV	2.04E-16	1.35E+10%	(-5.41E-8, 5.41E-8)	1.43E-6%
TLAG IIV	3.34E-9	985%	(-6.11E-8, 6.78E-8)	0.00578%
Proportional RV	0.334	2.16%	(0.320, 0.348)	57.8%
Additive RV	1.17	3.65%	(1.09, 1.25)	1.08

CL/F = apparent systemic clearance; FOCE = first order conditional estimation; IIV = inter-individual variability; KA = absorption rate constant; RSE = relative standard error; RV = residual variability; TLAG = lag time; V_z/F = apparent volume of distribution.
Source: 125M.sum (Appendix 16.2.10)

Attempts were made to remove the IIV of absorption rate constant (KA) and TLAG from the base model since their 90% confidence intervals (CIs) contained 0. However, the condition number became larger than 1000, indicating that the model was ill-conditioned after the removal of the KA IIV or TLAG IIV from the model. Thus, all IIVs were kept in the model.

For one subject in the 30 mg dose group, the pre-dose maltol glucuronide concentration was 6.21 mg/L, which had been treated as an outlier. However, the exclusion of this record from the NONMEM data set induced the model failure to converge or a condition number of larger than 1000. Thus, this concentration record was included in the PPK analysis of maltol glucuronide.

Covariate selection:

A series of covariates were tested as potential parameters affecting the PPK model. Covariates that were tested for significance in this analysis included continuous covariates (body weight, body mass index [BMI], and age) and categorical covariates (sex, race, ethnicity, and concomitant administration of laxative and proton pump inhibitor). The missing continuous covariates were imputed using the population median value for subjects of the same sex. There was no imputation for any missing categorical covariate values.

All the shrinkage values for the base model (Run 125M) were larger than 30%, suggesting that IIV versus covariate plots may not be useful in identifying meaningful covariates. Therefore, each of potential covariates was tested for CL/F, Vz/F, KA, and TLAG in the model. However, none of the covariates were found to influence any parameters. Thus, the base model (Run 125M) was used as the final PPK model.

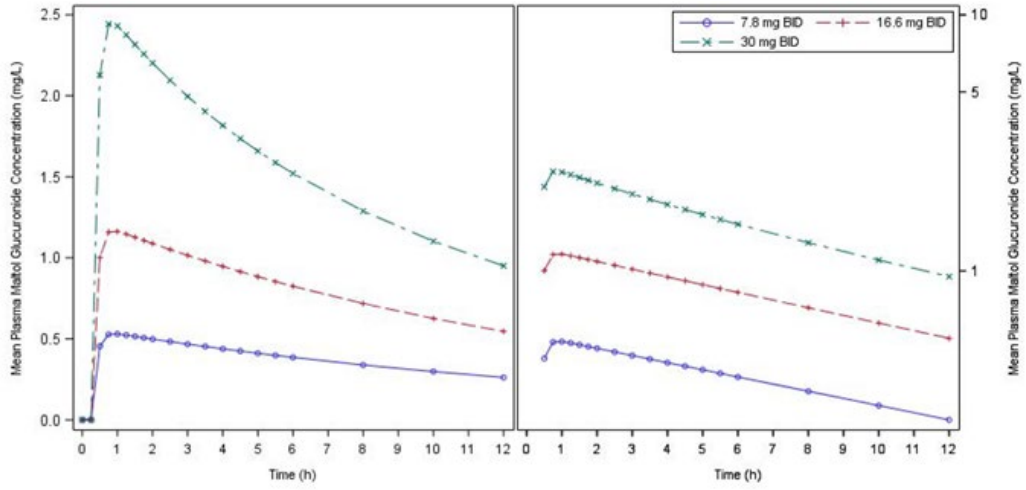
Final Model:

The final model was evaluated using visual predictive check (VPC). One thousand simulations were performed using the parameters defined in the final model (Run 125M) with the 5th, 10th, 50th, 90th, and 95th percentiles generated from these simulation (Run pc-125Mcopy).

The maltol glucuronide concentration on Day 1 for each subject was predicted using the final PPK model. The relative time points included pre-first dose (time 0), 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 8, 10, and 12 hours post-dose.

The plot of predicted mean plasma maltol glucuronide concentrations by dose group on linear and semi-logarithmic scales on Day 1 for the FAS/ITT Population is shown in Figure 10.

Figure 10. Plot of Predicted Mean Plasma Maltol Glucuronide Concentrations (mg/L) by Dose Group on Linear and Semi-Logarithmic Scales on Day 1 – Full Analysis Set/Intent-to-Treat Population



Ferric maltol 7.8 mg, 16.6 mg, and 30 mg includes 52.39 mg, 111.497 mg, and 201.5 mg of maltol, respectively.
Lower limit of quantitation for maltol glucuronide = 0.0500 mg/L.
BID = twice daily.

Table 23 summarises the PK parameters for predicted maltol glucuronide by treatment on Day 1 for the FAS/ITT Population. Non-compartment analysis (NCA) was performed to calculate the PK parameters on Day 10 using the predicted concentrations of maltol glucuronide on Day 1.

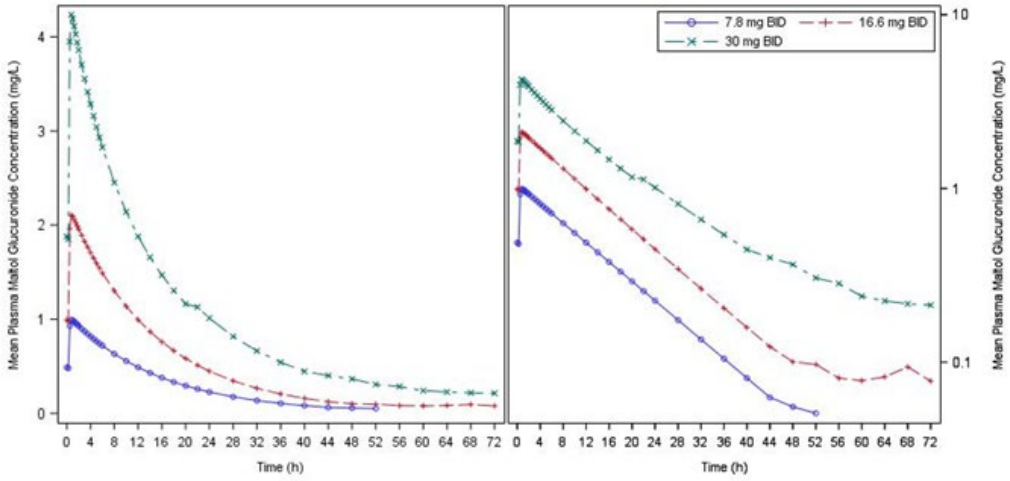
Table 23. Summary of Pharmacokinetic Parameters for Predicted Maltol Glucuronide (mg/L) by Treatment on Day 1 – Full Analysis Set/Intent-to-Treat Population

PK Parameter (Unit)	Statistic	Ferric Maltol 7.8 mg BID	Ferric Maltol 16.6 mg BID	Ferric Maltol 30 mg BID
	n	12	13	12
	Mean (SD)	0.5299 (0.02245)	1.1632 (0.18435)	2.4518 (1.29590)
C_{max} (mg/L)	Geo. mean (CV%)	0.5295 (4.1)	1.1501 (15.7)	2.2351 (43.9)
	n	12	13	12
T_{max} (h)	Median (min, max)	1.000 (1.00, 1.00)	1.000 (0.75, 1.00)	1.000 (0.75, 1.00)
	n	12	13	12
	Mean (SD)	10.806 (0.4707)	10.447 (1.8503)	11.384 (5.4738)
$t_{1/2}$ (h)	Geo. mean (CV%)	10.796 (4.3)	10.304 (17.2)	10.111 (58.1)
	n	12	13	12
	Mean (SD)	2.585 (0.0968)	5.613 (0.7589)	11.090 (3.9033)
$AUC_{0\text{-}6h}$ (h·mg/L)	Geo. mean (CV%)	2.584 (3.7)	5.567 (13.4)	10.566 (32.3)
	n	12	13	12
	Mean (SD)	4.504 (0.1442)	9.665 (1.0481)	18.323 (4.0658)
$AUC_{0\text{-}12h}$ (h·mg/L)	Geo. mean (CV%)	4.502 (3.1)	9.614 (10.8)	17.929 (21.9)
	n	12	13	12
	Mean (SD)	8.590 (0.2025)	17.862 (0.9328)	34.372 (4.5052)
$AUC_{0\text{-}inf}$ (h·mg/L)	Geo. mean (CV%)	8.588 (2.3)	17.840 (5.1)	34.119 (12.5)
	n	12	13	12
	Mean (SD)	0.06426 (0.002770)	0.06817 (0.011387)	0.07966 (0.054178)
λ_z (1/h)	Geo. mean (CV%)	0.06420 (4.3)	0.06727 (17.2)	0.06856 (58.1)

Ferric maltol 7.8 mg, 16.6 mg, and 30 mg includes 52.39 mg, 111.497 mg, and 201.5 mg of maltol, respectively.
Geometric CV% = $100 \times (\exp(SD^2) - 1)^{0.5}$, where SD was the SD of the logarithm-transformed data.
λ_z = apparent first order terminal elimination rate constant; $AUC_{0\text{-}6h}$ = area under the plasma concentration curve from time 0 to 6 hours; $AUC_{0\text{-}12h}$ = area under the plasma concentration curve from time 0 to 12 hours; $AUC_{0\text{-}inf}$ = area under the plasma concentration curve from time 0 to infinity; BID = twice daily; C_{max} = maximum plasma concentration; CV = coefficient of variation; Geo. = geometric; max = maximum; min = minimum; PK = pharmacokinetic; SD = standard deviation; $t_{1/2}$ = half-life; T_{max} = time to reach maximum plasma concentration.
Source: Post-text Table 14.2.4

The final PPK model was used to predict the maltol glucuronide concentration on Day 10 for each subject. The relative time points included pre-last dose (time 0), 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 28, 32, 36, 40, 44, 48, 52, 56, 60, 64, 68, and 72 hours post-dose. Figure 11 presents a plot of predicted mean plasma maltol glucuronide concentrations by dose group on linear and semi-logarithmic scales on Day 10 for the FAS/ITT Population.

Figure 11. Plot of Predicted Mean Plasma Maltol Glucuronide Concentrations (mg/L) by Dose Group on Linear and Semi-Logarithmic Scales on Day 10 – Full Analysis Set/Intent-to-Treat Population



Ferric maltol 7.8 mg, 16.6 mg, and 30 mg includes 52.39 mg, 111.497 mg, and 201.5 mg of maltol, respectively.
Lower limit of quantitation for maltol glucuronide = 0.0500 mg/L.
BID = twice daily.

Table 24 summarises PK parameters for predicted maltol glucuronide by treatment on Day 10 for the FAS/ITT Population. Non-compartment analysis was performed to calculate the PK parameters on Day 10 using the predicted concentrations of maltol glucuronide on Day 10.

Table 24. Summary of Pharmacokinetic Parameters for Predicted Maltol Glucuronide (mg/L) by Treatment on Day 10 – Full Analysis Set/Intent-to-Treat Population

PK Parameter (Unit)	Statistic	Ferric Maltol 7.8 mg BID	Ferric Maltol 16.6 mg BID	Ferric Maltol 30 mg BID
	n	12	13	12
	Mean (SD)	0.9926 (0.02349)	2.1028 (0.13342)	4.2355 (0.78110)
C_{max} (mg/L)	Geo. mean (CV%)	0.9923 (2.3)	2.0989 (6.4)	4.1818 (16.0)
	n	12	13	12
T_{max} (h)	Median (min, max)	0.750 (0.75, 0.75)	0.750 (0.75, 0.75)	0.750 (0.75, 0.75)
	n	12	13	12
	Mean (SD)	0.4804 (0.01639)	0.9762 (0.10586)	1.8496 (0.67761)
C_{trough} (mg/L)	Geo. mean (CV%)	0.4802 (3.3)	0.9714 (10.2)	1.6963 (51.9)
	n	12	13	12
	Mean (SD)	0.8360 (0.01889)	1.7531 (0.08795)	3.4186 (0.29995)
$C_{ave(0-6h)}$ (mg/L)	Geo. mean (CV%)	0.8359 (2.2)	1.7510 (5.1)	3.4068 (8.7)
	n	12	13	12
	Mean (SD)	5.016 (0.1133)	10.518 (0.5277)	20.511 (1.7997)
AUC_{0-6h} (h·mg/L)	Geo. mean (CV%)	5.015 (2.2)	10.506 (5.1)	20.441 (8.7)
	n	12	13	12
	Mean (SD)	8.590 (0.2024)	17.862 (0.9327)	34.368 (4.4981)
AUC_{0-Tau} (h·mg/L)	Geo. mean (CV%)	8.588 (2.3)	17.840 (5.1)	34.116 (12.5)
	n	12	13	12
R_{Cmax}	Mean (SD)	1.875 (0.0537)	1.836 (0.2109)	1.956 (0.6210)
	n	12	13	12
$R_{AUC(0-6h)}$	Mean (SD)	1.942 (0.0582)	1.899 (0.2286)	2.030 (0.6695)

Ferric maltol 7.8 mg, 16.6 mg, and 30 mg includes 52.39 mg, 111.497 mg, and 201.5 mg of maltol, respectively.
Geometric CV% = $100 \times (\exp(SD^2) - 1)^{0.5}$, where SD was the SD of the logarithm-transformed data.
Tau = 12 hours for BID dosing regimens.
AUC_{0-6h} = area under the plasma concentration curve from time 0 to 6 hours; AUC_{0-Tau} = area under the plasma concentration curve from time 0 to Tau; BID = twice daily; $C_{ave(0-6h)}$ = average steady state plasma concentration form 0 to 6 hours; C_{max} = maximum plasma concentration; C_{trough} = minimum concentration between dose time and dose time + Tau; CV = coefficient of variation; Geo. = geometric; max = maximum; min = minimum; PK = pharmacokinetic; $R_{AUC0-6h}$ = accumulation ratio based on AUC_{0-6h} after first dose and last dose; R_{Cmax} = accumulation ratio based on maximum concentrations after first dose and last dose; SD = standard deviation; T_{max} = time to reach maximum plasma concentration.

- *For serum iron and TSAT:*

Model development:

The NONMEM data set for iron and TSAT PPK analysis contained 422 concentration records from 37 subjects, including 221 concentration records for iron and 221 concentration records for TSAT. Missing or BQL values for iron (4 records) and TSAT (four records) were excluded from PPK analysis (data set STIRON10315AUG181035.csv).

In the previous PPK analysis in adult subjects, the iron concentration was approved to fit a one-compartment model well. Also, as elimination phase data available in this paediatric study was limited, the one-compartment FOCE base model using ADVAN2, TRANS2 was used for iron concentration directly. The IIV term was implemented using an exponential function to maintain positive PK parameter estimates. Random RV was expressed using the combined additive and proportional model.

Table 25 presents the parameter estimates for the base model. The KA IIV and additive RV have been fixed as zero; otherwise the model would be ill-conditioned.

Table 25. Base Model Parameter Estimates (Run 130)

Base Model Parameter Estimates – FOCE Method				
Parameter	**Final Estimate**	**% RSE**	**95% Bound**	**Variability**
CL/F (L/h)	0.836	15.6	0.58 – 1.09	-
V_z/F (L)	28.7	18.9	18.1 – 39.3	-
KA (1/h)	0.683	22.7	0.379 – 0.987	-
CL/F IIV	0.673	33.3%	0.234 – 1.11	82%
V_z/F IIV	0.36	40.8%	0.0719 – 0.648	60%
KA IIV	0.00	-	-	-
Proportional RV	0.0374	38.2%	0.0937 – 0.0654	19.3
Additive RV	0.00	-	-	-

CL/F = apparent systemic clearance; FOCE = first order conditional estimation; IIV = inter-individual variability; KA = absorption rate constant; RSE = relative standard error; RV = residual variability; V_z/F = apparent volume of distribution.

Covariate selection:

Covariates that were tested for significant effect in this analysis included continuous covariates (body weight, BMI, height, age, baseline Hb, and baseline TSAT) and categorical covariates (sex, race, and concomitant administration of laxative and proton pump inhibitor). The missing value for continuous covariate were imputed using the population median value for subjects of the same sex. There was no imputation for any missing categorical covariate values. Each covariate was tested in the model for significance on CL/F, Vz/F, and KA.

Table 26 summarises the covariates added to base model. Each covariate was tested in the model for significance (OFV >3.84) on CL/F, Vz/F, and KA, and the most significant one was chosen to add in the base model in each round.

Table 26. Results of Forward Selection Process

Round	Run No.	Most Significant Covariate-Parameter Model	OFV	Change in OFV from Previous Round Model
	130	Base model	-318.01	-
1	164	PPI-V	-325.45	-7.44
2	214	TSAT0-V	-332.44	-6.99
3	230*	WT-CL	-337.55	-5.11

* Full model.
CL = apparent clearance; OFV = objective function value; No. = number; PPI = proton pump inhibitor; TSAT0 = baseline transferrin saturation; V = apparent volume of distribution; WT = body weight.
Source: 130.sum, 164.sum, 214.sum, and 230.sum (Appendix 16.2.10)

Full model:

Table 27 summarises the parameter estimates for the full model.

Table 27. Full Model Parameter Estimates (Run 230)

Full Model Parameter Estimates – FOCE Method				
Parameter	**Final Estimate**	**% RSE**	**95% Bound**	**Variability**
CL/F (L/h)	0.769	25.5	0.385 – 1.15	-
V_2/F (L)	29.0	28.5	12.8 – 45.2	-
KA (1/h)	0.623	27.0	0.294 – 0.952	-
PPI	1.64	32.1	0.609 – 2.67	-
TSAT0/MDTSAT0	0.632	46.8	0.0518 – 1.21	-
WT/MDWT	-0.491	49.9	-0.971 – -0.0108	-
CL/F IIV	0.791	55.2	-0.0655 – 1.65	88.9%
V_2/F IIV	0.339	56.3	-0.0354 – 0.713	58.2%
Proportional RV	0.0304	51.3	-0.000176 – 0.0610	17.4%
Additive RV	0.00	-	-	

CL/F = apparent systemic clearance; FOCE = first order conditional estimation; IIV = inter-individual variability; KA = absorption rate constant; MDWT = median of baseline body weight; MDTSAT0 = median of baseline transferrin saturation; PPI = proton pump inhibitor; RSE = relative standard error; RV = residual variability; TSAT0 = baseline transferrin saturation; V_2/F = apparent volume of distribution; WT = body weight.
Source: 230.sum (Appendix 16.2.10)

Covariates included in the full model were removed one by one from the full model. Based on the OFV change, the most non-significant covariate was moved from each round to form a new multi-variable model. P>0.001 (OFV change <10.8) indicates statistical non-significance. This removal continued until removal of any covariate resulted in an OFV increase >10.8. Table 28 presents the results of the backward covariate deletion procedure.

Table 28. Results of Backward Covariate Deletion

Round	Run No.	Removed-Covariate – Parameter Model	OFV	Change in OFV from Previous Round Model
	230	Full model	-337.55	-
1	301	WT-CL	-332.44	5.11
2	304	PPI-V	-330.47	1.97
3	305	TSAT0-V	-318.01	11.46

CL = apparent clearance; No. = number; OFV = objective function value; PPI = proton pump inhibitor; TSAT0 = transferrin saturation at baseline; V = apparent volume of distribution; WT = body weight.
Source: 230.sum, 301.sum, 304.sum, and 305.sum (Appendix 16.2.10)

The backward elimination process resulted in removal of all the covariates and the final model was actually the same as the base model 130. The relative standard errors (RSEs) for the final model parameters (CL/F, Vz/F, and KA) were less than 25% and the RSEs for IIV were less than 41%, suggesting that precision of the parameter estimation was well.

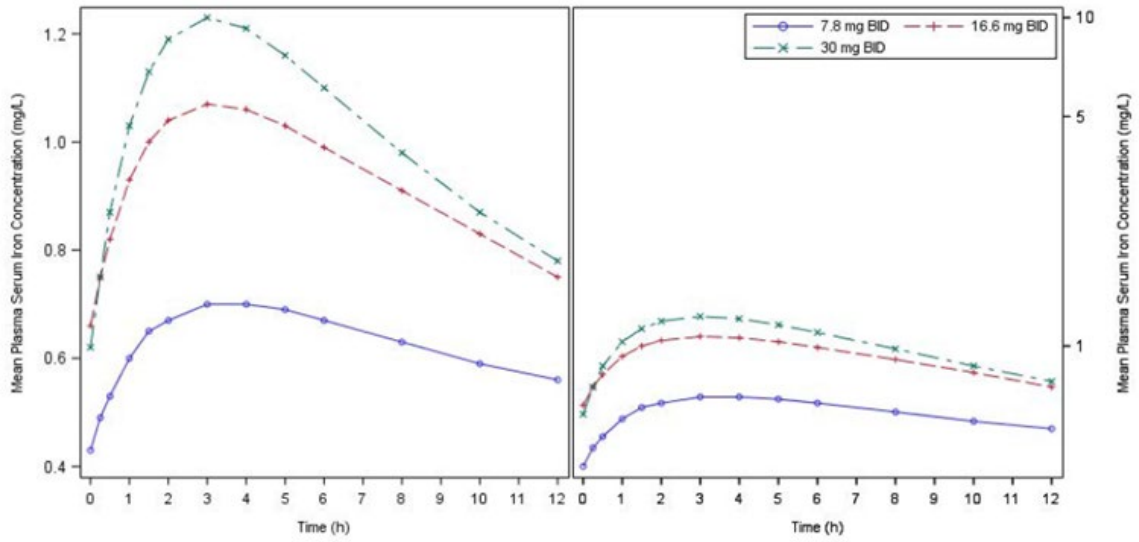
The final model 305 was evaluated using VPC. One thousand simulations were performed using the parameters defined in the final model (305.sum) with the 5th, 10th, 50th, 90th, and 95th percentiles generated from these simulation (Run pc-305). The results showed that 10.1% of the observed data fell outside of the 90% CI for the simulated data, showing that the final model described the concentration well.

