CLINICAL STUDY PROTOCOL

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

Protocol Number:	ST10-01-305
Test Drug:	Ferric Maltol (ST10)
EudraCT Number:	2018-000078-31
IND Number:	114832
Study Name:	FORTIS
Sponsor:	Shield TX (UK) Limited, Northern Design Centre, Baltic Business Quarter, Gateshead Quays, NE8 3DF United Kingdom
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Confidentiality Statement

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3 ABBREVIATION INDEX

AE	Adverse Event
ALT	Alanine Aminotransferase
ANOVA	Analysis of variance
ANCOVA	Analysis of Covariance
AST	Aspartate Aminotransferase
AUC	Area Under the Plasma Concentration Curve
AUC_{last}	Area under the Plasma Concentration curve from 0 up to the last measurable concentration (non-below) quantification limit after dosing
$AUC_{(0\text{-}inf)}$	Area Under the Plasma Concentration Curve for 0-infinity
BID	Twice Daily
BNF	British National Formulary
BUN	Blood Urea Nitrogen
BP	Blood pressure
C	Celsius
CA	Competent Authority
CD	Crohn's Disease
CI	Confidence Interval
CKD	Chronic Kidney Disease
C_{max}	Maximum Plasma Concentration
CL/F	Apparent Systemic Clearance
COVID-19	Coronavirus disease 2019
CRO	Contract Research Organisation
CS	Clinically Significant
CSR	Clinical Study Report
dL	Deciliter
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Case Report Form
eGFR	Estimated Glomerular Filtration Rate
EMA	European Medicines Agency
ESA	Erythropoiesis Stimulating Agent
EU	European Union
FAS	Full Analysis Set
FDA	Food and Drug Administration
Fe^{3+}	Ferric iron
FOCE	First Order Conditional Estimation
FO	First Order Estimation

GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GGT	Gamma-Glutamyl Transpeptidase
GI	Gastrointestinal
GMP	Good Manufacturing Practice
h	Hour
Hrs	Hours
Hb	Haemoglobin
IBD	Inflammatory Bowel Disease
ICH	International Conference on Harmonisation
ID	Iron Deficiency
IDA	Iron Deficiency Anaemia
IEC	Independent Ethics Committee
IMP	Investigational Medical Product
IMPD	Investigational Medicinal Product Dossier
IND	Investigational New Drug
iPSP	Initial Paediatric Study Plan
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISF	Investigator Site File
ITT	Intention-To-Treat
IUD	Intrauterine Contraceptive Devices
IV	Intravenous
m	Month
MAA	Marketing Authorisation Application
MedDRA	Medical Dictionary for Regulatory Activities
mL	Millilitre
NCA	Non-compartmental analysis
NCS	Non-Clinically Significant
NTBI	Non-Transferrin Bound Iron
OFP	Oral Ferrous Product
OTC	Over-the-counter
PHI	Protected Health Information
PI	Prescribing Information
PIP	Paediatric Investigational Plan
PK	Pharmacokinetics
PP	Per Protocol
PSP	Paediatric Study Plan
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2

SD	Standard Deviation
TEAE	Treatment-emergent Adverse event
TESAE	Treatment-emergent Serious Adverse event
TIBC	Total Iron Binding Capacity
TLAG	The delay between the time of dosing and time of appearance of concentration in the sampling compartment
T_{max}	Time to Maximum Plasma Concentration
TSAT	Transferrin Saturation
UC	Ulcerative Colitis
UIBC	Unsaturated Iron Binding Capacity
US	United States
V/F	Apparent Volume of Distribution
WHO	World Health Organization
yrs	Years

4 SYNOPSIS

Title	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
Protocol Number	ST10-01-305
Study Name	FORTIS
Test Drug	Ferric maltol oral suspension
Comparator	Ferrous sulfate oral liquid
Phase	Phase 3
Sites	Approximately 20 sites
Study Rationale	The existing scientific and clinical experience with ferric maltol in the treatment of IDA in patients with inflammatory bowel disease (IBD) and chronic kidney disease (CKD) supports its further investigation in the treatment of iron deficiency/IDA in children and adolescents, in line with the Paediatric Investigation Plan (PIP) for ferric maltol that has been reviewed and approved by the European Medicines Agency (PIP reference: EMEA-001195-PIP 01-11) and the Paediatric Study Plan (PSP) agreed with the US FDA (IND 114832). Ferric maltol makes iron available in the gastrointestinal tract, providing the iron in a biologically labile form for uptake across duodenal mucosal cells and ultimate haematopoiesis and storage on ferritin. Randomised Phase III studies (ST10-01-301/302) have demonstrated that ferric maltol over a 12-week period effectively increases Hb by over 2 g/dL compared to baseline in iron deficiency anaemic patients with inflammatory bowel disease (IBD). Ferric maltol was also demonstrated to be well tolerated (87% of adult subjects completing 12 weeks of study treatment) and with a side effect profile comparable to the placebo group. These data formed the basis of a Marketing Authorisation

Application (MAA) submission and subsequent EU centralised marketing authorisation.