-Iron concentration:

The iron concentration on Day 1 and Day 10 for each subject were simulated using the final PPK model. The relative time points included pre-first dose (time 0), 0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, and 12 hours post-dose. The individual predicted PK parameters such as Cmax and AUC were calculated using NCA with the predicted iron concentration-time data.

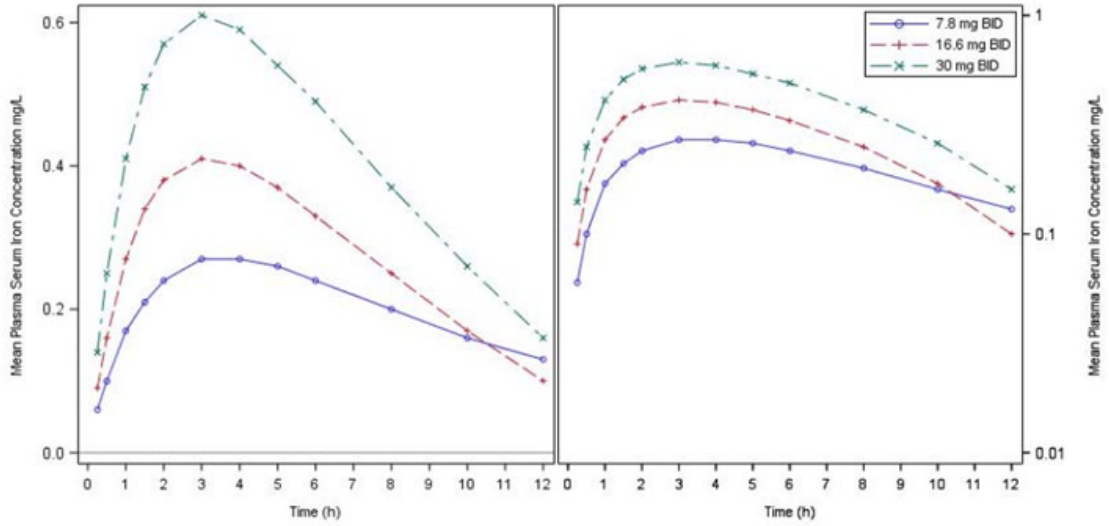
Figure 12 through Figure 15 present predicted mean serum iron concentrations and mean change from baseline by dose group on linear and semi-logarithmic scales on Day 1 and Day 10 for the FAS/ITT Population.

Figure 12. Plot of Predicted Mean Serum Iron Concentrations (mg/L) by Dose Group on Linear and Semi-Logarithmic Scales on Day 1 – Full Analysis Set/Intent-to-Treat Population



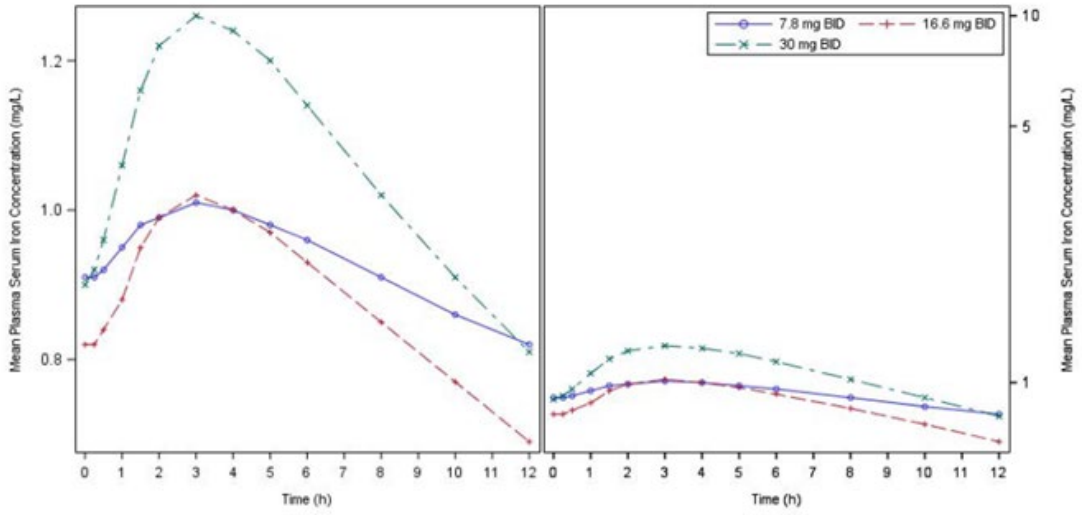
Lower limit of quantitation for serum iron = 0.1 mg/L.
BID = twice daily.

Figure 13. Plot of Predicted Mean Serum Iron Concentrations (mg/L) Change from Baseline by Dose Group on Linear and Semi-Logarithmic Scales on Day 1 – Full Analysis Set/Intent-to-Treat Population



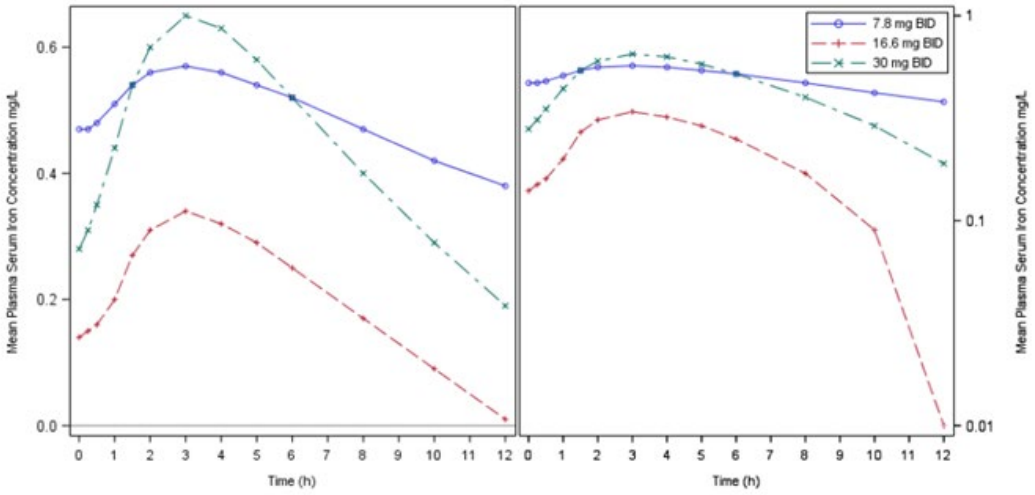
Baseline was defined as the predicted Day 1 pre-dose concentration. Lower limit of quantitation for serum iron = 0.1 mg/L.
BID = twice daily.

Figure 14. Plot of Predicted Mean Serum Iron Concentrations (mg/L) by Dose Group on Linear and Semi-Logarithmic Scales on Day 10 – Full Analysis Set/Intent-to-Treat Population



Lower limit of quantitation for serum iron = 0.1 mg/L.
BID = twice daily.

Figure 15. Plot of Predicted Mean Serum Iron Concentration (mg/L) Change from Baseline by Dose Group on Linear and Semi-Logarithmic Scales on Day 10 – Full Analysis Set/Intent-to-Treat Population



Baseline was defined as the predicted Day 1 pre-dose concentration. Lower limit of quantitation for serum iron = 0.1 mg/L.
BID = twice daily.

Table 29 and Table 30 summarizes PK parameters for predicted serum iron by treatment on Day 1 and Day 10, respectively, for the FAS/ITT Population.

Table 29. Summary of Pharmacokinetic Parameters for Predicted Serum Iron (mg/L) by Treatment on Day 1 – Full Analysis Set/Intent-to-Treat Population

PK Parameter (Unit)	Statistic	Ferric Maltol 7.8 mg BID	Ferric Maltol 16.6 mg BID	Ferric Maltol 30 mg BID
C_{max} (mg/L)	n	12	13	12
	Mean (SD)	0.7030 (0.19765)	1.0681 (0.30405)	1.2328 (0.47471)
	Geo. Mean (CV%)	0.6790 (28.0)	1.0264 (30.8)	1.1594 (37.0)
C_{trough} (mg/L)	n	12	13	12
	Mean (SD)	0.4316 (0.17662)	0.6579 (0.34415)	0.6169 (0.34023)
	Geo. mean (CV%)	0.4018 (40.4)	0.5804 (56.8)	0.5355 (63.9)
Change from C_{max} to C_{trough} (mg/L)	n	12	13	12
	Mean (SD)	0.2715 (0.11873)	0.4102 (0.22155)	0.6159 (0.32320)
	Geo. mean (CV%)	0.2481 (47.2)	0.3612 (55.9)	0.5561 (47.7)
T_{max} (h)	n	12	13	12
	Median (min, max)	4.000 (2.00, 4.00)	3.000 (2.00, 4.00)	3.000 (3.00, 5.00)
λ_z (1/h)	n	12	13	12
	Mean (SD)	0.03284 (0.018494)	0.04692 (0.015376)	0.06167 (0.027527)
	Geo. mean (CV%)	0.02866 (58.2)	0.04480 (32.0)	0.05585 (52.1)
$t_{1/2}$ (h)	n	12	13	12
	Mean (SD)	27.418 (13.6860)	16.158 (4.8174)	14.043 (8.6331)
$AUC_{0\text{-}6h}$ (h·mg/L)	n	12	13	12
	Mean (SD)	3.928 (1.1318)	5.963 (1.7793)	6.711 (2.5721)
	Geo. mean (CV%)	3.790 (28.2)	5.716 (31.6)	6.308 (37.4)
$AUC_{0\text{-}12h}$ (h·mg/L)	n	12	13	12
	Mean (SD)	7.610 (2.2241)	11.168 (3.3166)	12.295 (4.3641)
	Geo. mean (CV%)	7.346 (27.7)	10.713 (31.2)	11.612 (36.6)
$AUC_{0\text{-}inf}$ (h·mg/L)	n	12	13	12
	Mean (SD)	30.729 (16.9498)	29.331 (12.2395)	29.589 (17.9143)
	Geo. mean (CV%)	27.029 (55.8)	27.222 (41.4)	25.748 (58.0)
CL/F (L/h)	n	12	13	12
	Mean (SD)	0.324 (0.1517)	0.654 (0.2441)	1.321 (0.6945)
V_z/F (L)	n	12	13	12
	Mean (SD)	10.462 (3.1033)	14.244 (4.8183)	22.114 (7.2315)

Geometric CV% = $100 \times (\exp(SD^2) - 1)^{0.5}$, where SD was the SD of the logarithm-transformed data.
λ_z = apparent first order terminal elimination rate constant; $AUC_{0\text{-}6h}$ = area under the serum concentration curve from time 0 to 6 hours; $AUC_{0\text{-}12h}$ = area under the serum concentration curve from time 0 to 12 hours; $AUC_{0\text{-}inf}$ = area under the serum concentration curve from time 0 to infinity; BID = twice daily; CL/F = apparent systemic clearance; C_{max} = maximum serum concentration; C_{trough} = pre-dose serum concentration; CV = coefficient of variation; Geo. = geometric; max = maximum; min = minimum; PK = pharmacokinetic; SD = standard deviation; $t_{1/2}$ = half-life; T_{max} = time to reach maximum serum concentration; Vz/F = apparent volume of distribution.

Table 30. Summary of Pharmacokinetic Parameters for Predicted Serum Iron (mg/L) by Treatment on Day 10 – Full Analysis Set/Intent-to-Treat Population

PK Parameter (Unit)	Statistic	Ferric Maltol 7.8 mg BID	Ferric Maltol 16.6 mg BID	Ferric Maltol 30 mg BID
C_{max} (mg/L)	n	11	11	12
	Mean (SD)	1.0338 (0.40238)	1.0462 (0.32215)	1.3034 (0.67410)
	Geo. mean (CV%)	0.9716 (37.5)	0.9972 (34.4)	1.1403 (61.0)
C_{trough} (mg/L)	n	11	11	12
	Mean (SD)	0.8086 (0.38617)	0.6837 (0.22925)	0.7548 (0.49581)
	Geo. mean (CV%)	0.7331 (48.9)	0.6470 (36.8)	0.6180 (75.8)
Change from C_{max} to C_{trough} (mg/L)	n	11	11	12
	Mean (SD)	0.2251 (0.08362)	0.3625 (0.15333)	0.5486 (0.32367)
	Geo. mean (CV%)	0.2093 (43.7)	0.3354 (42.9)	0.4805 (57.3)
T_{max} (h)	n	11	11	12
	Median (min, max)	3.000 (0.00, 4.00)	3.000 (0.00, 4.00)	3.000 (0.00, 4.00)
$C_{ave\ (0\text{-}6h)}$ (mg/L)	n	11	11	12
	Mean (SD)	0.9748 (0.39783)	0.9557 (0.29645)	1.1667 (0.61420)
	Geo. mean (CV%)	0.9107 (39.4)	0.9101 (34.8)	1.0122 (63.6)
$AUC_{0\text{-}6h}$ (h·mg/L)	n	11	11	12
	Mean (SD)	5.849 (2.3870)	5.734 (1.7787)	7.000 (3.6852)
	Geo. mean (CV%)	5.464 (39.4)	5.461 (34.8)	6.073 (63.6)
$AUC_{0\text{-}Tau}$ (h·mg/L)	n	11	11	12
	Mean (SD)	11.151 (4.7564)	10.579 (3.4160)	12.784 (6.9293)
	Geo. mean (CV%)	10.346 (41.7)	10.028 (36.5)	10.987 (66.5)
CL_{ss}/F (L/h)	n	11	11	12
	Mean (SD)	0.808 (0.3089)	1.757 (0.6673)	3.264 (2.2297)
R_{Cmax}	n	11	11	12
	Mean (SD)	1.511 (0.4347)	1.032 (0.2906)	1.046 (0.3632)
$R_{AUC(0\text{-}6h)}$	n	11	11	12
	Mean (SD)	1.529 (0.4673)	1.020 (0.3170)	1.038 (0.3973)

Geometric CV% = $100 \times (\exp [SD^2] - 1)^{0.5}$, where SD was the SD of the logarithm-transformed data.
Tau = 12 hours.
$AUC_{0\text{-}6h}$ = area under the serum concentration curve from time 0 to 6 hours; $AUC_{0\text{-}Tau}$ = area under the serum concentration curve from time 0 to Tau; BID = twice daily; $C_{ave(0\text{-}6h)}$ = average steady state serum concentration form 0 to 6 hours; CL_{ss}/F = apparent serum clearance at steady state; C_{max} = maximum serum concentration; C_{trough} = minimum concentration between dose time and dose time + Tau; CV = coefficient of variation; Geo. = geometric; max = maximum; min = mininum; PK = pharmacokinetic; $R_{AUC(0\text{-}6h)}$ = accumulation ratio based on $AUC_{0\text{-}6h}$ after first dose and last dose; R_{Cmax} = accumulation ratio based on maximum concentrations after first dose and last dose; SD = standard deviation; T_{max} = time to reach maximum serum concentration.

-Transferrin saturation:

Transferrin saturation could not be analyzed using a PK model since the unit of TSAT is percent and cannot be correlated to dose amount to estimate CL/F and Vz/F. Since TSAT was calculated using iron concentration divided by TIBC, and the explorative data analysis showed TSAT and iron have a linear correlation, the TSAT was analyzed using a direct effect PD model.

The attempts were first made to fit the TSAT data to a sigmoidal maximum effect (Emax) model, and the resulting value was close to 1 and the condition number exceeded 1000. Then a linear model Y=A*X+B was tested but the 90% CI of B contained 0, which indicated the intercept can be removed from the equation. The model was finally simplified to Y=A*X, where Y is TSAT and X is iron concentration. Table 31 presents the parameter estimates. Different methods were tested to optimize the Epison parameters, but additive RV was considered to perform the best.

Table 31. Pharmacodynamic Model Parameter Estimates (Run PD16)

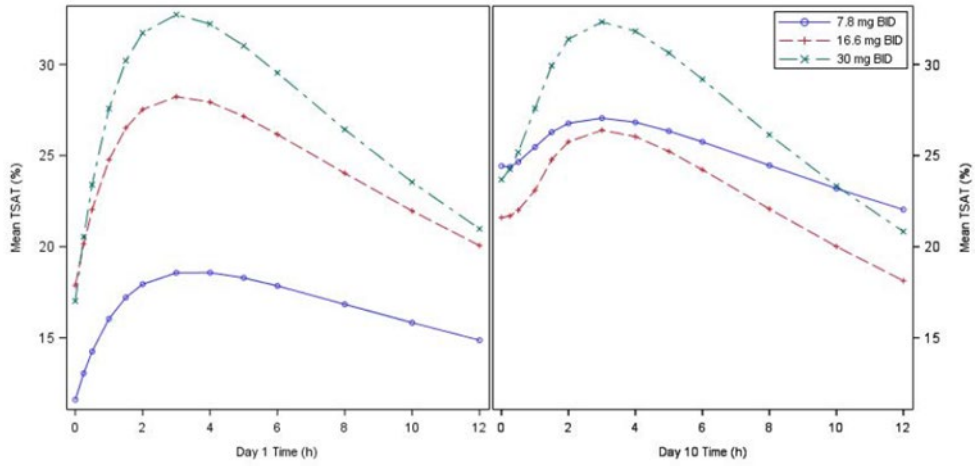
Model Parameter Estimates – FOCE Method				
Parameter	**Final Estimate**	**% RSE**	**95% Bound**	**Variability**
A	26.4	2.71%	25.0 – 27.8	-
IIV	0.0261	33.8%	0.00879 – 0.0434	16.2%
Additive RV	3.66	68.0%	-1.22 – 8.54	191%

A = the typical value of fixed effect (Theta) in the pharmacodynamic model Y=A*X; FOCE = first order conditional estimation; IIV = inter-individual variability; RSE = relative standard error; RV = residual variability.
Source: PD16.sum (Appendix 16.2.10)

The individual predicted TSAT on Day 1 and Day 10 at pre-dose (time 0), 0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, and 12 hours post-dose was calculated using the PD model parameter and individual predicted iron concentration. The predicted PD parameters such as Rmax and AUC above were calculated using the predicted TSAT value-time data.

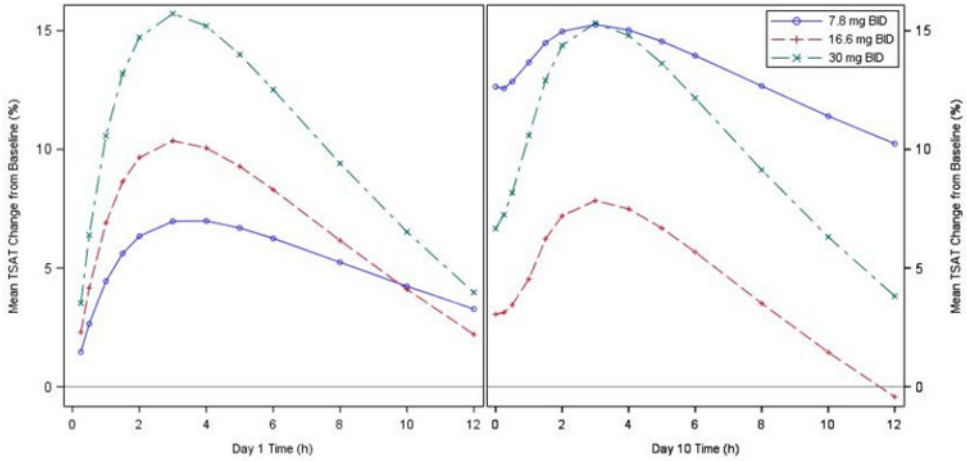
Figure 16 and Figure 17 show predicted mean TSAT and mean TSAT change from baseline by dose group on a linear scale on Day 1 and Day 10, respectively, for the FAS/ITT Population.

Figure 16. Plot of Predicted Mean Transferrin Saturation (%) by Dose Group on Linear Scale on Days 1 and 10 – Full Analysis Set/Intent-to-Treat Population



BID = twice daily; TSAT = transferrin saturation.
Source: Post-text Figure 14.2.4.3

Figure 17. Plot of Predicted Mean Transferrin Saturation (%) Change from Baseline by Dose Group on Linear Scale on Days 1 and 10 – Full Analysis Set/Intent-to-Treat Population



Baseline was defined as the predicted Day 1 pre-dose concentration.
BID = twice daily; TSAT= transferrin saturation.
Source: Post-text Figure 14.2.4.4

Table 32 and Table 33 summarizes the PD parameters for predicted TSAT by treatment on Day 1 and Day 10, respectively, for the FAS/ITT Population.

Table 32. Summary of Pharmacodynamic Parameters for Predicted Transferrin Saturation (%) by Treatment on Day 1 – Full Analysis Set/Intent-to-Treat Population

PD Parameter (Unit)	Statistic	Ferric Maltol 7.8 mg BID	Ferric Maltol 16.6 mg BID	Ferric Maltol 30 mg BID
Baseline (%)	n	12	13	12
	Mean (SD)	11.5 (5.66)	16.8 (9.25)	15.8 (9.31)
R_{max} (%)	n	12	13	12
	Mean (SD)	18.680 (7.1300)	28.261 (8.4784)	32.845 (10.5913)
R_{min} (%)	n	12	13	12
	Mean (SD)	11.332 (5.8329)	16.882 (8.7095)	16.372 (8.5934)
T_{max} (h)	n	12	13	12
	Median (min, max)	4.000 (2.00, 4.00)	3.000 (2.00, 4.00)	3.000 (3.00, 5.00)
T_{min} (%)	n	12	13	12
	Median (min, max)	0.000 (0.00, 12.00)	0.000 (0.00, 12.00)	0.000 (0.00, 12.00)
$AUC_{0\text{-}6h}$ (h·%)	n	12	13	12
	Mean (SD)	104.50 (41.009)	158.21 (50.723)	179.47 (60.259)
	Geo. mean (CV%)	98.68 (34.7)	150.10 (35.9)	170.34 (35.3)
$AUC_{0\text{-}12h}$ (h·%)	n	12	13	12
	Mean (SD)	202.55 (80.708)	296.43 (94.826)	329.93 (106.191)
	Geo. mean (CV%)	191.30 (34.3)	281.42 (35.6)	313.75 (35.1)
AUC_{Above_B} (h·%)	n	12	13	12
	Mean (SD)	65.17 (35.661)	95.09 (47.912)	140.36 (51.746)
AUC_{Below_B} (h·%)	n	12	13	12
	Mean (SD)	0.6187 (2.06579)	0.8184 (2.23672)	0.4336 (1.44146)
AUC_{Net_B} (h·%)	n	12	13	12
	Mean (SD)	64.55 (36.375)	94.27 (48.944)	139.93 (52.317)
$Time_{Above\_B}$ (h)	n	12	13	12
	Mean (SD)	11.571 (1.0820)	11.559 (1.0792)	11.794 (0.6566)
$Time_{Below\_B}$ (h)	n	12	13	12
	Mean(SD)	0.429 (1.0820)	0.441 (1.0792)	0.206 (0.6566)

Geometric CV% = $100 \times (\exp[SD^2] - 1)^{0.5}$, where SD was the SD of the logarithm-transformed data.
$AUC_{0\text{-}6h}$ = area under the effect versus time curve from time 0 to 6 hours; $AUC_{0\text{-}12h}$ = area under the effect versus time curve from time 0 to 12 hours; AUC_{Above_B} = area under the response curve that is above baseline; AUC_{Below_B} = area that is below the baseline and above the response curve; AUC_{Net_B} = AUC_{Above_B} – AUC_{Below_B}; BID = twice daily; CV = coefficient of variation; Geo. = geometric; max = maximum; min = minimum; PD = pharmacodynamic; SD = standard deviation; R_{max} = maximum response; R_{min} = minimum response; $Time_{Above\_B}$ = total time that response is ≥ baseline; $Time_{Below\_B}$ = total time that response is < baseline; T_{max} = time to reach maximum response; T_{min} = time to reach minimum response.
Source: Post-text Table 14.2.16

Table 33. Summary of Pharmacodynamic Parameters for Predicted Transferrin Saturation (%) by Treatment on Day 10 – Full Analysis Set/Intent-to-Treat Population

PD Parameter (Unit)	Statistic	Ferric Maltol 7.8 mg BID	Ferric Maltol 16.6 mg BID	Ferric Maltol 30 mg BID
Baseline (%)	n	11	11	12
	Mean (SD)	11.7 (5.88)	17.4 (10.04)	15.8 (9.31)
R_{max} (%)	n	11	11	12
	Mean (SD)	27.779 (13.8630)	27.214 (6.6996)	33.524 (13.6332)
R_{min} (%)	n	11	11	12
	Mean (SD)	21.854 (12.8339)	17.913 (5.4528)	19.548 (11.1849)
T_{max} (h)	n	11	11	12
	Median (min, max)	3.000 (0.00, 4.00)	3.000 (0.00, 4.00)	3.000 (0.00, 4.00)
T_{min} (%)	n	11	11	12
	Median (min, max)	0.500 (0.00, 12.00)	12.000 (0.25, 12.00)	6.500 (0.00, 12.00)
$AUC_{0\text{-}6h}$ (h·%)	n	11	11	12
	Mean (SD)	157.43 (81.693)	149.40 (37.799)	180.14 (76.193)
	Geo. mean (CV%)	142.46 (47.5)	144.04 (30.9)	164.01 (49.7)
$AUC_{0\text{-}12h}$ (h·%)	n	11	11	12
	Mean (SD)	300.51 (161.459)	275.90 (75.038)	329.09 (145.229)
	Geo. mean (CV%)	269.79 (49.7)	264.63 (33.0)	296.88 (52.7)
AUC_{Above_B} (h·%)	n	11	11	12
	Mean (SD)	163.91 (115.825)	93.86 (93.312)	149.72 (133.089)
AUC_{Below_B} (h·%)	n	11	11	12
	Mean (SD)	4.1263 (9.21005)	26.3242 (47.60260)	10.6378 (21.61702)
AUC_{net_B} (h·%)	n	11	11	12
	Mean (SD)	159.79 (122.348)	67.54 (128.058)	139.09 (146.905)
$Time_{Above\_B}$ (h)	n	11	11	12
	Mean (SD)	10.241 (3.9859)	8.567 (5.5268)	9.602 (4.2963)
$Time_{Below\_B}$ (h)	n	11	11	12
	Mean(SD)	1.759 (3.9859)	3.433 (5.5268)	2.398 (4.2963)

Geometric CV% = $100 \times (\exp [SD^2] - 1)^{0.5}$, where SD was the SD of the logarithm-transformed data.
$AUC_{0\text{-}6h}$ = area under the effect versus time curve from time 0 to 6 hours; $AUC_{0\text{-}12h}$ = area under the effect versus time curve from time 0 to 12 hours; AUC_{Above_B} = area under the response curve that is above baseline; AUC_{Below_B} = area that is below the baseline and above the response curve; $AUC_{net\_B} = AUC_{Above\_B} - AUC_{Below\_B}$; BID = twice daily; CV = coefficient of variation; Geo. = geometric; max = maximum; min = minimum; PD = pharmacodynamic; SD = standard deviation; R_{max} = maximum response; R_{min} = minimum response; $Time_{Above\_B}$ = total time that response is ≥ baseline; $Time_{Below\_B}$ = total time that response is < baseline; T_{max} = time to reach maximum response; T_{min} = time to reach minimum response.

2.3.3. Pharmacodynamics

Mechanism of action

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). The complex dissociates on uptake from the gastro-intestinal tract and the complex itself does not enter the systemic circulation.

Primary and secondary pharmacology

Study ST10-01-103

- *Iron markers and non-transferrin bound iron analysis:*

Changes from baseline in iron markers (TIBC, UIBC, and ferritin) and TSAT by visit (Day 1 and Day 10) and time point (1 to 2 hours post-dose and 2 to 3 hours post-dose) for the FAS/ITT Population are summarized in Table 34.

Table 34. Summary of Change from Baseline in Iron Markers and TSAT by Visit and Time Point

Parameter (Unit) Visit/Time Point Statistic	Ferric Maltol 7.8 mg BID (N=12)	Ferric Maltol 16.6 mg BID (N=13)	Ferric Maltol 30 mg BID (N=12)	Total (N=37)
Transferrin (g/L)				
Change from baseline to Day 1/1 to 2 hours				
n	6	6	5	17
Mean (SD)	-0.090 (0.0597)	-0.120 (0.2285)	-0.142 (0.0698)	-0.116 (0.1383)
Median (min, max)	-0.100 (-0.15, 0.00)	-0.060 (-0.54, 0.09)	-0.140 (-0.21, -0.03)	-0.130 (-0.54, 0.09)
Change from baseline to Day 1/2 to 3 hours				
n	6	6	5	17
Mean (SD)	0.057 (0.1331)	-0.075 (0.1111)	-0.096 (0.1387)	-0.035 (0.1383)
Median (min, max)	0.090 (-0.13, 0.18)	-0.025 (-0.22, 0.02)	-0.060 (-0.33, 0.02)	-0.010 (-0.33, 0.18)
Change from baseline to Day 10/1 to 2 hours				
n	5	5	6	16
Mean (SD)	-0.176 (0.2284)	-0.286 (0.1795)	-0.265 (0.1190)	-0.244 (0.1718)
Median (min, max)	-0.210 (-0.37, 0.19)	-0.390 (-0.43, -0.02)	-0.260 (-0.42, -0.07)	-0.260 (-0.43, 0.19)
Change from baseline to Day 10/2 to 3 hours				
n	6	6	5	17
Mean (SD)	0.013 (0.2104)	-0.115 (0.1506)	-0.132 (0.1596)	-0.075 (0.1784)
Median (min, max)	0.080 (-0.37, 0.23)	-0.085 (-0.39, 0.02)	-0.180 (-0.29, 0.07)	-0.060 (-0.39, 0.23)
TIBC (µmol/L)				
Change from baseline to Day 1/1 to 2 hours				
n	6	6	5	17
Mean (SD)	-2.50 (1.628)	-3.05 (7.770)	-2.96 (1.662)	-2.83 (4.522)
Median (min, max)	-2.95 (-3.9, 0.7)	0.00 (-18.3, 2.4)	-3.20 (-4.6, -0.7)	-2.70 (-18.3, 2.4)
Change from baseline to Day 1/2 to 3 hours				
n	6	6	4	16
Mean (SD)	0.85 (3.004)	-7.80 (12.233)	-1.63 (4.610)	-3.01 (8.532)
Median (min, max)	1.05 (-2.9, 4.6)	-3.05 (-30.8, 1.7)	-0.20 (-8.3, 2.2)	-0.20 (-30.8, 4.6)
TIBC (µmol/L) (continued)				
Change from baseline to Day 10/1 to 2 hours				
n	5	5	6	16
Mean (SD)	-3.34 (4.113)	-7.36 (9.406)	-5.93 (1.449)	-5.57 (5.620)
Median (min, max)	-4.10 (-7.2, 3.4)	-3.60 (-22.2, 0.2)	-5.90 (-8.0, -3.7)	-5.50 (-22.2, 3.4)
Change from baseline to Day 10/2 to 3 hours				
n	6	6	4	16
Mean (SD)	0.85 (3.123)	-1.97 (3.516)	-1.10 (3.671)	-0.69 (3.422)
Median (min, max)	1.55 (-4.8, 3.7)	-1.95 (-6.1, 2.4)	-1.05 (-5.2, 2.9)	0.25 (-6.1, 3.7)
UIBC (µmol/L)				
Change from baseline to Day 1/1 to 2 hours				
n	6	6	5	17
Mean (SD)	-6.12 (1.959)	-7.83 (6.452)	-10.28 (5.289)	-7.95 (4.916)
Median (min, max)	-5.15 (-8.8, -4.3)	-6.35 (-18.3, -1.6)	-10.20 (-18.1, -5.0)	-5.90 (-18.3, -1.6)
Change from baseline to Day 1/2 to 3 hours				
n	6	6	5	17
Mean (SD)	-3.88 (4.367)	-11.58 (11.116)	-9.82 (10.617)	-8.35 (9.210)
Median (min, max)	-4.55 (-8.9, 3.2)	-7.85 (-28.8, -1.2)	-4.50 (-23.6, -1.1)	-5.00 (-28.8, 3.2)
Change from baseline to Day 10/1 to 2 hours				
n	5	5	6	16
Mean (SD)	-15.86 (9.899)	-13.70 (8.211)	-11.73 (10.301)	-13.64 (9.087)
Median (min, max)	-19.70 (-24.9, 0.5)	-10.00 (-26.5, -6.9)	-9.95 (-31.0, -3.0)	-12.35 (-31.0, 0.5)
Change from baseline to Day 10/2 to 3 hours				
n	6	6	5	17
Mean (SD)	-9.68 (5.993)	-6.63 (9.955)	-12.86 (5.653)	-9.54 (7.537)
Median (min, max)	-10.95 (-15.6, 0.0)	-3.40 (-23.8, 2.8)	-11.10 (-21.5, -6.8)	-9.90 (-23.8, 2.8)

The mean transferrin concentration decreased from baseline to Day 1 at 1 to 2 hours post-dose for all dose groups and at 2 to 3 hours post-dose for the 16.6 mg and 30 mg dose groups. The mean transferrin concentration decreased from baseline to Day 10 at 1 to 2 hours post-dose for all dose groups and at 2 to 3 hours post-dose for the 16.6 mg and 30 mg dose groups.

The mean TIBC decreased from baseline to Day 1 at 1 to 2 hours post-dose for all dose groups and at 2 to 3 hours post-dose for the 16.6 mg and 30 mg dose groups. The mean TIBC decreased from baseline to Day 10 at 1 to 2 hours post-dose for all dose groups and at 2 to 3 hours post-dose for the 16.6 mg and 30 mg dose groups.

The mean UIBC decreased from baseline to Day 1 at 1 to 2 hours and 2 to 3 hours post-dose for all dose groups. The mean UIBC decreased from baseline to Day 10 at 1 to 2 hours and 2 to 3 hours post-dose for all dose groups.

The mean ferritin concentration decreased from baseline to Day 1 at 1 to 2 hours post-dose for all dose groups and increased from baseline to Day 1 at 2 to 3 hours post-dose for the 16.6 mg dose group. The mean ferritin concentration increased from baseline to Day 10 at 1 to 2 hours and 2 to 3 hours post-dose for the 16.6 mg and 30 mg dose groups.

All subjects were negative for NTBI on Day 1 at all-time points. All but 2 subjects were negative for NTBI on Day 10 at all-time points: 1 subject in the 30 mg dose group was positive for NTBI on Day 10 at pre-dose and 1 subject in the 16.6 mg dose group was positive for NTBI on Day 10 at 3 to 4 hours post-dose (Table 35).

Table 35. Summary of Negative and Positive Non-Transferrin Bound Iron (eLPI) by Visit and Time Point – Full Analysis Set/Intent-to-Treat Population

Parameter (Unit) Visit/Time Point Statistic	Ferric Maltol 7.8 mg BID (N=12)	Ferric Maltol 16.6 mg BID (N=13)	Ferric Maltol 30 mg BID (N=12)	Total (N=37)
NTBI (eLPI)				
Day 1/pre-dose				
N'	12	13	12	37
Negative, n (%)	12 (100.0)	13 (100.0)	12 (100.0)	37 (100.0)
Positive, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Day 1/0.5 to 1 hour				
N'	6	6	5	17
Negative, n (%)	6 (100.0)	6 (100.0)	5 (100.0)	17 (100.0)
Positive, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Day 10/pre-dose				
N'	10	11	12	33
Negative, n (%)	10 (100.0)	11 (100.0)	11 (91.7)	32 (97.0)
Positive, n (%)	0 (0.0)	0 (0.0)	1 (8.3)	1 (3.0)
Day 10/0.5 to 1 hour				
N'	5	5	5	15
Negative, n (%)	5 (100.0)	5 (100.0)	5 (100.0)	15 (100.0)
Positive, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

N' is the number of subjects who had evaluable measurement at the specified visit. The % was calculated as 100*n/N'.
BID = twice daily; NTBI = non-transferrin bound iron.
Source: Post-text Table 14.2.21

- Haemoglobin concentration and absolute reticulocyte count:

The mean Hb concentration decreased from baseline to Day 10 for all dose groups. The mean absolute reticulocyte count increased from baseline to Day 10 for the 7.8 mg and 30 mg dose groups and decreased from baseline for the 16.6 mg dose group (Table 36).

Table 36. Summary of Change From Baseline in Haemoglobin Concentration (g/dL) and Absolute Reticulocyte Count (1012/L) by Visit – Full Analysis Set/Intent-to-Treat Population

Parameter (Unit) Visit Statistic	Ferric Maltol 7.8 mg BID (N=12)	Ferric Maltol 16.6 mg BID (N=13)	Ferric Maltol 30 mg BID (N=12)	Total (N=37)
Haemoglobin concentration (g/dL)				
Baseline				
n	12	13	12	37
Mean (SD)	12.27 (0.856)	12.75 (1.067)	12.37 (1.418)	12.47 (1.124)
Median (min, max)	12.20 (10.9, 13.9)	12.60 (11.2, 14.6)	12.80 (9.1, 14.4)	12.60 (9.1, 14.6)
Day 10				
n	11	11	12	34
Mean (SD)	11.89 (0.846)	12.35 (0.836)	12.33 (1.792)	12.20 (1.243)
Median (min, max)	11.90 (10.5, 13.4)	12.40 (10.5, 13.5)	12.20 (8.1, 14.8)	12.20 (8.1, 14.8)
Change from baseline to Day 10				
n	11	11	12	34
Mean (SD)	-0.45 (0.301)	-0.33 (1.097)	-0.03 (0.789)	-0.26 (0.795)
Median (min, max)	-0.40 (-1.0, -0.1)	-0.40 (-2.5, 1.1)	-0.05 (-1.1, 1.3)	-0.30 (-2.5, 1.3)
Absolute reticulocyte (10^{12}/L)				
Baseline				
n	12	13	12	37
Mean (SD)	0.054 (0.0239)	0.071 (0.0150)	0.058 (0.0256)	0.061 (0.0225)
Median (min, max)	0.050 (0.01, 0.10)	0.070 (0.04, 0.09)	0.050 (0.03, 0.12)	0.060 (0.01, 0.12)
Day 10				
n	5	10	5	20
Mean (SD)	0.066 (0.0513)	0.069 (0.0213)	0.088 (0.0217)	0.073 (0.0308)
Median (min, max)	0.060 (0.02, 0.15)	0.065 (0.04, 0.10)	0.080 (0.06, 0.11)	0.070 (0.02, 0.15)
Change from baseline to Day 10				
n	5	10	5	20
Mean (SD)	0.016 (0.0358)	-0.001 (0.0218)	0.036 (0.0114)	0.013 (0.0277)
Median (min, max)	0.010 (-0.02, 0.07)	-0.005 (-0.04, 0.03)	0.040 (0.02, 0.05)	0.010 (-0.04, 0.07)

n = number of subjects with values at both the baseline and post-baseline visit.
Baseline was defined as the last value observed before the first dose.
BID = twice daily; max = maximum; min = minimum; SD = standard deviation.
Source: Post-text Table 14.2.23

2.3.4. PK/PD modelling

See section 2.3.2. Population Pharmacokinetic Analysis, for reference.

2.3.5. Discussion on clinical pharmacology

Within this procedure, three different studies have been submitted: ST10-01-103 (Phase 1 – PK, safety and tolerability), ST10-01-104 (Phase 1 – PK and food effect) and ST10-01-305 (Phase 3 – efficacy, safety and PK).

Analytical methods and sample analysis

Different analytes were measured in blood samples obtained from the three studies. These analytes could be total iron, maltol, maltol glucuronide, iron markers and non-transferrin bound iron. Analytical methods and sample analysis concerning studies ST10-01-103 and ST10-01-104 are assessed due to their relevance to this procedure.

A summary of total iron analytical method was submitted, which confirms compliance with acceptance criteria for main validation parameters, including precision, accuracy, range, stability, and interference. While full validation including primary data was not provided herein, the analytical method was assessed in previous regulatory procedures. The corresponding bioanalytical ST1001103 and ST1001104 reports are consistent with the validated method and meet the predefined acceptance criteria.

The analytical method used for the quantification of maltol glucuronide was assessed in previous procedures and considered acceptable. In this submission, the MAH provided a partial validation to extend the LTS of study samples for maltol and maltol glucuronide determination. The validation provided is considered acceptable as it is in line with the ICHM10 Guideline, so the LTS of study samples is extended up to 263 days at -20ºC.

Overall, quantification of maltol glucuronide in samples from study ST10-01-103 was carried out in line with the analytical method validated. However, in the report provided, it was indicated that the storage of various samples was outside the acceptable range before being received at ABS Laboratories. Since the duration of the excursion is unknown, it cannot be determined whether the storage of samples is covered by validated stability data. Consequently for future analyses, the impacted samples should be discarded.

Study ST10-01-104

Study ST10-01-104 was carried out to assess the PK of the absorption of iron from ferric maltol capsules and oral suspension and additionally, to study the influence of food.

Sampling time points went from t=0h (pre-dose) to t=24h (post-dose). According to the study report and to responses to request for supplementary information, baseline corrected serum iron AUCinf in all four conditions was not calculated for many subjects since the apparent terminal elimination rate constant (Lambda z) cannot be calculated for such subjects who do not exhibit a terminal elimination phase in their concentration-time profiles.

The wash-out period was of at least 48 hours. According to the MAH, the elimination half-life of total iron in serum ranged between 16 and 19 hours. Apparently, the wash-out period of 48 hours does not cover more than 5 times the half-life of the analyte, as stated in the ICH M13A and *the Guideline on the investigation of bioequivalence.* Considering that iron is an endogenous substance, a baseline correction should be applied in each period, so the possible carry-over effect would be eliminated by subtracting the pre-dose value.

The test meal provided in fed state is considered adequate and in accordance with the *Guideline on Bioequivalence*.

All 32 subjects who were randomised, completed the study. Only one major deviation was declared (not consuming the entire test meal prior to dosing) but considering that it was only in one patient and this type of meal is considered the worst-case scenario, it is not necessary to exclude this subject from the analysis.

The PK parameters were estimated for baseline corrected and baseline uncorrected total iron (among other analytes). Statistical calculations for baseline corrected total iron parameters AUC0-∞ and total AUClast was provided upon request. According to the clinical study report, 32 subjects completed the study according to protocol and were therefore included in the statistical analysis. However, the MAH provided the results of AUClast-baseline corrected values for: 25 subjects (capsule fed), 27 subjects (suspension fed), 32 subjects (capsule fasted) and 31 subjects (suspension fasted). Missing values are not justified nor explained in the provided documentation.

For baseline corrected iron, Tmax was observed in the first sampling point (pre-dose) in various patients for both formulations mainly in fed conditions.

Considering that iron is an endogenous substance, for the evaluation of pharmacokinetics and the effect of food, only the results provided of baseline corrected iron were assessed.

The 90% confidence intervals calculated for AUClast and Cmax were not within the normal range of acceptability (80.00 – 125.00%) for the comparison between ferric maltol suspension/capsules for

both fasted and fed state (PK assessment), neither for the comparison between ferric maltol capsules or ferric maltol suspension in fasted/fed state (food effect assessment). Therefore, currently, bioequivalence between both formulations cannot be assumed neither pharmacokinetic equivalence between administrating ferric maltol suspension or capsules in fasted or fed conditions. Nevertheless, data from study ST10-01-104 indicate that both formulations facilitate iron absorption. The clinical relevance of the observed differences remains uncertain, noting the substantial interindividual variability typically associated with iron-replacement therapy. Ultimately, the effectiveness of ferric maltol in adolescents (12–17 years) will be driven by its absorption profile, and treatment response should be monitored using standard biochemical and haematological parameters.

Pharmacokinetics and Pharmacodynamics:

Study ST10-01-103 enrolled children aged 10 to <18 years, which received ferric maltol capsules in doses of 7.8 mg, 16.6 mg, and 30 mg BID, for 9 days and one dose on Day 10.

Administration of ferric maltol resulted in an increased iron uptake in subjects who completed their treatment, as shown through measurement of serum iron and TSAT. However, the serum iron concentrations and plasma concentrations of maltol and maltol glucuronide showed different exposure time patterns.

The exposure of maltol glucuronide (maximum plasma concentration [Cmax] and Areas under the curve [AUCs]) were estimated using the predicted maltol glucuronide concentrations from the PPK model and then the dose proportionality was assessed using a power model. The results showed that dose proportionality existed over the dose range tested in this study, although the predicted Cmax of plasma maltol glucuronide on Day 10 slightly deviated from dose proportionality.

The PK characterization of maltol and maltol glucuronide in the paediatric patients (N=37) between 10 and <18 years of age is highly questionable based on the experimental evidence available, and the population PK model developed, which limits the characterization of the clinical pharmacology properties of the drug formulation and the dosing regimen selected. Relevant uncertainties remain after the evaluation regarding the quality of the data to fully inform about the PK properties of both analytes. The MAH stated that most of maltol observations were below the limit of quantification and were not used for model development. This represents a major limitation on its PK characterization in the target population. The MAH proposed a one-compartment model with first order absorption with TLAG and first order elimination kinetics as the structural PPK model for plasma maltol glucuronide (metabolite) and no characterization of plasma maltol (parent) was provided since most observations were below the limit of quantification. Although the adequacy to describe the time-course profiles of plasma maltol glucuronide is questionable, the structural definition of the PPK model does not consider the formation of the metabolite from the parent analyte. In addition, the modelling evaluation is lacking since no GOF, VPC, NPDE, bootstrap analyses were provided according to the EMA guideline on Population PK analysis (CHMP/EWP/185990/06). The MAH was advised to adapt the information regarding the clinical pharmacology in the target population to the recommended instructions in the EMA guideline. The preliminary evaluation of the PPK model adequacy revealed several model misspecifications and relevant limitations of the PPK model proposed. Relative standard errors are high (>60%) with fixed parameters with very or null evidence supporting the selected value together with 95% confidence bounds of final parameter estimates including the value 0 within their interval. All of this indicates that the parameter estimate is extremely imprecise and unstable. In addition, the MAH stated that relevant limitations regarding model stability were found during the model building

process, suggesting that the experimental data is not suitable enough to estimate the structural parameters. Given the limited number of subjects and observations per subject, it might be recommended to reduce the number of estimated parameters to ensure model stability and fixed parameters should be justified accordingly. Similarly, the previously collected PK evidence in adult patients could partially help in the characterization of ferric maltol in adolescents equal or older than 12 years of age. Once the PPK model is considered fit-for-purpose, the PK/PD modelling approach could be evaluated. Overall, the data seems insufficient at this stage for developing a PPK model capable of characterizing the PK/PD properties of the drug and, therefore, informing about the optimal dosing regimen in the target population. The PPK analysis is regarded as descriptive only and the extension of the indication can be accepted considering the clinical data available (see Clinical part); however, the PPK model is not considered suitable for use in future variations or for supporting future regulatory changes.

The exposure of iron (Cmax and AUCs) was estimated using the non-compartmental analysis method with the predicted iron concentrations and then dose proportionality was assessed using a power model. The results showed that dose proportionality for iron did not exist over the dose range tested in this study. Day 1 iron exposure parameters increased less than dose proportionally probably because of the plateauing effect observed between the 16.6 mg and 30 mg doses, and the Day 10 iron exposure parameters were comparable across the 3 doses.

No relevant information could be derived from the PK/PD model proposed since model predictions are not a reliable endpoint for predicting PD outcomes (serum TSAT).

ST10-01-305, enrolled subjects aged 2 to <18 years, who received ferric maltol at two dose levels: 15 mg per dose (in subjects aged 2-11 years) and 30 mg per dose (in subjects aged 12 to <18 years).

As the majority of samples analyzed for the parent analyte were found to be BLQ, the emphasis for PK analysis was placed on maltol glucuronide and serum iron. However, the number of measurable concentrations used in pharmacokinetic parameter calculation were highly limited, and a non-compartmental analysis with only three sampling points is highly deficient. Therefore, while these results may provide limited insight into general trends, they are not sufficient to support the characterization of the compound's pharmacokinetic profile.

These trends showed a slight decrease in Cmax of maltol glucuronide in both age groups and in AUC0-t for the 10-17 years age group when comparing Day 1 and Days 7 to 10 for the 15 mg BID ferric maltol group.

For the 30 mg BID ferric maltol group, the data demonstrated a moderate increase in Cmax (21%). Additionally, a notable delayed of Tmax was observed on Days 7 to 10 compared to Day 1 (from 0.52h on Day 1 to 3.63h on Day 7-10).

For all age groups, the majority of pre-dose maltol glucuronide levels on Days 7 to 10 were undetectable or approaching undetectable, indicating no notable maltol glucuronide accumulation; and for infants (1 month to <2 years), maltol glucuronide was detected in the urine, indicating that ferric maltol is metabolized and excreted via the renal pathway.

An increase in baseline-corrected serum iron was also observed to some extent in both the 15 mg (patients 2 to 11 years) and 30 mg (patients 12 to 17 years) dosing groups.

For the 15 mg BID ferric maltol group, a slight increase in both Cmax and AUC0-t of baseline-corrected serum iron was observed between Day 1 and Days 7 to 10 for patients in the 2 to 9 years age range. In contrast, for the 10 to 17 years age range, both Cmax and AUC0-t were lower, 48% and 97% respectively on Days 7 to 10 compared to Day 1.

For the 30 mg BID ferric maltol group, a moderate increase in both Cmax and AUC0-t was noted between Day 1 and Days 7 to 10 in the 10 to 17 years of age population. Additionally, a delayed Tmax was observed on Days 7 to 10 compared to Day 1 from 2h to 6.63h.

2.3.6. Conclusions on clinical pharmacology

Bioequivalence between ferric maltol suspension or capsules and pharmacokinetic equivalence between administrating both formulations in fasted or fed conditions were not established. Although the clinical relevance of the observed differences remains uncertain, there is limited impact on this application since the MAH only applied for an extension of indication for the existing presentation.

As the clinical pharmacology properties of serum maltol and serum maltol glucuronide have not been properly characterized, the PPK analysis is regarded as descriptive only and the extension of the indication can still be accepted considering the clinical data available.

2.4. Clinical efficacy

2.4.1. Main study

Study ST10-01-305: Phase III, 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 sulfate 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.

Methods

The study enrolled children aged 1 month to <18 years with IDA. Children aged 2 to <18 years were randomized (1:1) to receive either ferric maltol oral suspension or ferrous sulphate oral liquid.

All subjects aged 2 to 9 years of age were administered 15 mg BID of ferric maltol, all subjects aged 10 to 11 years of age received 15 mg BID of ferric maltol, and all subjects aged 12 to <18 years of age were administered 30 mg BID of ferric maltol. Children aged 1 month to <2 years were pre-assigned to receive 0.1 mL/kg ferric maltol suspension.

The PK results were further stratified by age, into two groups: 2 to 9 years of age and 10 to <18 years of age sub-groups. Therefore, the 10 to <18 years of age sub-group consisted of 2 dosing groups (15 mg BID and 30 mg BID).

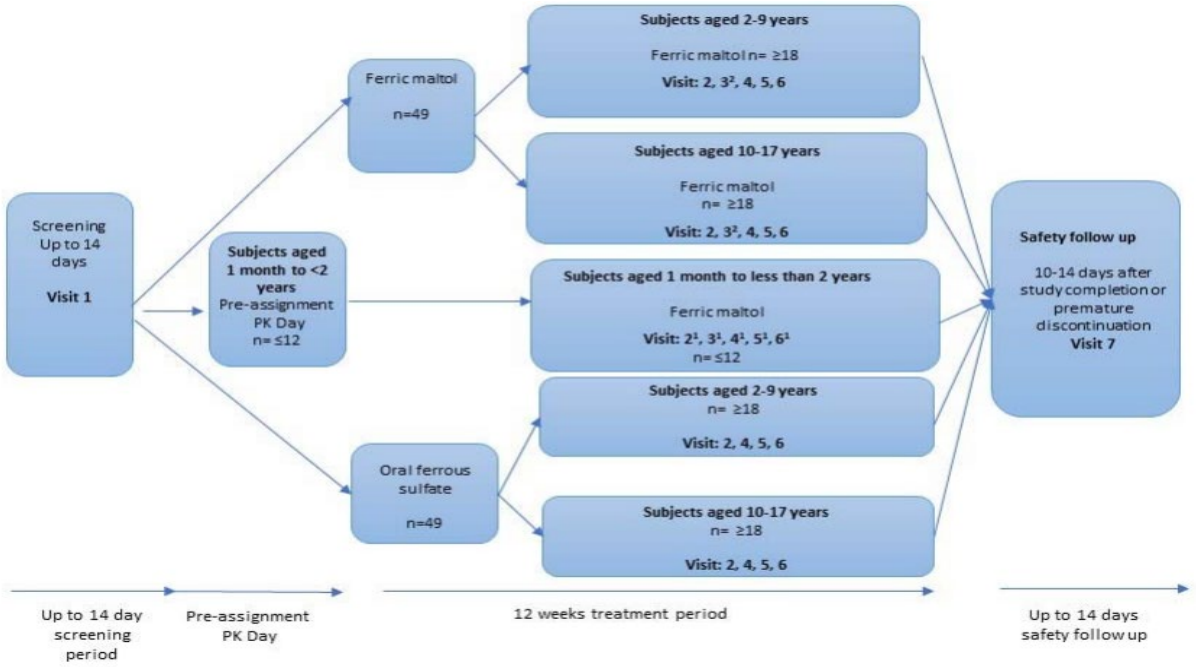
Table 37. Overview of Study ST10-01-305

Study design	Treatments and number of subjects treated	Treatment duration	Study status
Phase 3, randomized, open-label, active controlled, multicentre, comparative study.	**Cohort A Treatment:** Ferric maltol, oral suspension, BID – 1 month to < 2 years: 0.6 mg/kg/dose – 2-11 years: 15 mg/dose – 12-17 years: 30 mg/dose • Randomized: Ferric maltol randomized: 31	12 weeks	Finished

Study design	Treatments and number of subjects treated	Treatment duration	Study status
	Ferric maltol assigned[1]:4 • Completed: Ferric maltol: 28 Ferric maltol assigned[1] : 3 **Cohort B Comparator:** Ferrous sulphate (125 mg/ml), oral liquid 3 mg/kg/dose, BID • Randomized: Ferrous sulphate: 30 • Completed Ferrous sulphate: 25 **Total Randomized: 65** **Total Completed: 56**		

[1] Ferric maltol assigned group included only infants 1 month to <2 years of age. There is no ferrous sulphate comparison for this age group

Figure 18. Design schematics of Study ST10-01-305



1: Only applicable if subjects aged 1 month to < 2 years continues to the assigned treatment phase.
2: Visit 3 will only be performed for the first 18 subjects .

Study participants

Inclusion Criteria

A patient who met all of the following criteria was eligible to participate in the study:

- Patients must have been willing and able to comply with the study requirements and to provide written informed consent. In the case of patients under the age of legal consent, the legal guardian(s) must have provided informed consent and the patient must have provided assent per local and national requirements;
- Patients must have been ≥ 1 month and ≥ 17 years of age at the time of informed consent;
- Patients must have had iron deficiency anaemia defined by the criteria below (as measured by the central laboratory at the Screening visit);

Hb thresholds defining anemia by age and gender were as follows:

  - Children (1 month to <5 years): <11.0 g/dl;
  - Children (5 years to <12 years): <11.5 g/dl;
  - Children (12 years): <12.0 g/dl;
  - Female child (≥13 years): <12.0 g/dl; and
  - Male child (≥13 years): <13.0 g/dl.
  - Ferritin thresholds defining anaemia were as follows:
  - Ferritin <30 < µg/L; or
  - Ferritin <50 < µg/L with TSAT <20%.

- Female patients of childbearing potential must have agreed to use a highly effective method of contraception (which included complete abstinence) until study completion and for at least 4 weeks following their final study visit. Highly effective contraception was defined as a method which resulted in a low failure rate (i.e., less than 1% per year when used consistently and correctly), such as implants, injectables, some intrauterine contraceptive devices, a vasectomized partner, or oral contraceptive medications.

  The need for contraception and compliance with contraception requirements were assessed at every visit for adolescent patients, and urine pregnancy testing was performed at each visit for female patients of childbearing potential.

Exclusion criteria

A patient who met any of the following exclusion criteria was not eligible for participation in the study:

- Patients who had anaemia due to any cause other than iron deficiency, including, but not limited to, untreated or untreatable severe malabsorption syndrome;
- Patients who had received any of the following prior to Screening:
  a) Screening would have occurred within 28 days of intramuscular or IV injection or administration of depot iron preparation;
  b) Screening would have occurred within 7 days of administration of single agent iron preparations;
  c) Screening would have occurred within 12 weeks of blood transfusion, or a scheduled blood transfusion or donation during the study period;

d) Screening would have occurred within 28 days of administration of erythropoiesis stimulating agents or administration during the study; or
e) Screening would have occurred within 14 days of administration of COVID-19 vaccination.

- Patients who had a vitamin B12 or folic acid deficiency as determined by the central laboratory
  Screening results. Patients may have started vitamin B12 or folate replacement and rescreened
  after at least 2 weeks;
- Patients who had a concomitant disease that would have significantly compromised iron absorption or absorbed iron utilization, such as swallowing disorders and/or extensive small bowel resection;
- Patients who had a history of active peptic ulcer;
- Patients who had a chronic renal disease (eGFR <60 mL/min/1.73m2), as assessed at Screening based on serum creatinine;
- Patients who had a known hypersensitivity or allergy to either the active substance or excipients of ferric maltol or ferrous sulfate;
- Patients who had a known contraindication for treatment with iron preparations (e.g., hemochromatosis, chronic haemolytic disease, sideroblastic anaemia, thalassemia, or lead intoxication induced anaemia);
- Patients who had impaired liver function as indicated by alanine aminotransferase or aspartate transaminase >2 times the upper normal limit as measured at the Screening visit;
- Patients who had an active acute inflammatory disease, including an IBD flare or disease exacerbation, which in the opinion of the Investigator was clinically significant;
- Patients who had active chronic or acute infectious diseases requiring antibiotic treatment;
- Patients who were pregnant or breast feeding;
- Patients who had concomitant medical conditions with extensive active bleeding, other than menstrual cycles.
- Patients who had menorrhagia may have been included at the Investigator's discretion;
- Patients who had scheduled or expected hospitalization and/or surgery during the course of the study;
- Patients who had participated in any other interventional clinical study within 28 days prior to Screening;
- Patients who were diagnosed as COVID-19 positive by SARS-CoV-2-reverse transcription polymerase chain reaction (RT-PCR) within 28 days prior to Screening;
- Patients who had a cardiovascular, liver, renal, hematologic, psychiatric, neurologic, gastrointestinal, immunologic, endocrine, metabolic, respiratory, or central nervous system disease that, in the opinion of the Investigator, may have adversely affected the safety of the patient and/or objectives of the study drug, or severely limited the lifespan of the patient; and
- Any other unspecified reason that, in the opinion of the Investigator or the Sponsor, made the patient unsuitable for enrolment.

Treatments

The investigational/study treatment for this study was ferric maltol while the comparator was ferrous sulfate.

Ferric maltol group:

The ferric maltol oral suspension contained 30 mg elemental iron in the form of 231.5 mg ferric maltol in 5 mL suspension.

Patients aged 1 month to 17 years randomized or assigned to oral ferric maltol received the doses presented in Table 38. Design schematics of Study ST10-01-305 for the duration of the study (12 weeks), including 2 PK days. The first 12 patients randomized to ferric maltol in each age sub-group (2 to 9 years and 10 to 17 years) entered a PK phase from Visit 2 (PK Day 1) until Visit 3 (PK Day 2) with 2 PK days.

Ferric maltol oral suspension was taken every morning and evening at least 30 minutes after a meal. Patient weight was recorded at each clinic visit, and for patients aged 1 month to <2 years, study drug dosing was administered as per the previous clinical site visit weight.

Table 38. Design schematics of Study ST10-01-305

Age	Treatment	Dose/Frequency	Suspension Equivalent	Administration Route
1 month-<2 years	Ferric maltol oral suspension	0.6 mg/kg/dose, BID	0.1 mL/kg/dose	Oral
2-11 years	Ferric maltol oral suspension	15 mg per dose, BID	2.5 mL per dose	Oral
12-17 years	Ferric maltol oral suspension	30 mg per dose, BID	5 mL per dose	Oral
BID = twice daily. Source: Protocol (Appendix 16.1.1)				

Comparator (ferrous sulfate) group

Ferrous sulfate oral liquid 125 mg/mL (25 mg/mL elemental iron) or equivalent concentration was administered under the Protocol and used for all children/adolescents randomized to this group. Patients aged 2 to 17 years randomized to oral ferrous sulfate received the dose presented in Table 39 for the duration of the study (12 weeks).

For patients aged 2 to 17 years, 0.24 mL per kg body weight of ferrous sulfate, up to a maximum of 8 mL, was given daily in 2 divided doses. Patient weight was recorded at each clinic visit and study drug dosing was administered as per the previous clinical site visit weight.

Table 39. Comparator: ferrous sulfate group dosing

Age	Treatment	Dose/Frequency	Liquid Equivalent	Administration Route
2-17 years	Ferrous sulfate oral liquid	3 mg/kg/dose, BID	0.12 mL/kg/dose	Oral
BID = twice daily. Source: Protocol (Appendix 16.1.1)				

PK Sampling

PK was assessed in terms of serum iron, corrected serum iron, TSAT, TIBC, transferrin, UIBC, maltol, and maltol glucuronide.

Blood sampling for maltol and maltol glucuronide assessment was carried out pre-dose, and then 2 further times between 0.5 to 10 hours post-dose in subjects 2 to <18 years of age.

Blood samples for the remaining iron markers were collected pre-dose, and then 2 further times between 0.5 to 6 hours post-dose in subjects 2 to <18 years of age, similar to the sampling

timepoints for the maltol/maltol glucuronide. To reduce sampling burden, subjects were assigned to 4 PK sample schedule groups (each consisting of 3 subjects), as follows:

Table 40. Sample schedule groups (n =3 subjects/group)

PK Sample Schedule PK Day 1 and PK Day 2	PK Sample Schedule Group 1 (N=3)	PK Sample Schedule Group 2 (N=3)	PK Sample Schedule Group 3 (N=3)	PK Sample Schedule Group 4 (N=3)
Pre-dose (0 hour)	X	X	X	X
0.5-1 hour	X	X		
1-2 hours	X		X	
2-3 hours		X		X
3-4 hours			X	
4-6 hours				X

N = number of subjects; PK = pharmacokinetic(s).
Source: ST10-01-305 CSR, Table 6

In children aged 1 month to <2 years, during the pre-assignment PK visit, PK blood samples were collected pre-dosing (0 hour), and at 0.5 to 3 hours, 3 to 6 hours, and 7 to 12 hours post-dose, with samples taken at least 1.0 hour apart. On PK Day 2 (Visit 3), PK blood samples were collected pre-dosing (0 hour), and at 1.0 to 2.0 hours, 3.0 to 4.0 hours, and 10.0 to 12.0 hours.

Additionally, urine samples for PK assessment were collected from subjects aged 1 month to <2 years, pre-dosing and at 0.5 and 3 hours, 3 to 6 hours, and 7 to 12 hours post-dose.

Objectives

Primary Objectives

1. To compare the safety and gastrointestinal tolerability of ferric maltol oral suspension and ferrous sulfate oral liquid in children and adolescents aged 2 to 17 years, and to assess the safety and tolerability of ferric maltol oral suspension in children aged 1 month to <2 years, in the treatment of iron deficiency anaemia during the 12-week Treatment Period; and

2. To assess the effect on Hb in children and adolescents aged 1 month to 17 years after BID ferric maltol oral suspension administration for 12 weeks.

Secondary Objectives

1. To assess the PK in children and adolescents aged 2 to 17 years after a single dose of ferric maltol oral suspension on Visit 2 (PK Day 1), after BID administration for at least 6 days, and on Visit 3 (PK Day 2) after a single morning dose, through measurement of serum iron, corrected serum iron, TSAT, and plasma maltol and maltol glucuronide;

2. To assess the effect on iron markers in children and adolescents aged 1 month to 17 years after BID ferric maltol oral suspension administration for 12 weeks;

3. To assess the PK in children aged 1 month to <2 years after a single dose of ferric maltol oral suspension (pre-assignment PK visit), after BID administration for at least 6 days, and on Visit 3 (PK Day 2) after a single morning dose, through measurement of serum iron, corrected serum iron, TSAT (PK Day 2 only), plasma (PK Day 2 only), and urine concentration of maltol and maltol glucuronide;

4. To assess the effect in children aged 1 month to <2 years after BID administration for at least 6 days and on Visit 3 (PK Day 2) after a single morning dose, on serum transferrin, TIBC, and unsaturated iron-binding capacity (UIBC);

5. To assess the effect in children aged 2 to 17 years after a single dose of ferric maltol oral suspension on Visit 2 (PK Day 1), after BID administration for at least 6 days, and on Visit 3 (PK Day 2) after a single morning dose, on serum transferrin, TIBC, and UIBC; and

6. To compare the palatability from an age-appropriate scoring system of ferric maltol oral suspension and ferrous sulfate oral liquid.

Outcomes/endpoints

Primary endpoints:

- Safety and gastrointestinal tolerability:
    - Treatment-emergent adverse events (AEs) (TEAEs);
    - Treatment-emergent serious AEs (SAEs) (TESAEs); and
    - TEAEs leading to premature discontinuation of study drug/PK assessments from baseline to Week 12.
- Change in Hb concentration from baseline to Week 12.

Secondary endpoints:

- PK analysis of serum iron, corrected serum iron, TSAT, TIBC, transferrin, UIBC, maltol, and maltol glucuronide in children and adolescents aged 1 month to 17 years in the ferric maltol group;
- Changes in iron markers from baseline to Week 4;
- Changes in iron markers from baseline to Week 12;
- Achieving Hb concentration within normal range at Week 12;
- Qualitative assessments from patient questionnaires that allowed evaluation of the acceptability, palatability, and ease of use; and
- Maltol and maltol glucuronide in urine from both PK Days for patients aged 1 month to <2 years.

Sample size

In total, up to 110 patients could have been recruited into the study. Up to 98 patients could have been randomized in the 2 to 17 years cohort and up to 12 patients could have been assigned in the 1 month to <2 years cohort. The aim was to recruit up to 49 patients in each treatment group in the 2 to 17 years cohort. At least 12 patients in each age group (i.e., 24 patients in total) could have been included in the PK analysis of the ferric maltol oral suspension group. A sample size of 49 patients in the ferric maltol group would have provided at least 80% power to demonstrate that the lower bound of the 95% CI for increase in Hb at 12 weeks, compared to baseline, was above 0. This approach assumed that the SD of the change from baseline would be 1.2 g/dL or lower and the true mean change at least 0.5 g/dL.

Interim analysis: An interim analysis and associated stopping rules were added to the study to address low recruitment rates. As fewer than 91 patients in total had been randomized when 32 ferric maltol patients had completed, an interim analysis of the primary effectiveness endpoint (change in Hb concentration from baseline to Week 12) was conducted. Since change in Hb concentration from baseline to Week 12 was considered significant, the study stopped recruitment. If it had not been considered significant, the study would have continued (all patients would have been assigned to ferric maltol) until 54 patients had been recruited in the ferric maltol arm. The interim analysis used a Pocock spending function. The interim analysis was based on a (100-3.45)% 2-sided CI. If the study had not stopped after the interim analysis, the final analysis would have been based on a (100-2.57)% 2-sided CI.

In the end 31 patients were randomized in the ferric maltol arm and 30 patients in the ferrous sulfate arm, and 4 patients were assigned in the assigned ferric maltol arm. Hypothesis testing was performed in the interim analysis to test the hypothesis that the Hb change from baseline to Week 12 is >0 for ferric maltol. It was significant, so the MAH stopped recruiting.

Randomisation

Subjects aged 2-17 were randomised 1:1 to receive ferric maltol oral suspension or ferrous sulfate oral liquid. The randomization scheme was stratified by co-variates for age (2 to 9 years and 10 to 17 years) and sex (male and female). A minimum of 18 patients were to be recruited into each age group with 25% of either sex.

Blinding (masking)

No blinding has been performed in this study.

Protocol deviations

Randomized Population/Intention-to-Treat Population: The Intention-to-Treat (ITT) Population is defined as all patients who were randomized/assigned to treatment arms.

Modified Intention-to-Treat Population: The modified ITT (mITT) Population is defined as all patients in the ITT Population who received at least 1 treatment dose.

Per-Protocol Population: The Per-Protocol (PP) Population consists of those randomized/assigned patients who did not have major Protocol deviations during the study or discontinue the study early, leading to non-existence of post-baseline assessment. Data was reviewed prior to database lock to identify patients to be included/excluded from the PP Population.

Safety Population: The Safety Population is defined as all randomized/assigned patients who received at least 1 dose of study drug. All safety data were analyzed using the Safety Population.

Pharmacokinetic Population (Full Analysis Set): The PK Population is defined as all randomized/assigned patients who had at least 1 dose of study drug and who had at least 1 evaluable post-dose PK sample (applicable only for the ferric maltol group). All PK data were analyzed using the PK Population. Days of exposure to study drug are summarized by treatment based on the Safety Population, with descriptive statistics and with counts and percentages of patients with exposure in the following categories:

- ≤ 6 days;
- 7 to 27 days;
- 28 to 55 days;
- 56 to 83 days; and
- ≥ 84 days.

Percent compliance to the study drug regimen is summarized by treatment, based on the Safety Population, with descriptive statistics and with counts and percentages of patients, with compliance in the following categories: <80%, 80 to 120%, and >120%. However, it was decided that patients with a total compliance during the study period of <70% would be excluded from the PP Population.

Demographic and baseline characteristics

- Age (years) and age categories (1 month to <2 years, 2 to 9 years, and 10 to 17 years);
- Sex;

- Childbearing potential, if a female or undifferentiated;
- Race;
- Ethnicity;
- Height/length (cm);
- Weight; and
- Body mass index (kg/m2).

Demographic and baseline characteristics are summarized with descriptive statistics or counts and percentages of patients as appropriate by treatment, and in total for all randomized/assigned patients, split by age categories of 1 month to 2 years and 2 to 17 years.

Statistical methods

Baseline is defined as the last measurement prior to the first treatment dose of study drug. Version 2.0, 10 July 2024 of the SAP states that missing data have not been imputed unless otherwise specified.

Categorical data are generally summarized with counts and percentages of patients. Continuous data are generally summarized with descriptive statistics including n (number of non-missing values), mean, median, standard deviation (SD), and range (minimum and maximum). For PK parameters, descriptive statistics also include coefficient of variation (CV%), geometric mean (GM), and GM CV%.

The efficacy primary endpoint involved hypothesis testing (compared with baseline). The study's safety primary endpoints were analyzed by descriptive statistics only. The secondary endpoints were also analyzed by descriptive statistics only. Thus, no formal testing strategy or adjustments of the Type I error were employed for the evaluation of secondary endpoints.

Primary efficacy analysis

The change in Hb concentration from baseline to Week 12 is summarized based on the mITT Population for each treatment group using descriptive statistics summarized by mean, SD, median, and range (minimum and maximum).

The efficacy of ferric maltol was assessed via the change in Hb concentration from baseline to Week 12 using a mixed model for repeated measures (MMRM) approach. The analysis included fixed effects for treatment, visit, and treatment-by-visit interaction, along with a covariate of the baseline value as a continuous covariate. In the MMRM model, both assigned and randomized ferric maltol patients were included in the ferric maltol arm. A separate analysis was performed including only randomized patients.

Sensitivity analysis

The change in Hb concentration from baseline to Week 12 is summarized for patients randomized/assigned when the endpoint was designated as secondary and for patients randomized/assigned after the endpoint was changed to a primary endpoint. The change in Hb concentration from baseline to Week 12 is also assessed for the ITT and PP Populations.

Secondary analysis

The secondary endpoints are reported for each treatment group using descriptive statistics summarized by mean, median, and range (minimum and maximum), and 95% CI for the mean, where applicable, split by age group.

Any measurement obtained after a patient received a blood transfusion or received an IV iron or erythropoiesis stimulating agent were excluded from the analysis.

Descriptive summary statistics are summarized for children and adolescents aged 1 month to 17 years in the ferric maltol group for the PK analysis of serum iron, corrected serum iron, TSAT, transferrin, TIBC, UIBC, maltol, and maltol glucuronide.

Changes in iron markers from baseline to Weeks 4 and 12

The secondary analysis of the change from baseline to Weeks 4 and 12 in iron markers (serum iron, serum corrected iron, transferrin, TSAT, TIBC, UIBC, and ferritin) is summarized using descriptive summary statistics. In this analysis, missing Week 4 and Week 12 values were imputed using a last observation carried forward approach, in which the last available post-baseline measurement was used in the analysis.

Achieving hemoglobin concentration within normal range at Week 12

The number and percentage of patients achieving normal range, based on the central laboratory's reference range, at Week 12 is summarized by treatment group.

Table 41. Haemoglobin reference ranges.

Age Group	Hemoglobin Reference Range (g/dL)
Pediatric	
30 days to <6 months	9.0 – 12.5
6 months to <6 years	10.2 – 13.0
6 to 11 years old	11.5 – 15.5
12 to 17 years old female	12.0 – 16.0
12 to 17 years old male	13.0 – 16.0
Adult	
Male	13.6 – 18.0
Female	12.0 – 16.0
Source: Laboratory Manual (Appendix 16.1.10)	

Palatability and acceptability scoring

Patients 2 to 17 years of age on Visit 2 and Visit 4 received a 5-point Facial Hedonic Scale, which was completed immediately after the administration of ferric maltol oral suspension or ferrous sulfate oral liquid. Patients were free to ask for support in completing the questionnaires from parents/legal guardian and clinical site staff. Patients completed the Visit 2, 5-point Facial Hedonic Scale at the clinical site, immediately after dosing. Patients could complete the Visit 4, 5-point Facial Hedonic Scale at the clinical site or at home after the visit at the clinical site and dispensation of Visit 4 treatment, immediately after dosing. If patients required support in completing the questionnaires from clinical site staff, it was recommended the dosing and subsequent questionnaire completion occurred at the clinical site. Questionnaires should have been completed immediately after dosing, once a day (morning or evening dose). Hedonic expression was converted to scores of 1 to 5 with 1 being the most positive expression and 5 the most negative. The data from the scales was transformed into numbers for descriptive statistics.

Changes in the Conduct of the Study or Planned Analyses

In Protocol Amendment 5, Version 4.1, dated 06 July 2023, a potential interim analysis and associated stopping rules were added to the study to address low recruitment rates. As fewer than 91 patients in total had been randomized when 32 ferric maltol patients had completed, per the final Protocol Version 4.1 and Statistical Analysis Plan, an interim analysis of the primary effectiveness endpoint (change in Hb concentration from baseline to Week 12) was conducted. Since change in Hb concentration from baseline to Week 12 was considered significant, the study stopped recruitment. If it had not been considered significant, the study would have continued.

Every effort was made to recruit up to 12 patients in the 1 month to <2 years age group; however, the cohort was not completed (for reasons related to feasibility) at the time the study was stopped, and the study was completed without that full cohort. Additionally, Exclusion Criterion 6 in Section 9.3.2 of the CSR was updated to present the correct eGFR unit for chronic renal disease from 60 mL/min/m2 to 60 mL/min/1.73m2.

Changes in the Conduct of the Study

The original Protocol (Version 1.0) was dated 22 March 2021. There were a total of 6 Protocol Amendments to the original Protocol. The first Protocol Amendment (Version 1.1, dated 18 May 2021) included the following key changes:

- Clarification that patients aged 1 month to <2 years should take a single dose of ferric maltol after both a pre-dose blood and urine sample in the Pre-Assignment and Assigned Treatment Phase; and
- Clarification that Visit 3 must occur 7 to 10 days from Visit 2.

Other Protocol Amendments include: UK-specific Protocol Amendment 2, Version 2.0, dated 05 October 2021; US-specific Protocol Amendment 2, Version 2.1, dated 28 October 2021; Protocol Amendment 3, Version 3.0, dated 03 November 2022; Protocol Amendment 4, Version 4.0, dated 14 March 2023; and Protocol Amendment 5, Version 4.1, dated 06 July 2023.

Notably, Protocol Amendment Version 4.0 was not implemented due to additional FDA feedback received after its finalization, which was subsequently included in Protocol Amendment Version 4.1. No patients were enrolled under Protocol Amendment Version 4.0 and this version was not submitted to sites; it was submitted to the FDA and submitted and approved by the Medicines and Healthcare Product Regulatory Agency.

There were 2 Protocol Administrative Letters. The first Protocol Administrative Letter dated 22 December 2022 directed Investigators to cease enrollment into ferric maltol PK Groups 5 and 6 for the 10 to 17 years of age group for sites following Protocol Version 2.0 and Version 2.1. The second Protocol Administrative Letter dated 22 June 2023 directed Investigators to cease enrollment into ferric maltol PK Groups 5 and 6 for all age groups (2 to 17 years of age) for sites following Protocol Version 3.0.

Table 42. Summary of changes in Protocol from v.4.0 version to 4.1

Summary of Key Changes and Applicable Sections

Key Change	Section(s)	Justification
Removal of ferrous sulfate sample size reduction	4, 6.2, 7.1, 8.6, 12	Change in randomization was deemed premature at this stage of the study by FDA. This parameter is therefore being removed from the protocol (it was not implemented).
Removal of late timepoints in PK sampling for younger cohort (2-9 years) to match sampling for older age group (10-17 years)	4, 5.6, 7.1, 9.2, 10.2, 10.3, 10.9.2	Removal of late timepoints in both age groups will improve recruitment and reduce PK sample size. Agreed with FDA
Addition of potential interim analysis and associated stopping rules	4, 12, 14.7	The Implementation of interim analysis after 32 subjects complete 12 weeks treatment in ferric maltol arm, if recruitment rates still low and Inclusion of 2-sided testing for Hb change from baseline as measure of efficacy will address low recruitment if still an issue after 3 new sites have been opened for a reasonable period of time (approx. 6 months) and will include a quantitative measure of efficacy. The stopping rules and proposed statistical evaluation of efficacy were developed by a blinded statistician, based on data from previous Ferric Maltol studies in adults.
Removal of blood draws during pre-assignment PK in infants	4 6.2, 7.1, 7.5, 9.2, 10.4, 10.9.2	Data generated on 2 infants tested to date indicate that urine analysis is a satisfactory surrogate for plasma clearance of maltol and maltol glucuronide. Only urine will be collected and analysed for maltol and maltol glucuronide on the Pre-assignment PK day. Both serum and urine will be collected on PK day 2 and analysed for iron parameters as well as maltol and maltol glucuronide.
Inclusion of quantitative efficacy measure	4, 12, 14.7	The Implementation of interim analysis after 32 subjects complete 12 weeks treatment in ferric maltol arm, if recruitment rates still low and Inclusion of 2-sided testing for Hb change from baseline as measure of efficacy will address low recruitment if still an issue after 3 new sites have been opened for a reasonable period of time (approx. 6 months) and will include a quantitative measure of efficacy. The stopping rules and proposed statistical evaluation of efficacy were developed by a blinded statistician, based on data from previous Ferric Maltol studies in adults.

Changes in the Planned Analysis

The original Statistical Analysis Plan (Version 1.0) was dated 13 June 2024. There was one Amendment to the original Statistical Analysis Plan (Version 2.0, dated 10 July 2024), which provided minor clarifications and corrections, including the specification that only CSR-reportable Protocol deviations were to be summarized, addition of weight to baseline characteristics, and

clarification for analysis visits and primary analysis (clarifying that patients both randomized and assigned to ferric maltol treatment were to be analyzed as 1 group).

Notably, Protocol Amendment Version 4.0 reclassified the change in Hb concentration from baseline to Week 12 as a primary endpoint instead of a secondary endpoint to support an eventual paediatric indication at the recommendation of the FDA.

Thus, the Statistical Analysis Plan included a sensitivity analysis to assess the change in Hb concentration from baseline to Week 12 for patients randomized/assigned when the endpoint was designated as secondary and for patients randomized/assigned after the endpoint was changed to a primary endpoint.

Other changes made in the Statistical Analysis Plan from the Protocol-specified analyses included the following:

- It was clarified that the primary analysis for change in Hb was to be based on the mITT Population, and additional sensitivity analyses were to be based on the ITT and PP Populations. This approach deviates from Section 12.2.3 of the original Protocol, which indicated that sensitivity analyses were not applicable; and
- Change in iron markers from baseline to Week 4 was added as a secondary endpoint, which deviates from the secondary endpoints listed in Section 6.4 of the original Protocol.

Additionally, percent compliance to the study drug regimen is summarized by treatment, based on the Safety Population, with descriptive statistics and with counts and percentages of patients, with compliance in the following categories: <80%, 80 to 120%, and >120%.

However, at a joint meeting to discuss patients to be excluded from the PP Population, it was decided that patients with a total compliance during the study period of <70% would be excluded from the PP Population.

The age calculation description was updated to state that age was calculated based on the patient's informed consent date and year of birth and was set to align with the collected age group classification specified on the case report form.

Ad hoc tables and figures developed after database lock included:

- Tables presenting a summary of Hb concentration for pooled ferric maltol patients for the mITT and PP Populations;
- Tables presenting a summary of Hb concentration for ferric maltol patients at the 15 mg and 30 mg dose levels for the mITT Population including patients 2 to 17 years of age;
- Boxplot figures of Hb concentrations for the mITT Population including patients 2 to 17 years of age, 2 to 9 years of age, and 10 to 17 years of age;
- A spaghetti plot figure of Hb concentration for assigned ferric maltol patients for the mITT Population including patients 1 month to <2 years of age;
- A scatterplot figure of the dose level versus age at randomization for ferric maltol patients for the mITT Population including patients 2 to 17 years of age;
- Scatterplot figures of the change in Hb concentration to Week 4 and Week 12 versus age at randomization for the ferric maltol patients for the mITT Population including patients 2 to 17 years of age; and
- Scatterplot figures of the change in transferrin saturation from baseline to Week 4 and Week 12 versus age at randomization for the ferric maltol patients for the mITT Population including patients 2 to 17 years of age.

Finally, the Statistical Analysis Plan defined the PP Population as follows: "The PP Population consists of those randomized/assigned patients who did not have major Protocol deviations during the study" (Appendix 16.1.9). Upon review of the data on 07 August 2024, 1 patient was identified to have discontinued the study early and to have not received study drug, thus having no post-baseline assessments. However, this patient was not able to be excluded from the PP Population as

the patient did not have a Protocol deviation that was considered major (i.e., a deviation that may have impacted the primary efficacy assessment leading to exclusion from the PP Population) during the study. In order to include only patients with post-baseline assessments in the PP Population, the definition of the PP Population was updated to "all patients in the ITT Population who did not have any major Protocol deviations during the study or discontinue the study early, leading to non-existence of post-baseline assessments" after database lock.

Results

Participant flow

Table 43. Disposition all enrolled patients

	Ferrous Sulfate (N=30) n (%)	Ferric Maltol (N=31) n (%)	Ferric Maltol Assigned (N=4) n (%)	Total (N=65) n (%)
Enrolled	30 (100.0)	31 (100.0)	4 (100.0)	65 (100.0)
Discontinued early	5 (16.7)	3 (9.7)	1 (25.0)	9 (13.8)
Primary reason for discontinuation:				
Withdrawal of consent	4 (13.3)	1 (3.2)	1 (25.0)	6 (9.2)
Adverse event	1 (3.3)	0 (0.0)	0 (0.0)	1 (1.5)
Other	0 (0.0)	2 (6.5)	0 (0.0)	2 (3.1)
Discontinued early due to COVID-19[1]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Completed the study	25 (83.3)	28 (90.3)	3 (75.0)	56 (86.2)

% = 100 × n/N.
Infants 1 month to <2 years of age were included in the Ferric Maltol Assigned treatment column. There is no Ferrous Sulfate comparison for this age group.
1. These patients would have also been included in the discontinued early section.
COVID-19 = Coronavirus Disease 2019.

Recruitment

Table 44. Status of the study as of 25th July 2023 is tabulated below.

FPFV	No. Screened	No. Randomized	No. Completed	No/ Dropped	No. Sites Activated
03Nov21	122	52	41	4	19[1]

1. 2 additional sites in start-up; 1 site closed due to bankruptcy

Slow Overall Recruitment

The study has been much slower to recruit than expected based on feasibility activities. This is mainly due to a much higher screen failure rate observed compared to expected (>50% compared to 17%). Screen failures are mainly due to screening Hb levels above inclusion criteria.

The study was originally planned to complete enrolment within 20 months. Nevertheless, as of 20 months after FPFV (November 2021) fewer than 55% of the targeted 98 subjects had been recruited. Based on current enrolment rates of 3 patients per month, the study would take a further 15 months to recruit (total of 36 months) for all 98 patients.

Imbalance in Sex

Based on current demographics, of the 52 subjects recruited to date, only 23% are male. If a cap is implemented for female patients in order to achieve a minimum of 25% males recruited overall, the study would take more than an additional 15 months to recruit.

Other Measures Already Taken to Address Recruitment

It should be noted that other measures have already been implemented in an attempt to boost recruitment with only minimal impact on recruitment rates; these include site booster visits to increase PI and study staff engagement, minor updates to the protocol which did not impact key elements, increased advertising, reach out to patient advocacy groups, website launch for study sites and patients; opening 2 additional new sites.

Conduct of the study

Protocol Deviations

Most Protocol deviations were related to the investigational product. A summary is provided on the table below.

Table 45. CSR-Reportable Protocol Deviations

Deviation Category	Ferrous Sulfate (N=30) n (%)	Ferric Maltol (N=31) n (%)	Ferric Maltol Assigned (N=4) n (%)	Total (N=65) n (%)
Any CSR-reportable protocol deviations	13 (43.3)	7 (22.6)	4 (100.0)	24 (36.9)
INVESTIGATIONAL PRODUCT	10 (33.3)	1 (3.2)	1 (25.0)	12 (18.5)
STUDY PROCEDURES	1 (3.3)	5 (16.1)	3 (75.0)	9 (13.8)
BREACHES IN GCP	2 (6.7)	0 (0.0)	0 (0.0)	2 (3.1)
RESTRICTED CONCOMITANT MEDICATION CHANGE	0 (0.0)	1 (3.2)	0 (0.0)	1 (1.5)

% = 100 x n/N.
Infants 1 month to < 2 years are included in the Ferric Maltol Assigned treatment column. There is no Ferrous sulfate comparison for this age group.

Baseline data

Table 46. Demographic and Baseline Characteristics – All enrolled Patients – 2 years to 17 years.

Characteristic Statistic/Category	Ferrous Sulfate (N=30)	Ferric Maltol (N=31)	Total (N=61)
Age (years)			
n	30	31	61
Mean	12.3	12.8	12.6
Standard deviation	4.63	3.80	4.20
Median	13.0	14.0	14.0
Minimum	2	4	2
Maximum	17	17	17
Age group, n (%)			
2 years to 9 years	7 (23.3)	7 (22.6)	14 (23.0)
10 years to 17 years	23 (76.7)	24 (77.4)	47 (77.0)
Sex, n (%)			
Female	22 (73.3)	23 (74.2)	45 (73.8)
Male	8 (26.7)	8 (25.8)	16 (26.2)
Included in PK Population, n (%)	NA	20 (64.5)	20 (32.8)
2 years to 9 years	NA	7 (22.6)	7 (11.5)
Female	NA	3 (9.7)	3 (4.9)
Male	NA	4 (12.9)	4 (6.6)
10 years to 17 years (15 mg dose)	NA	3 (9.7)	3 (4.9)
Female	NA	3 (9.7)	3 (4.9)
Male	NA	0 (0.0)	0 (0.0)
10 years to 17 years (30 mg dose)	NA	10 (32.3)	10 (16.4)
Female	NA	9 (29.0)	9 (14.8)
Male	NA	1 (3.2)	1 (1.6)
Childbearing potential, n (%)[1]			
Yes	17 (77.3)	18 (78.3)	35 (77.8)
No	5 (22.7)	5 (21.7)	10 (22.2)
Ethnicity, n (%)			
Hispanic or Latino	12 (40.0)	13 (41.9)	25 (41.0)
Not Hispanic or Latino	18 (60.0)	18 (58.1)	36 (59.0)
Not reported	0 (0.0)	0 (0.0)	0 (0.0)
Unknown	0 (0.0)	0 (0.0)	0 (0.0)
Race, n (%)			
White	16 (53.3)	18 (58.1)	34 (55.7)
Black or African American	11 (36.7)	9 (29.0)	20 (32.8)
Asian	3 (10.0)	3 (9.7)	6 (9.8)
Other	0 (0.0)	1 (3.2)	1 (1.6)

Table 47. Demographic and Baseline Characteristics – All enrolled Patients – 2 years to 17 years. (Continued)

Characteristic Statistic/Category	Ferrous Sulfate (N=30)	Ferric Maltol (N=31)	Total (N=61)
Height/Length (cm)			
n	30	31	61
Mean	150.4	153.4	151.9
Standard deviation	23.62	20.26	21.84
Median	159.0	160.0	160.0
Minimum	88	101	88
Maximum	185	176	185
Weight (kg)			
n	30	31	61
Mean	57.50	51.88	54.65
Standard deviation	25.659	19.901	22.897
Median	57.70	53.00	55.20
Minimum	12.0	16.3	12.0
Maximum	127.7	94.6	127.7
Body mass index (kg/m^2)			
n	30	31	61
Mean	23.8276	21.1826	22.4834
Standard deviation	6.24648	5.47127	5.96691
Median	23.2677	20.3223	22.3522
Minimum	15.379	13.420	13.420
Maximum	37.312	36.953	37.312

% = 100 × n/N.
Baseline was defined as the last measurement prior to the first treatment dose of study drug. Age was calculated based on the patient's informed consent date and year of birth and was set to align with the collected age group classification specified on the case report form.
1. Denominator was based on the number of females and undifferentiated randomized/assigned.
NA = not applicable; PK = pharmacokinetic(s).
Source: Post-text Table 14.1.3.2

Numbers analysed

In total, 65 (100.0%) patients were included in the Randomized/ITT Population, 64 (98.5%) patients were included in the Safety Population, 64 (98.5%) patients were included in the mITT Population, 58 (89.2%) patients were included in the PP Population, and 23 (35.4%) patients were included in the PK Population. One (1.5%) patient who did not receive study drug was excluded from the Safety Population, mITT Population, and PK Population

Patients were excluded from the PP Population if they met criteria including, but not limited to, the following: early study discontinuation leading to non-existence of post-baseline assessments, dispensation of the incorrect study drug dose, or total compliance during the study period of <70%.

Outcomes and estimation

Primary analysis

The change in Hb concentration from baseline to Week 12 is summarized based on the mITT Population for each treatment group (Table 48) using descriptive statistics summarized by mean, SD, median, and range (minimum and maximum).

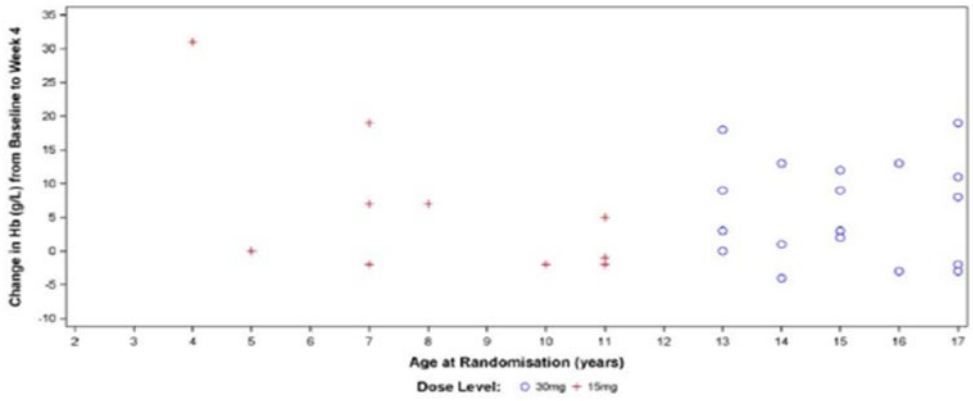
The efficacy of ferric maltol was assessed via the change in Hb concentration from baseline to Week 12 using a mixed model for repeated measures (MMRM) approach. The analysis included fixed effects for treatment, visit, and treatment-by-visit interaction, along with a covariate of the baseline value as a continuous covariate. In the MMRM model, both assigned and randomized ferric maltol patients were included in the ferric maltol arm. A separate analysis was performed including only randomized patients.

Table 48. Summary of Hb (g/L) Concentration – mITT Population

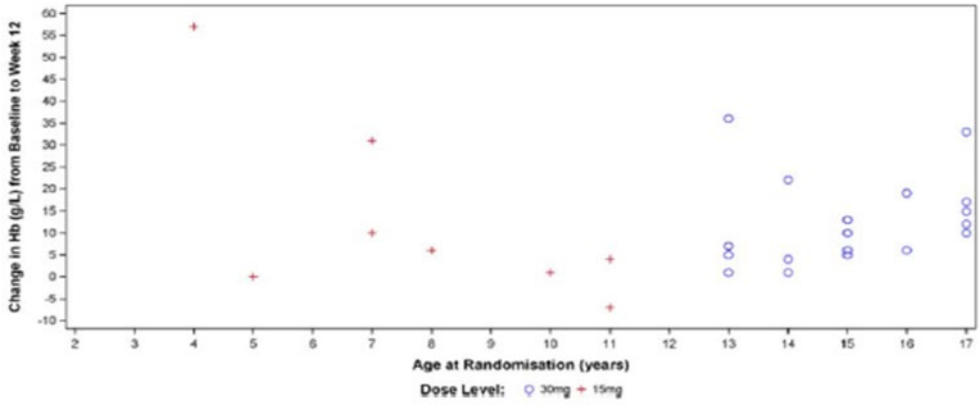
Visit Statistic	Ferrous Sulfate (N=30)	Ferric Maltol (N=31)	Ferric Maltol Assigned (N=3)	Total (N=64)
Baseline				
n	30	31	3	64
Mean	107.1	105.4	98.0	105.8
Standard deviation	8.84	10.96	8.00	9.95
Median	108.0	108.0	98.0	108.0
Minimum	72	69	90	69
Maximum	120	118	106	120
Day 28				
n	27	29	NA	56
Mean	116.1	111.0	-	113.4
Standard deviation	8.53	7.74	-	8.46
Median	118.0	111.0	-	113.0
Minimum	93	92	-	92
Maximum	130	130	-	130
Change from baseline to Day 28				
n	27	29	NA	56
Mean	8.9	6.0	-	7.4
Standard deviation	9.62	8.45	-	9.07
Median	8.0	3.0	-	6.5
Minimum	-6	-4	-	-6
Maximum	36	31	-	36
Day 84				
n	24	26	3	53
Mean	118.6	117.6	115.7	117.9
Standard deviation	10.44	7.97	6.43	8.99
Median	120.0	118.5	113.0	119.0
Minimum	94	100	111	94
Maximum	140	136	123	140
Change from baseline to Day 84				
n	24	26	3	53
Mean	11.5	12.5	17.7	12.3
Standard deviation	13.97	13.89	13.61	13.72
Median	9.0	8.5	13.0	9.0
Minimum	-7	-7	7	-7
Maximum	68	57	33	68

Baseline was defined as the last measurement prior to the first treatment dose of study drug.
The Ferric Maltol treatment group includes only patients who were randomized to Ferric Maltol.
Hb = hemoglobin; mITT = modified Intention-to-Treat; NA = not applicable.
Source: Post-text Table 14.2.1.1.1

Figure 19 Scatterplots of changes in Hb (g/L) from baseline to week 4 and to week 12 in mITT 2 years – 17 years population.



Baseline was defined as the last measurement prior to the first treatment dose of study drug.
Age was calculated based on the patient's informed consent date and year of birth and was set to align with the collected age group classification specified on the case report form.
Hb = hemoglobin; mITT = modified Intention-to-Treat.



Baseline was defined as the last measurement prior to the first treatment dose of study drug.
Age was calculated based on the patient's informed consent date and year of birth and was set to align with the collected age group classification specified on the case report form.
Hb = hemoglobin; mITT = modified Intention-to-Treat.
Source: Post-text Figure 14.2.3.2a

Changes made to the Statistical Analysis Plan from the Protocol-specified analyses included the following:

- It was clarified that the primary analysis for change in Hb was to be based on the mITT Population, and additional sensitivity analyses were to be based on the ITT and PP Populations. This approach deviates from Section 12.2.3 of the original Protocol, which indicated that sensitivity analyses were not applicable.

- Change in iron markers from baseline to Week 4 was added as a secondary endpoint, which deviates from the secondary endpoints listed in Section 6.4 of the original Protocol.

Table 49. Summary of Hb (g/L) Concentration – Ferric Maltol Patients with 15 mg dose level – mITT Population – 10 to 17 years old.

Visit Statistic	Ferric Maltol (N=3)
Baseline	
n	3
Mean	110.0
Standard deviation	6.93
Median	114.0
Minimum	102
Maximum	114
Day 28	
n	3
Mean	110.7
Standard deviation	3.21
Median	112.0
Minimum	107
Maximum	113
Change from Baseline to Day 28	
n	3
Mean	0.7
Standard deviation	3.79
Median	-1.0
Minimum	-2
Maximum	5
Day 84	
n	2
Mean	112.5
Standard deviation	7.78
Median	112.5
Minimum	107
Maximum	118
Change from Baseline to Day 84	
n	2
Mean	-1.5
Standard deviation	7.78
Median	-1.5
Minimum	-7
Maximum	4

Baseline was defined as the last measurement prior to the first treatment dose of study drug.
The ferric maltol treatment group includes only patients who were randomized to ferric maltol.
Hb = hemoglobin; mITT = modified Intention-to-Treat.

Table 50. Summary of Hb (g/L) Concentration – Ferric Maltol Patients with 30 mg dose level – mITT Population – 10 to 17 years old.

Visit Statistic	Ferric Maltol (N=21)
Baseline	
n	21
Mean	106.9
Standard deviation	9.22
Median	110.0
Minimum	86
Maximum	118
Day 28	
n	19
Mean	112.3
Standard deviation	8.74
Median	112.0
Minimum	92
Maximum	130
Change from Baseline to Day 28	
n	19
Mean	5.9
Standard deviation	7.16
Median	3.0
Minimum	-4
Maximum	19
Day 84	
n	18
Mean	119.3
Standard deviation	7.47
Median	119.5
Minimum	100
Maximum	136
Change from Baseline to Day 84	
n	18
Mean	12.3
Standard deviation	10.02
Median	10.0
Minimum	1
Maximum	36
Baseline was defined as the last measurement prior to the first treatment dose of study drug. The ferric maltol treatment group includes only patients who were randomized to ferric maltol. Hb = hemoglobin; mITT = modified Intention-to-Treat.	

The LS mean (± standard error) change from baseline to Week 12 was 12.51 (± 1.825) g/L for the ferrous sulfate group and 10.98 (± 1.682) g/L for the ferric maltol group. Both groups showed a statistically significant (2-sided p-value <0.0001) increase in Hb from baseline to Week 12.

Table 51. Analysis of Change in Hb Concentration – mITT Population.

Description Statistic	Ferrous Sulfate (N=30)	Ferric Maltol (N=34)
Number of patients	28	33
Change from baseline to Week 12		
LS mean	12.51	10.98
Standard error	1.825	1.682
96.55% confidence interval	(8.56, 16.46)	(7.34, 14.62)
p-value (2-sided)	<0.0001	<0.0001

Only participants with both baseline and at least 1 post-baseline measurement are included. Baseline was defined as the last measurement prior to the first treatment dose of study drug.
All participants with a missing Week 12 measurement were imputed using a LOCF approach in which the last available post-baseline measurement was used in the analysis.
LS means, standard errors, confidence intervals, and p-values are from a MMRM analysis with fixed effects for treatment, visit, and treatment-by-visit interaction, and baseline values as a continuous covariate.
Hb = hemoglobin; LOCF = last observation carried forward; LS = least squared; mITT = modified Intention-to-Treat; MMRM = mixed model for repeated measures.
Source: Post-text Table 14.2.1.2.2

Secondary analysis

Changes in iron markers from baseline to Weeks 4 and 12

For iron, the mean change from baseline to Week 4 (Day 28) appeared greatest in the assigned ferric maltol group, followed by the ferrous sulfate group, and then the ferric maltol group.

However, at Week 12 (Day 84), the greatest mean change from baseline was observed in the ferric maltol group (5.77 µ mol/L).

For TSAT, the mean change from baseline to Week 4 (Day 28) values followed the same trend as for iron, with the greatest increase observed in the assigned ferric maltol group. However, at Week 12 (Day 84), similar mean changes from baseline were observed in the ferric maltol group (7.7%) and the ferrous sulfate group (6.5%).

For ferritin, the mean change from baseline to Week 4 (Day 28) and to Week 12 (Day 84) appeared greatest in the ferrous sulfate group compared to the ferric maltol and assigned ferric maltol groups.

Table 52. Summary of selected iron markets – mITT Population

	Ferrous Sulfate (N=30)	Ferric Maltol (N=31)	Ferric Maltol Assigned (N=3)	Total (N=64)
Ferritin (µg/L)				
Baseline				
n	30	31	3	64
Mean	15.8	12.7	8.7	14.0
Standard deviation	11.10	10.69	8.14	10.82
Median	14.0	8.0	5.0	10.0
Minimum	2	2	3	2
Maximum	46	47	18	47
Ferritin (µg/L)				
Day 28[1]				
n	28	31	1	60
Mean	31.1	15.3	8.0	22.6
Standard deviation	21.37	10.81	-	18.28
Median	30.5	13.0	8.0	17.0
Minimum	4	3	8	3
Maximum	68	55	8	68
Ferritin (µg/L)				
Change from baseline to Day 28[1]				
n	28	31	1	60
Mean	15.9	2.6	5.0	8.9
Standard deviation	16.81	6.22	-	13.90
Median	14.5	2.0	5.0	4.0
Minimum	-21	-8	5	-21
Maximum	43	25	5	43
Ferritin (µg/L)				
Day 84[2]				
n	28	31	3	62
Mean	35.8	20.7	15.0	27.2
Standard deviation	34.89	12.99	5.29	26.17
Median	26.5	17.0	17.0	19.5
Minimum	4	4	9	4
Maximum	127	63	19	127
Ferritin (µg/L)				
Change from baseline to Day 84[2]				
n	28	31	3	62
Mean	20.6	8.1	6.3	13.6
Standard deviation	30.97	11.06	8.74	22.97
Median	3.5	5.0	4.0	5.0
Minimum	-19	-11	-1	-19
Maximum	92	34	16	92
Iron (µmol/L)				
Baseline				
n	30	31	3	64
Mean	8.90	6.81	3.23	7.62
Standard deviation	7.621	5.162	1.429	6.442
Median	7.45	5.50	2.90	5.50
Minimum	2.1	2.3	2.0	2.0
Maximum	37.8	20.6	4.8	37.8

	Ferrous Sulfate (N=30)	Ferric Maltol (N=31)	Ferric Maltol Assigned (N=3)	Total (N=64)
Iron (µmol/L)				
Day 28[1]				
n	28	31	3	62
Mean	16.37	11.66	19.03	14.14
Standard deviation	13.877	8.592	23.908	12.119
Median	12.25	7.90	7.70	8.95
Minimum	3.2	3.6	2.9	2.9
Maximum	60.5	36.7	46.5	60.5
Iron (µmol/L)				
Change from baseline to Day 28[1]				
n	28	31	3	62
Mean	7.94	4.85	15.80	6.77
Standard deviation	15.992	7.432	24.096	12.880
Median	4.10	2.40	2.90	3.00
Minimum	-18.6	-3.3	0.9	-18.6
Maximum	56.2	31.3	43.6	56.2
Iron (µmol/L)				
Day 84[2]				
n	28	31	3	62
Mean	12.08	12.58	4.30	11.95
Standard deviation	9.226	8.424	0.900	8.700
Median	9.85	10.60	4.30	10.00
Minimum	3.2	3.9	3.4	3.2
Maximum	39.9	36.7	5.2	39.9
Iron (µmol/L)				
Change from baseline to Day 84[2]				
n	28	31	3	62
Mean	3.64	5.77	1.07	4.58
Standard deviation	8.911	8.518	0.577	8.519
Median	1.70	5.00	1.40	3.30
Minimum	-13.0	-13.4	0.4	-13.4
Maximum	33.3	31.3	1.4	33.3
Transferrin saturation (%)				
Baseline				
n	30	31	2	63
Mean	10.7	8.4	3.0	9.3
Standard deviation	8.46	7.60	0.00	8.00
Median	9.0	5.0	3.0	6.0
Minimum	2	2	3	2
Maximum	37	32	3	37
Transferrin saturation (%)				
Day 28[1]				
n	28	31	3	62
Mean	21.3	14.1	16.3	17.5
Standard deviation	18.30	11.09	18.93	15.26
Median	17.0	9.0	8.0	11.5
Minimum	3	3	3	3
Maximum	83	41	38	83

	Ferrous Sulfate (N=30)	Ferric Maltol (N=31)	Ferric Maltol Assigned (N=3)	Total (N=64)
Transferrin saturation (%)				
Change from baseline to Day 28[1]				
n	28	31	2	61
Mean	11.5	5.7	17.5	8.8
Standard deviation	20.10	8.81	24.75	15.54
Median	7.0	3.0	17.5	4.0
Minimum	-17	-3	0	-17
Maximum	71	36	35	71
Transferrin saturation (%)				
Day 84[2]				
n	28	31	3	62
Mean	16.4	16.0	6.0	15.7
Standard deviation	13.72	11.54	1.73	12.40
Median	12.0	13.0	5.0	12.0
Minimum	3	4	5	3
Maximum	54	46	8	54
Transferrin saturation (%)				
Change from baseline to Day 84[2]				
n	28	31	2	61
Mean	6.5	7.7	2.0	7.0
Standard deviation	12.39	10.14	0.00	11.03
Median	3.0	5.0	2.0	4.0
Minimum	-17	-16	2	-17
Maximum	45	36	2	45

Baseline was defined as the last measurement prior to the first treatment dose of study drug.
The Ferric Maltol treatment group includes only patients who were randomized to Ferric Maltol.
1. All patients with a missing Day 28 measurement were imputed using a LOCF approach in which the last available post-baseline measurement was used.
2. All patients with a missing Day 84 measurement were imputed using a LOCF approach in which the last available post-baseline measurement was used.

LOCF = last observation carried forward; mITT = modified Intention-to-Treat.

Achieving haemoglobin concentration within normal range at Week 12

Overall, responders (defined as patients with an Hb concentration within normal range at Week 12 were captured in all groups, with the highest percentage of responders in the assigned ferric maltol group (3 [100.0%]), followed by the ferrous sulfate group (16 [53.3%]), and the ferric maltol group (12 [38.7%]).

Table 53. Summary of Hb Concentration Responders at week 12 – mITT Population

Category	Statistic	Ferrous Sulfate (N=30)	Ferric Maltol (N=31)	Ferric Maltol Assigned (N=3)
Number of patients				
Responder	n (%)	16 (53.3)	12 (38.7)	3 (100.0)
Non-responder	n (%)	14 (46.7)	19 (61.3)	0 (0.0)

% = n/N × 100.
A responder was defined as a patient with an Hb concentration within normal range at Week 12. The normal ranges were based on the central laboratory's manual. Patients with a missing Week 12 value were assumed to be non-responders.
Hb = hemoglobin; mITT = modified Intention-to-Treat.

Palatability and acceptability scoring

Regarding palatability, in children 2 to 5 years of age, on Day 1, the 4 ferrous sulfate group patient responses were 1 each for very bad, bad, OK, and good. The 2 ferric maltol group patient responses were very bad. On Day 28, the 3 ferrous sulfate group patient responses and the 2 ferric maltol group patient responses were all OK, suggesting that both treatments are palatable in infants.

In children 6 to 17 years of age, on Day 1, a higher percentage of patients reported a range of positive responses in the ferric maltol group compared to the ferrous sulfate group for the palatability parameters of taste, smell, and ease of taking the medication. This distribution of responses remained similar in both treatment groups between Day 1 and Day 28. Patient responses to the question of overall acceptance were similarly positive between treatments on both Day 1 and Day 28. By Day 28, more positive responses regarding the question of ease of swallowing were reported for patients in the ferric maltol group compared to ferrous sulfate group, and for the refusal of medication and whether patients had spat out the medication questions, mostly positive responses (indicating most patients did not refuse or spit out their medication) were recorded for both ferric maltol and ferrous sulfate groups. These reported responses suggest ferric maltol is just as, or more palatable, than ferrous sulfate.

Sensitivity analysis

Primary analysis: mITT population of 2 to 17 years

Table 54. Analysis of change of Hb concentration mITT population 2 years to 17 years

Description Statistic	Ferrous Sulfate (N=30)	Ferric Maltol (N=31)
Number of Subjects	28	30
Change from Baseline to Week 12		
LS Mean	12.36	10.69
Standard error (SE)	1.866	1.802
96.55% confidence interval (CI)	(8.31, 16.40)	(6.78, 14.60)
p-value (two-sided)	<0.0001	<0.0001

Only participants with both baseline and at least one post-baseline measurement will be included. Baseline is defined as the last measurement prior to the first treatment dose of study drug.
All participants with a missing Week 12 measurement will be imputed using a last observation carried forward (LOCF) approach in which the last available post-baseline measurement will be used in the analysis.
Least squares (LS) means, standard errors, confidence intervals, and p-values are from a mixed model for repeated measures (MMRM) analysis with fixed effects for treatment, visit and treatment-by-visit interaction and baseline values as a continuous covariate.

Primary analysis: PP population

Table 55. Sensitivity analysis of change of Hb concentration PP population 2 years to 17 years

Description Statistic	Ferrous Sulfate (N=24)	Ferric Maltol (N=31)
Number of Subjects	24	30
Change from Baseline to Week 12		
LS Mean	11.60	10.67
Standard error (SE)	2.131	1.906
96.55% confidence interval (CI)	(6.97, 16.23)	(6.53, 14.81)
p-value (two-sided)	<0.0001	<0.0001

Only participants with both baseline and at least one post-baseline measurement will be included. Baseline is defined as the last measurement prior to the first treatment dose of study drug.
All participants with a missing Week 12 measurement will be imputed using a last observation carried forward (LOCF) approach in which the last available post-baseline measurement will be used in the analysis.
Least squares (LS) means, standard errors, confidence intervals, and p-values are from a mixed model for repeated measures (MMRM) analysis with fixed effects for treatment, visit and treatment-by-visit interaction and baseline values as a continuous covariate.

Primary analysis: ITT population 2 to 17 years

Table 56. Sensitivity analysis of change of Hb concentration PP population 2 years to 17 years

Description Statistic	Ferrous Sulfate (N=30)	Ferric Maltol (N=31)
Number of Subjects	28	30
Change from Baseline to Week 12		
LS Mean	12.36	10.69
Standard error (SE)	1.866	1.802
96.55% confidence interval (CI)	(8.31, 16.40)	(6.78, 14.60)
p-value (two-sided)	<0.0001	<0.0001

Only participants with both baseline and at least one post-baseline measurement will be included. Baseline is defined as the last measurement prior to the first treatment dose of study drug.
All participants with a missing Week 12 measurement will be imputed using a last observation carried forward (LOCF) approach in which the last available post-baseline measurement will be used in the analysis.
Least squares (LS) means, standard errors, confidence intervals, and p-values are from a mixed model for repeated measures (MMRM) analysis with fixed effects for treatment, visit and treatment-by-visit interaction and baseline values as a continuous covariate.

Primary analysis: mITT population 12 to 17 years (submitted upon request)

Table 57. Summary of haemoglobin (g/L) concentration in subjects aged 12 to 17 years (mITT population)

Visit Statistic	**Ferrous sulphate (N=19)**	**Ferric Maltol (N=21)**
Baseline		
n	19	21
Mean ± SD	107.3 ± 10.85	106.9 ± 9.22
Day 28		
n	19	19
Mean ± SD	115.6 ± 9.96	112.3 ± 8.74
Change from Baseline to Day 28		
n	19	19
Mean ± SD	8.3 ± 10.92	5.9 ± 7.16
Day 56		
n	0	1
Mean	-	123.0
Change from Baseline to Day 56		
n	0	1
Mean	-	6.0
Day 84		
n	16	18
Mean ± SD	118.1 ± 12.30	119.3 ± 7.47
Change from Baseline to Day 84		
n	16	18
Mean ± SD	10.3 ± 16.92	12.3 ± 10.02

Baseline is defined as the last measurement prior to the first treatment dose of study drug.

Table 58. Analysis of change in haemoglobin (g/L) concentration in subjects aged 12 to 17 years (mITT population)

Description Statistic	**Ferrous sulphate (N=19)**	**Ferric Maltol (N=21)**
Number of subjects	19	20
Change from Baseline to Week 12 (Day 84)		
LS Mean	11.36	11.39
Standard error (SE)	2.426	2.364
96.55% confidence interval (CI)	(6.03, 16.69)	(6.19, 16.58)
p-value (two-sided)	<0.0001	<0.0001

Only participants with both baseline and at least one post-baseline measurement will be included. Baseline is defined as the last measurement prior to the first treatment dose of study drug.

All participants with a missing Week 12 measurement will be imputed using a last observation carried forward (LOCF) approach in which the last available post-baseline measurement will be used in the analysis.
Least squares (LS) means, standard errors, confidence intervals, and p-values are from a mixed model for repeated measures (MMRM) analysis with fixed effects for treatment, visit and treatment-by-visit interaction and baseline values as a continuous covariate.

Summary of main study

The following table summarises the efficacy results from the main study supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 59. Summary of Efficacy for trial *ST10-01-305*

Study identifier	ST10-01-305			
Design	Randomised, open-label, active-controlled, multicentre, comparative study			
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	12 weeks not applicable not applicable		
Hypothesis	Change from baseline is significant			
Treatments groups	active	Ferric maltol, 12 weeks, 31 patients (2 to 17 years)		
	control	Ferrous sulfate, 12 weeks, 30 patients (2 to 17 years)		
	Active (assigned)	Ferric maltol, 12 weeks, 4 patients (1 month to 2 years)		
Endpoints and definitions	Co-Primary endpoints	• Safety and gastrointestinal tolerability: • Change in Hb concentration from baseline to Week 12.		
	Secondary endpoints	• PK analysis of serum iron, corrected serum iron, TSAT, TIBC, transferrin, UIBC, maltol, and maltol glucuronide in children and adolescents aged 1 month to 17 years in the ferric maltol group; • Changes in iron markers from baseline to Week 4; • Changes in iron markers from baseline to Week 12; • Achieving Hb concentration within normal range at Week 12; • Qualitative assessments from patient questionnaires that allowed evaluation of the acceptability, palatability, and ease of use; and • Maltol and maltol glucuronide in urine from both PK Days for patients aged 1 month to <2 years.		
Database lock	22/10/2024			
Results and Analysis				
Analysis description	**Primary Analysis**			
Analysis population and time point description	ITT (all randomized) mITT (at least one dose taken) PP (no major protocol deviations)			
Descriptive statistics and estimate variability	Treatment group	Ferric maltol	Ferrous sulfate	Ferric maltol (assigned)
	Baseline number of subjects	30	31	3

	Baseline means	107.1	105.4	98.0
	Baseline standard deviations	8.84	10.96	8.00
	Day 84 number of subjects	24	26	3
	Day 84 means	118.6	117.6	115.7
	Day 84 standard deviations	13.97	13.89	13.61
Effect estimate per comparison	Primary endpoint: Change from baseline of Hb	Ferric maltol	Ferrous sulfate	
		12.51	10.98	
		1.825	1.683	
		<0.0001	<0.0001	
Notes	-			
Analysis description	**Secondary endpoint analysis** The secondary endpoints are reported for each treatment group using descriptive statistics summarized by mean, median, and range (minimum and maximum), and 95% CI for the mean, where applicable, split by age group. Any measurement obtained after a patient received a blood transfusion or received an IV iron or erythropoiesis stimulating agent were excluded from the analysis. Descriptive summary statistics are summarized for children and adolescents aged 1 month to 17 years in the ferric maltol group for the PK analysis of serum iron, corrected serum iron, TSAT, transferrin, TIBC, UIBC, maltol, and maltol glucuronide. **Changes in iron markers from baseline to Weeks 4 and 12** The secondary analysis of the change from baseline to Weeks 4 and 12 in iron markers (serum iron, serum corrected iron, transferrin, TSAT, TIBC, UIBC, and ferritin) is summarized using descriptive summary statistics. In this analysis, missing Week 4 and Week 12 values were imputed using a last observation carried forward (LOCF) approach, in which the last available post-baseline measurement was used in the analysis.			

2.4.2. Discussion on clinical efficacy

The MAH requested an extension of indication for Feraccru to include treatment of adolescent patients aged between 12 and 17 years for the treatment of iron deficiency. Similarly to adults, iron deficiency in children is assessed based on a combination of parameters in clinical practice, including haematological and iron metabolism indices. Oral iron supplements are considered first line of treatment, and duration of treatment should be sufficient to normalize not only the Hb value but also to restore the iron stores. Within this procedure, study ST10-01-305 was submitted to support efficacy, safety and PK.

Design and conduct of clinical studies

Efficacy and safety of ferric maltol in adolescents (Feraccru) is supported by Phase 3 clinical study ST10-01-305. This was a randomized, open-label, active controlled, multicentre study between ferric maltol oral suspension and ferrous sulphate oral liquid.

This study aimed to compare the safety and gastrointestinal tolerance of ferric maltol oral suspension versus ferrous sulphate oral liquid in children and adolescents aged 2 to under 18, assess ferric maltol's safety in infants aged 1 month to under 2 years, and evaluate its effect on hemoglobin across ages 1 month to under 18 years. Secondary goals were to examine ferric maltol's pharmacokinetics, impact on iron markers, and palatability. The Phase 3 study incorporated an additional non-comparative treatment arm with ferrous sulphate that was not included in the primary efficacy comparison. Children with IDA aged 1 month to under 18 years were enrolled; those 2 to under 18 were randomized to either treatment, receiving age-specific doses of ferric maltol. Infants received 0.1 mL/kg ferric maltol suspension.

A total of 65 patients (61 randomized and 4 assigned) were enrolled in the study, and 56 (86.2%) patients completed the study. Consequently, 65 (100.0%) patients were included in the Randomized/ITT Population, 64 (98.5%) patients were included in the Safety Population, 64 (98.5%) patients were included in the mITT Population, 58 (89.2%) patients were included in the PP Population, and 23 (35.4%) patients were included in the PK Population. One (1.5%) patient who did not receive study drug was excluded from the Safety Population, mITT Population, and PK Population. Initial sample size planned was amended, considering that sex does not have impact on iron absorption or Hb synthesis in the targeted population. Proposed modifications were endorsed by PDCO.

Hypothesis testing comparing baseline Hb and week 12 Hb levels was performed for the ferric maltol and ferrous sulfate arms (two different tests). The change from baseline is modelled using a Mixed Model for Repeated Measures (MMRM). For each treatment, the model estimates the change from baseline at the last visit, and these results are presented along with their corresponding confidence intervals. Notwithstanding, no comparative statistical hypothesis testing was done between arms, so the study should not be labelled as comparative (rather as parallel-group). Descriptive analysis was proposed for the secondary and safety analysis.

Efficacy data and additional analyses

Data derived from Study ST10-01-305 indicates that an increase in mean Hb (from baseline) at Week 12 was observed within all age groups. Firstly, the mean (SD) change from baseline Hb reported for the assigned ferric maltol group (2-17 years) at Day 84 was 17.7 [±13.61] g/L. Besides, the LS mean (±standard error) change, from baseline to Week 12 was 12.51 (±1.825) g/L for the ferrous sulfate group and 10.98 (±1.682) g/L for the ferric maltol group. Both groups showed statistically significant (2-sided p-value <0.0001) increase in Hb from baseline to Week 12.

From a regulatory perspective and considering that the broaden indication is intended for adolescents from 12 to 17 years old, the MAH was requested to provide clinical information related to these patients. Results provided demonstrate that Hb raised from baseline. The mean (SD) change from baseline Hb reported for the assigned ferric maltol group (12-17 years) at Day 84 was 12.3 [±10.02] g/L. Besides, the LS mean (±standard error) change, from baseline to Week 12 was 11.36 (±2.426) g/L for the ferrous sulfate group and 11.39 (±2.364) g/L for the ferric maltol group. Both groups showed statistically significant (2-sided p-value <0.0001) increase in Hb from baseline to Week 12 (see also Table 57 and Table 58).

Results from study ST10-01-305 demonstrated the efficacy of an alternative formulation (oral suspension) for the treatment of IDA in adolescents; however, full extrapolation of these findings to the marketed capsule formulation is limited, as bioequivalence between the two formulations was not formally established (see clinical pharmacology discussion).

Notwithstanding the acknowledged limitations, results from study ST10-01-104 suggest that both formulations are capable of supporting oral iron absorption. The clinical relevance of the differences observed between formulations remains uncertain and should be interpreted in light of the substantial interindividual variability that is well recognised in iron absorption and iron-replacement therapy. Ultimately, the effectiveness of ferric maltol in adolescents (12–17 years) will be driven by its absorption profile, and treatment response should be monitored using standard biochemical and haematological parameters. Furthermore, since the absorption of ferric maltol from the capsules under fasted conditions is higher than the absorption from the oral suspension, there is no concern regarding efficacy.

The proposed posology is ferric maltol 30 mg administered twice daily in adolescent patients aged 12 to <18 years, which is aligned with the dosing regimen evaluated in the Phase III clinical study. With regard to the pharmaceutical form, the proposed formulation is considered appropriate for use in the intended adolescent population. However, this formulation is not suitable for dosing in patients below 12 years of age; therefore, its use in this population is not recommended. An appropriate warning reflecting this limitation has been included in the SmPC.

2.4.3. Conclusions on the clinical efficacy

Overall, the clinical efficacy data submitted in support of the proposed extension of indication indicate that ferric maltol is effective in increasing haemoglobin levels in adolescent patients aged 12 to 17 years. Evidence is primarily derived from a single Phase III study employing an oral suspension formulation, for which statistically significant increases in haemoglobin from baseline were observed in the relevant age subgroup. While direct clinical efficacy data with the marketed capsule formulation are lacking and bioequivalence between formulations was not formally demonstrated, supportive pharmacokinetic data indicate that both formulations allow for adequate oral iron absorption, considering administration of ferric maltol resulted in an increased iron uptake, as shown through measurement of serum iron and TSAT (see also clinical pharmacology discussion).

Furthermore, ST10-01-104 was not designed to establish bioequivalence between these pharmaceutical forms, but rather to fulfil the requirements of the agreed PIP. Also, the PPK analysis is considered merely descriptive (see conclusions on clinical pharmacology).

The clinical relevance of the observed differences between both presentations therefore remains uncertain and should be interpreted in the context of well-recognised interindividual variability typically associated with iron-replacement therapy. Taking into account the alignment of the proposed posology with that evaluated in the Phase III study, the suitability of the capsule formulation for adolescent use, and the higher absorption observed with the capsule formulation under fasted conditions, no major concerns regarding efficacy in the proposed population have been identified. Nevertheless, treatment response should be monitored using standard haematological and biochemical parameters, in line with clinical practice.

2.5. Clinical safety

Patient exposure

Study ST10-01-305: Overall, 25 (80.6%) patients (>2 years to <18 years), and 3 (100.0%) patients (<2 years) treated with ferric maltol were in the exposure category of 84 days.

Study ST10-01-103: Overall, 37 subjects received ferric maltol during the 10-day treatment period: 12 subjects in the 7.8 mg dose group, 13 subjects in the 16.6 mg dose group, and 12

subjects in the 30 mg dose group. The mean number of days of study drug exposure for each dose group was 9.9 days for the 7.8 mg dose group, 8.8 days for the 16.6 mg dose group, and 10.1 days for the 30 mg dose group. The mean study drug compliance was 97.81% for the 7.8 mg dose group, 85.83% for the 16.6 mg dose group, and 98.25% for the 30 mg dose group.

Adverse events

Study ST10-01-305

Among patients aged 1 month to <2 years, 3 (100.0%) patients experienced a total of 9 AEs; and of these patients, 2 (66.7%) patients experienced a total of 6 TEAEs. All TEAEs were classified as mild in severity (2 [66.7%] patients). One (33.3%) patient experienced an SAE that was considered treatment-emergent (TSAEs) that was assessed by investigator as non-related to treatment (wheezing (SOC Respiratory disorders).

Among patients aged 2 to 17 years, 18 (29.5%) patients experienced a total of 47 AEs; all AEs were considered treatment-emergent and all TEAEs were classified as mild or moderate in severity (14 [23.0%] patients and 4 [6.6%] patients, respectively). A higher number of patients randomized to ferrous sulfate reported study drug-related TEAEs compared to patients randomized to ferric maltol. Overall, 1 (1.6%) patient in the ferrous sulfate group had 2 TEAEs of abdominal pain and nausea, both qualified as mild according to severity, which were in the SOC of gastrointestinal disorders, considered study drug-related, and led to discontinuation of study medication. No patients treated with ferric maltol had any TEAEs leading to discontinuation of the study.

Incidence and severity of treatment related adverse events were not significantly different between both arms.

Among patients aged 2 to 17 years, similar numbers of TEAEs were reported between treatment groups. There were 18 (29.5%) patients who experienced a total of 47 TEAEs; the most common SOC for reported TEAEs was infections and infestations (5 [16.7%] patients experienced 6 TEAEs in the ferrous sulfate group and 4 [12.9%] patients experienced 4 TEAEs in the ferric maltol group) followed by gastrointestinal disorders (4 [13.3%] patients experienced 6 TEAEs in the ferrous sulfate group and 4 [12.9%] patients experienced 10 TEAEs in the ferric maltol group). The most common PT for reported TEAEs in the SOC of gastrointestinal disorders was nausea (3 [10.0%] patients experienced 3 TEAEs in the ferrous sulfate group and 2 [6.5%] patients experienced 3 TEAEs in the ferric maltol group).

Incidences of TEAEs in the SOC of gastrointestinal disorders, and in the PTs categorized by this SOC, were similar between treatment groups or only occurred in 1 patient. The severity of TEAEs in the SOC of gastrointestinal disorders were similar between the treatment groups with all TEAEs in both treatment groups being classified as mild or moderate in severity. One patient in the ferric maltol group experienced a moderate (study drug-related) TEAE in the SOC of gastrointestinal disorders, while all other TEAEs in the SOC of gastrointestinal disorders were considered mild in severity.

According to investigator assessment, aggression (SOC Psychiatric disorders) from an adolescent was considered as related to treatment.

There were no changes in safety serum biochemical parameters attributable to treatments. Some deviations from normal ranges in the chemistry Parameters affecting patients in both treatment arms with low incidence were assessed as not related/not relevant. A relation with the treatments cannot be established.

Study ST10-01-103

In total, 21 (56.8%) subjects experienced an adverse event. Of these, 20 (54.1%) subjects experienced a TEAE: 7 (58.3%) subjects in the 7.8 mg dose group, 6 (46.2%) subjects in the 16.6 mg dose group, and 7 (58.3%) subjects in the 30 mg dose group. Treatment-emergent adverse events were mostly mild and no subjects had a severe TEAE. Across all dose groups, 11 (29.7%) subjects had a TEAE not related to study drug and 9 (24.3%) subjects had a TEAE related to the study drug. No subjects died or experienced an SAE during the study. One subject was discontinued due to a TEAE that was considered unrelated to treatment.

There were not significant changes regarding haematological nor clinical chemistry parameters that would represent any concern on safety.

Overall, incidence of TEAEs, and particularly concerning GI and nervous system was higher for upper dose. The most common SOC of study drug-related TEAEs during the 10-day treatment period was GI disorders (8 [21.6%] subjects): 2 (16.7%) subjects in the 7.8 mg dose group, 1 (7.7%) subject in the 16.6 mg dose group, and 5 (41.7%) subjects in the 30 mg dose group. The most common study drug-related TEAEs were faeces discoloured (5 [13.5%] subjects), headache (3 [8.1%] subjects), dizziness (2 [5.4%] subjects), diarrhoea (2 [5.4%] subjects), and fatigue (2 [5.4%] subjects).

According to investigator, all study drug-related TEAEs had an outcome of recovered/resolved.

There were no subjects with a severe TEAE reported in the study. The most frequently reported SOCs of TEAEs were GI TEAEs (12 [32.4%] subjects); these were mild for 10 (27.0%) subjects and moderate for 2 (5.4%) of subjects. The second most frequently reported SOC of TEAEs were nervous system disorders (9 [24.3%] subjects); these were mild for 7 (18.9%) subjects and moderate for 2 (5.4%) subjects.

Study ST10-01-104

Overall, 8 (25.0%) subjects experienced TEAEs: 3 (9.4%) subjects each in the ferric maltol suspension/fed and ferric maltol suspension/fasted treatment periods and 2 (6.3%) subjects in the ferric maltol capsule/fasted treatment period. All TEAEs were mild in severity. 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.

The most commonly reported TEAE was headache (3 [9.4%] subjects): 1 (3.1%) subject in the ferric maltol capsule/fasted treatment period and 2 (6.3%) subjects in the ferric maltol suspension/fasted treatment period. There was a single GI TEAE: 1 (3.1%) subject in the ferric maltol suspension/fasted treatment period experienced hypoesthesia oral.

Nervous and GI disorders, the TEAEs by SOC most reported in paediatric studies, were only reported under fasted conditions/any formulation in this study. Nevertheless, as single dose treatments, in an adult population, it was not expected to provide relevant safety findings concerning the particular formulation.

Serious adverse event/deaths/other significant events

No adverse events leading to death occurred.

No serious adverse events were related with treatments under study.

One patient treated with ferric maltol (Study ST10-01-305) was reported to exhibit aggressive behaviour that was assessed to be related to treatment by investigator. TEAE was associated with

another event TEAE of SOC Gastrointestinal disorder "defecation urgency". If a relation of causality between both TEAEs existed, has not been sufficiently clarified.

Discontinuation due to adverse events

There were no discontinuations of treatment with Ferric maltol in adolescents. Discontinuation of a single patient in the group <2 years (Study ST10-01-305) was due to a viral infection.

One patient discontinued treatment in the active control arm due to 2 simultaneous GI-TEAEs (abdominal pain and mild nausea) of mild severity.

2.5.1. Discussion on clinical safety

The review of the safety data provided by the MAH for this paediatric indication extension (studies ST10-01-305/ ST10-01-103) shows a safety profile mostly consistent with the prior and well-established safety profile for ferric maltol capsules in adult patients. The safety profile was acceptable in sufficiently represented age subgroups (children >2 years, adolescents >12 years or adults) in study ST10-01-305. The safety profile of Feraccru remained similar regardless of formulation, according to the currently reported data and adult studies. However, the higher dose group (30mg-BID, capsules) in study ST10-01-103 showed an increased incidence of GI-TEAEs related to treatment (5/12 representing 41.7 % of patients) compared to longer exposure with oral suspension in Study ST10-01-305; the precise significance of this finding in a regular extended treatment period remains uncertain.

There were no relevant reasons for early discontinuation related to treatment with ferric maltol in the two studies. Treatment with ferric maltol (Study ST10-01-305) was withdrawn by one subject < 2 years for TSAE wheezing (viral induced wheeze), assessed as non-related, and dosing was interrupted in 2 subjects (2 to 17 years) due to infection (gastroenteritis) and GI TEAE (diarrhea). The most common types of TEAEs reported in both studies were similar, particularly infections (from diverse etiology) and Gastro-intestinal disorders with mild, mostly, and moderate severity. However, none of the events resulted in treatment modification or withdrawal from study. However, the incidence of TEAEs that might be related to the clinical condition, such those as under SOC infections and infestations, were overall more frequently reported along the study duration than GI events directly attributable to treatment in Study ST10-01-305.

Drug-related TEAEs were reported in Study ST10-01-103 by 9 (24.3%) subjects: 3 (25.0%) subjects in the 7.8 mg group, 1 (7.7%) subject in the 16.6 mg group, and by 5 (41.7%) subjects in the 30 mg group. The most frequently reported TEAEs were faeces discoloured (reported by 5 [13.5%] subjects), headache (reported by 3 [8.1%] subjects), and diarrhoea, dizziness and fatigue (each reported by 2 [5.4%] subjects). During the study, a few of the treatment-related TEAEs were recorded only in paediatric patients, i.e., were not recorded in adult patients in previous trials. In the 30 mg group, 5 treatment-related TEAES that were recorded only in children were reported in 2 subjects. These treatment-related TEAEs included 2 cases of dizziness, and 1 case each of anal incontinence, fatigue, and lethargy.

In study ST10-01-305, drug-related TEAEs were reported by 6 (9.8%) subjects aged 2 to <18 years. The most frequently reported drug-related TEAEs was nausea (2 events reported by 2 [3.6%] subjects in the ferrous sulphate group, and 1 event reported by 1 [3.2%] subject in the ferric maltol group). During the study 2 treatment-related TEAEs were recorded only in paediatric patients in the 30 mg group. These included 1 case of defecation urgency and 1 case of aggression, both reported by the same patient.

There were no clinically significant abnormalities, and no trends were observed in mean or individual clinical laboratory parameters (chemistry and hematology), vital signs, or physical examinations in any treatment group. There were also no clinically significant findings or TEAEs associated with clinical laboratory parameters, vital signs, or physical examinations in any treatment group. There were no relevant alterations of individual data Safety Chemistry or hematological Parameters, Alkaline Phosphatase nor other hepatic markers that are known AEs related to iron overload.

Comparative safety of Ferric maltol with active control ferrous sulfate (both as oral suspension [OS]) does not show significant differences in the safety profile (and aligned to the common profile of orally administered iron supplements) or increased incidence of adverse events, that otherwise were usually mild in severity. Only a single patient required discontinuation of ferrous sulfate due to simultaneous events of mild abdominal pain and mild nausea while none in the ferric maltol groups.

Neurological TEAEs (headache, lethargy, dizziness, psychomotor hyperactivity) were not reported in the active control group (Study ST10-01-305), while 2 subjects (9 events) in ferric maltol OS group (Study ST10-01-305) and 4 subjects treated with ferric maltol hard capsules (all strengths) (Study ST10-01-103) reported TEAEs under SOC Nervous system disorders which could be a sign of a higher incidence of these class. However, these TEAEs (lethargy, dizziness), assessed as non-related to treatment in Study ST10-01-305, are also symptoms of the underlying clinical condition (IDA) being treated. Related TEAE headache, as assessed by investigators, is associated to treatment with ferric maltol, some other iron supplements and a recognized symptom of the underlying disease.

It should be considered that the study ST10-01-305 is not sufficiently powered to show safety differences vs active control nor a complete safety profile. However, as stated by the MAH, ferric maltol represents an alternative treatment suitable when ferrous salts and other iron oral treatments for IDA are not well tolerated. The study population treated with ferric maltol included patients previously treated with ferrous sulfate or other salts. The MAH reported that information on whether these patients had lacked efficacy or were intolerant to any prior iron medications was not available.

The duration of exposure was higher in Study ST10-01-305, with a duration of exposure of approximately 12 weeks, representative of a regular treatment duration, supports comparability of safety findings and adequate interpretation. Considering that the OS as administered in study ST10-01-305 is less bioavailable compared to capsules; safety cannot be automatically extrapolated. In addition, an exposure of 10 days with the currently authorized formulation (Phase I uncontrolled study ST10-01-103/group 30mg-BID, capsules) for the extended indication proposal is insufficient to fully characterize the safety profile of the capsules following a complete treatment duration in these patients. Nevertheless, the therapeutic window of iron salts is considered wide, and no unexpected AE were reported. Both formulations, OS and capsules, seem reasonably safe and well tolerated by adolescents.

2.5.2. Conclusions on clinical safety

Treatment of iron deficiency anaemia with ferric maltol oral suspension (30 mg BID) in adolescent patients over 12 years of age is regarded as safe and well tolerated, exhibiting a safety profile comparable to that observed in adult studies. However, the limited sample size of these studies restricts the ability to provide a more detailed safety assessment.

It cannot be entirely ruled out that hard capsules may be less well tolerated than oral suspension, potentially leading to a higher incidence of adverse events, especially among younger adolescents, given the limited number of patients studied. Nonetheless, this is considered acceptable since the adverse events reported with both formulations were generally mild in nature.

Based on the available data, treatment with ferric maltol in adolescent patients aged 12 years and above is considered to have an acceptable safety profile.

2.6. PSUR cycle

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

2.7. Risk management plan

The MAH submitted an updated RMP version with this application.

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

The PRAC considered that the risk management plan version 9.1 is acceptable.

Safety concerns

Table 60 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 Worsening of IBD symptoms (in patients with this disease)
Missing information	None

Pharmacovigilance plan

There were only routine pharmacovigilance activities agreed in the RMP- this remains unchanged.

Risk minimisation measures

Table 61. 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**	**Routine risk minimisation measures:** SmPC Section 4.4 recommends that special care should be taken if other dietary and/or iron salt	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None

salts, methyldopa, tetracyclines or dimercaprol	supplementation are used concurrently. 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. Prescription only medicine. **Additional risk minimisation measures:** None	**Additional pharmacovigilance activities:** None
Important Potential Risk: **Worsening of IBD symptoms (in patients with this disease)**	**Routine risk minimisation measures:** SmPC Section 4.4 and PL Section 2 recommend that patients should avoid taking Feraccru if they are experiencing a "flare" of their IBD. Prescription only medicine. **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None

2.8. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2,4.8, 5.1 and 5.2 of the SmPC have been updated.

- 4.1 Therapeutic indications: Section updated to extend the therapeutic indication for adolescent patients aged 12 years and above.
- 4.2 Posology and method of administration: Section updated to present the posology for adolescent patients aged 12 years and above, as well as recommendations in children below 12 years of age highlighting that capsules do not allow appropriate dosing in this population.
- 4.8 Undesirable effects: Section updated with safety data in paediatric patients.
- 5.1 Pharmacodynamic properties: Section updated to include the efficacy data in paediatric patients.
- 5.2 Pharmacokinetic properties: Section updated to include additional data in adult healthy volunteers.

The Package Leaflet has been updated accordingly. Furthermore, the PI is brought in line with the latest QRD template version 10.4.

Changes were also made to the PI to bring it in line with the current Agency/QRD template, SmPC guideline and other relevant guideline(s) which were reviewed by QRD and accepted by the CHMP.

In addition, the list of local representatives in the PL has been revised to amend contact details for the representative(s).

2.8.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH considering that the changes to the package leaflet are minimal and do not require user consultation with target patient groups.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Iron deficiency (ID) is one of the most common micronutrient deficiencies globally and the most prevalent nutritional deficiency worldwide. ID may be caused by inadequate iron intake, excess iron loss (i.e., haemorrhage), or excess iron utilization (WHO, 2020). ID is manifested as iron deficiency anaemia (IDA) which is the most prevalent nutritional disorder and dietary iron deficiency. Patients with mild IDA are also mostly asymptomatic. However, when anaemia becomes more severe, patients may present with nonspecific symptoms such as fatigue, pallor, and dyspnoea on exertion.

During childhood, IDA has two peaks of incidence in infancy and adolescence, when there is a discrepancy between food intake and the elevated need of iron depending on the growth speed. During adolescence, contributing causes that compromise the iron supply include a low intake with the (often inadequate) diet, consumption of food products that reduce absorption, malnutrition, obesity, ID associated with sport, and, for females, the loss of iron during the menstrual cycle. In adolescents, the prevalence of IDA can be as high as 25-30% in countries with a low to medium social development index.

The diagnostic assessment of ID and IDA in children involves the combination of medical history, physical examination, and laboratory tests. Typical haematological features of IDA are decreased haemoglobin (Hb) levels, decreased mean corpuscular Hb concentration, decreased mean corpuscular volume, significant anisocytosis on a peripheral blood smear, elevated red cell distribution width, as well as decreased reticulocyte Hb concentration and reticulocyte count. Serum ferritin (ferritin) is considered to be the most efficient and cost-effective single indicator of iron status and is also the most widely used, giving a good indication of the size of the iron stores in the absence of infection and inflammation, thus helping to differentiate between IDA and anaemia of inflammation (AI). Ferritin can even be used for diagnosing even mild iron deficiencies.

The MAH seeks approval to extend the currently authorized indication "treatment of iron deficiency" in adults to adolescents aged 12 years and older.

3.1.2. Available therapies and unmet medical need

According to the available therapies the first approach to correct iron deficiencies is related to diet and lifestyle. Mild iron deficiency can be corrected by increasing the intake of iron-rich food (particularly those containing the better-absorbed heam iron), increasing the absorption of iron through avoiding concomitant intake of tea (for example), or concomitant ingestion of vitamin C. Introduction of iron-rich food/formula should be considered for asymptomatic infants aged 6 to 12 months who are at increased risk of iron deficiency anaemia, but infants and toddlers with suspected or proven iron deficiency anaemia should begin oral iron treatment. The ultimate goal of dietary changes or pharmacological treatment is the return of Hb concentrations to the age-appropriate reference range. The duration of treatment should be sufficient to normalize not only the Hb value, but also the iron stores. In the case of individuals with underlying diseases associated with iron deficiency anaemia, the primary disease must also be addressed.

The mainstay of treatment of iron deficiency anaemia is oral iron supplements. Ferrous compounds (sulfate, fumarate, and gluconate), which are available both in solid and liquid forms, are the most common due to the extremely low bioavailability of conventional ferric preparations. The usual adult dose is 180 mg of elemental iron/day in divided doses. Therapeutic doses can range from 100

to 200 mg of elemental iron/day, depending on severity of symptoms, ferritin levels, age of the patient, and gastrointestinal side effects. The daily recommended dose of elemental iron for infants and children is between 3 and 6 mg/kg separated in 2 to 3 intakes and up to a maximum daily dose of 180 or 200 mg (NICE Ferrous sulfate, 2024). Of the available iron formulations, ferrous sulphate is by far the most widely used oral iron product worldwide (Mantadakis et al., 2020), and ferrous salts such as iron sulphate, fumarate, and gluconate remain a mainstay of therapy in absolute ID, mainly because of the lower costs involved for the healthcare systems (Kumar et al., 2022, Camaschella, 2019).

Although oral iron supplementation is the main therapy for most adolescents with ID, in those who have an incomplete response, intravenous iron therapy is increasingly being used. The benefits of IV iron therapy include the rapid repletion of iron stores in addition to the resolution of anaemia, fewer gastrointestinal side effects, and relief for individuals struggling with long-term iron supplementation (Cohen and Powers, 2024).

3.1.3. Main clinical studies

The proposed variation is supported by the results from 2 clinical studies: a Phase 1 study (ST10-01-103) which assessed the pharmacokinetic, pharmacodynamics and safety of ferric maltol capsules in children aged 10 to <18 years with ID, and a Phase 3 study (ST10-01-305) which assessed the pharmacokinetics, and clinical efficacy and safety of ferric maltol oral suspension in children aged 2 to <18 years with IDA. An additional supportive Phase 1 study was also carrier out to compare the therapeutic equivalence between the ferric maltol oral suspension and the existing ferric maltol capsules in adult healthy volunteers under fed and fasted states (ST10-01-104).

The company carried out paediatric clinical studies with an oral suspension as specified in the agreed PIP but opted not to apply for a paediatric indication for this formulation. Instead, the applicant sought an extension of the indication for the hard capsules in adolescents. Results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

3.2. Favourable effects

The LS mean change in Hb concentrations from baseline to Week 12 (main endpoint) was 1.25 g/dL for the ferric maltol OS group in the overall population. Ferric maltol showed a statistically significant (2-sided p-value <0.0001) increase in Hb from baseline to Week 12.

3.3. Uncertainties and limitations about favourable effects

Efficacy and safety data from a Phase III study was performed using an oral suspension formulation and dosing device different to approved capsules. Also, this study was not powered to demonstrate a clinically relevant Hb increase, neither was designed to evaluate non-inferiority with ferrous sulphate solution.

The results of study ST10-01-104 are considered insufficient to establish a bridging between the formulation and mode of administration used in the pivotal study ST10-01-305 (oral suspension in fed state) and the formulation and mode of administration intended to be authorised in children >12 years old with this variation (capsules in fast state).

3.4. Unfavourable effects

Adverse events profile includes mainly gastrointestinal disorders; nausea, abdominal pain, changes in motility (constipation, diarrhoea), discoloured faeces, flatulence distension, discomfort with a very common frequency, and less commonly; vomiting or intestinal bacteria overgrowth (last one not observed in the paediatric studies). Other less commonly observed AEs are headache (nervous system disorders), increase of serum hepatic enzymes (GGT, AP) or TSH (not observed in the paediatric studies), thirst, acne, erythema, pain in extremities or joint stiffness (not reported in the paediatric studies).

In these new submitted clinical safety data, new adverse events related to treatment with ferric maltol have been reported: dizziness, anal incontinence, fatigue, and lethargy were reported in Study ST10-01-103 (capsules) and defecation urgency and aggression in Study ST10-01-305 (OS).

Adverse events related to treatment were mainly under SOC Gastrointestinal disorders, mild in severity, and more frequently reported with capsules than suspension.

Safety reported from study ST10-01-103, showed a significantly higher frequency of GI-AEs related to treatment with the capsules (30 mg/BID) during a much shorter period of exposure which might be related to a higher dose.

3.5. Uncertainties and limitations about unfavourable effects

The limited number of paediatric patients included, together with the differences in bioavailability between the oral suspension and the capsules, introduce uncertainties regarding the magnitude, severity and incidence of adverse events associated with ferric maltol hard capsules in the intended population.

3.6. Effects Table

Table 62. Effects Table for Feraccru for the treatment of iron deficiency in adolescents based on data in all children (mITT older than 2 years of age and younger than 18 years).

Effect	Unit	Treatment Ferric Maltol (N=31)	Control Ferrous sulphate (N=30)	Uncertainties / Strength of evidence	References
Favourable Effects ST10-01-305					
Mean Hb change from baseline to w12	g/dL (+/- SD)	(1.25 [+1.389]) p-value <0.0001	(1.15 [+1.397])	Unc: Study size, Unc: Descriptive only (non-comparative), different formulation used for the treatment arm)	ST10-01-305
Unfavourable Effects					
Gastrointestinal disorders	n (%) e	2 (6.5) 4	3 (10.0) 5	Unc: Underpowered study Unc: Age>10, <18 yo (30mg/BID)	ST10-01-305
Nausea	n (%) e	1 (3.2) 1	2 (6.7) 2		
Abdominal pain	n (%) e	0 (0.0) 0	1 (3.3) 1		
Vomiting	n (%) e	0 (0.0) 0	1 (3.3) 1		
Defaecation urgency	n (%) e	1 (3.2) 1	0 (0.0) 0		
Diarrhoea	n (%) e	1 (3.2) 1	0 (0.0) 0		
Faeces discolored	n (%) e	1 (3.2) 1	0 (0.0) 0		

Effect	Unit	Treatment Ferric Maltol (N=31)	Control Ferrous sulphate (N=30)	Uncertainties / Strength of evidence	References
Nervous system disorders (All Headache)	n (%) e	1 (3.2) 1	0 (0.0) 0		

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The main favourable effect of ferric maltol in the proposed adolescent population is its ability to increase haemoglobin levels. Study ST10-01-305 showed a statistically significant improvement in Hb from baseline to Week 12 in adolescents treated with ferric maltol oral suspension. Supportive pharmacodynamic data show that ferric maltol enables oral iron absorption. Although bioequivalence between the oral suspension used in the pivotal study and the marketed hard capsule formulation was not demonstrated, both formulations were shown to facilitate iron absorption.

Adverse events were mainly gastrointestinal and generally mild to moderate in severity. No new safety signals were identified. The limited size of the paediatric safety database, together with differences in formulation and exposure duration, introduces uncertainty regarding the precise incidence of adverse events during longer-term use of the capsule formulation in adolescents. Overall safety profile is consistent with those expected for oral iron therapies.

3.7.2. Balance of benefits and risks

Meaningful improvements in haemoglobin levels were demonstrated in adolescents treated with ferric maltol using an alternative formulation (oral suspension), supporting its efficacy in iron deficiency anaemia. Although extrapolation to the marketed capsule formulation is associated with limitations, supportive pharmacodynamic data indicate adequate iron absorption. The clinical relevance of the observed differences remains uncertain, considering the substantial interindividual variability typically associated with iron-replacement therapy. Furthermore, considering the wide therapeutic window of ferric maltol, the effectiveness and safety of ferric maltol in adolescents (12–17 years) will be driven by its absorption profile, and treatment response should be monitored using standard biochemical and haematological parameters. Ultimately, iron absorption from capsules under fasted conditions was higher than from the oral suspension, reducing concerns regarding therapeutic efficacy.

The safety profile of ferric maltol in adolescents is acceptable and consistent with that observed in adults and with the known profile of oral iron preparations. Adverse events were mainly gastrointestinal and generally mild to moderate in severity. While some uncertainty remains due to limited paediatric exposure and formulation differences, this is considered acceptable given the known therapeutic window of ferric maltol and consistency with known safety profile of oral iron preparations.

Overall, the benefits of ferric maltol in adolescents aged 12 years and above outweigh the identified risks and remaining uncertainties.

3.7.3. Additional considerations on the benefit-risk balance

N/A

3.8. Conclusions

Results from study ST10-01-305 demonstrate a statistically significant improvement in haemoglobin levels from baseline to Week 12 in paediatric patients treated with ferric maltol oral suspension, confirming effective absorption in this group. Consistent findings from study ST10 1 104 indicate that both the oral suspension and capsule formulations facilitate iron absorption, supporting the use of ferric maltol capsules. In adolescents aged 12–17 years, efficacy is closely associated with absorption profile, and monitoring through standard biochemical and haematological parameters is also recommended. Although differences in absorption between both formulations have been observed, their clinical relevance remains uncertain due to the significant interindividual variability inherent in iron-replacement therapy. Nevertheless, based on robust clinical experience with ferric maltol, no major differences in safety or efficacy are anticipated for adolescents between the ages of 12 and 17, supporting its continued use in this population.
The overall B/R of Feraccru remains positive. The extension of the indication to adolescents in the current variation application is considered approvable.

4. Recommendations

Outcome

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

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a Addition of a new therapeutic indication or modification of an approved one	Variation type II	I and IIIB

Extension of indication to include treatment of paediatric population (adolescents aged 12 years and above) for FERACCRU, based on results from phase 1 study ST10-01-103, phase 3 study ST10-01-305 and a supportive phase 1 study ST10-01-104. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 9.1 of the RMP has also been submitted. In addition, the Marketing authorisation holder (MAH) took the opportunity to update the list of local representatives in the Package Leaflet and to implement editorial changes to the PI. Furthermore, the PI is brought in line with the latest QRD template version 10.4.

The variation leads to amendments to the annexes I, IIIB and to the Risk Management Plan (RMP).

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annexes I, and IIIB and to the Risk Management Plan are recommended.

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

- **Risk management plan (RMP)**

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

In addition, an updated RMP should be submitted:

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

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0503/2023 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.