A randomised Phase III study (ST10-01-303) in 167 adult patients with IDA in Chronic Kidney Disease (CKD) over 16-week double blind phase and an open label 36-week treatment in 125 subjects demonstrated positive safety, efficacy and tolerability. Changes in TSAT, ferritin, and serum iron concentrations indicated an improvement in all iron parameters in the ferric maltol group compared to the placebo group and through the open-label 36-week treatment period to Week 52. Overall, ferric maltol resulted in clinically and statistically significant increase in Hb compared to placebo. These data, together with data from ST10-01-301/302, formed the basis of a New Drug Application (NDA) submission and subsequent US marketing authorisation.

Ferric maltol 30 mg capsules are approved for the treatment of Iron Deficiency in adults taken BID in the EU and Switzerland (Feraccru®) and in the US (Accrufer®).

As part of the paediatric clinical development, two Phase I PK studies were performed. The first one was to understand the kinetics of the absorption of iron and absorption and the elimination of maltol in a paediatric subject group in order to establish a safe and effective dose in children and adolescents, aged 10-17 years. All 3 doses of ferric maltol (7.8 mg, 16.6 mg, 30 mg) were well-tolerated and had a favourable safety profile over a 10-day period. The results from this PK study support the proposed dosing regimen planned for this study.

The second Phase I PK study was performed to compare therapeutic equivalence between the new oral ferric maltol suspension and the existing ferric maltol capsules in healthy adults under fed and fasted states. Both capsule and suspension were readily absorbed under both conditions with mean serum iron concentrations returning to baseline or slightly below at 24 hrs. As expected from the approved Prescribing Information, a food effect was observed for ferric maltol capsule with respect to C_{max} but a definitive food effect was not observed with respect to AUC_{last} and AUC_{inf} (90% CIs span the 80.00-125.00 criteria). Ferric maltol suspension had similar serum iron PK when administered in fasted or fed conditions with respect to C_{max} and AUC_{last}. There were no apparent differences between the formulations (suspension versus capsule) in the number of AEs and no study drug-related TEAEs for either formulation.

Objectives

Primary objective:

1. To compare the safety and gastrointestinal tolerability of ferric maltol oral suspension and ferrous sulfate oral liquid in children and adolescents aged 2 years to 17 years, and assess the safety and tolerability of ferric maltol oral suspension in children 1 month to less than 2 years, in the treatment of iron deficiency anaemia during the 12 weeks treatment period.

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

Secondary objectives:

1. 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), and after twice daily administration for at least 6 days, 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.

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

3. To assess the PK in children aged 1 month to less than 2 years of age after a single dose of ferric maltol oral suspension (Pre-assignment PK visit) and after twice daily administration for at least 6 days, on Visit 3 (PK Day 2) after a single morning dose, through measurement of serum iron, corrected serum iron, transferrin saturation (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 less than 2 years of age after twice daily administration for at least 6 days, on Visit 3 (PK Day 2) after a single morning dose, on serum transferrin, total and unsaturated iron binding capacity (TIBC, UIBC).

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

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

Endpoints

Primary endpoints:

- Safety and gastrointestinal tolerability
  - Treatment emergent Adverse Events (TEAEs)
  - Treatment-emergent Serious Adverse Events (TESAEs)
- Treatment-emergent Adverse Events 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, transferrin, TIBC, 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 12
- Achieving Hb concentration within normal range at Week 12
- Qualitative assessments from subject questionnaires that allow evaluation of the acceptability, palatability and ease of use
- Age 1 month to less than 2 years; maltol and maltol glucuronide in urine from both PK days in children aged 1 month to less than 2 years

Design

The study will comprise of the following stages:

- Screening: To determine subject eligibility for the study

(within 21 days prior to randomisation for each subject)

- Pre-assignment PK phase: only applicable for subjects aged 1 month to less than 2 years. Up to 28 days from Screening.

  All eligible subjects aged 1 month to less than 2 years will enter a Pre-assignment phase, 1-day Pharmacokinetic assessment day following a single dose of ferric maltol oral suspension. After a baseline urine sample is collected, subjects will take a single dose of 0.1 ml/kg ferric maltol suspension under supervision and then further urine samples from three timepoints up to 12 hours.

  The PK samples will be analysed and if evidence of metabolism and elimination of maltol is shown, these subjects will enter the treatment phase and be assigned to the ferric maltol arm.

  Randomised treatment: 12 weeks open label treatment

  - Subjects aged 2-17 will be randomised 1:1 to receive ferric maltol oral suspension or ferrous sulfate oral liquid.
    The first 12 subjects randomised to ferric maltol in each age sub-group (2 – 9 yrs, 10 – 17 yrs, respectively) will enter a Pharmacokinetic phase from Visit 2 (PK Day 1) till Visit 3 (PK Day 2) with 2 PK days. Following baseline pre-dose blood sample, subjects will take a single dose of 2.5 ml (2 yrs- 11 yrs) or 5 ml (12 yrs - 17 yrs) ferric maltol oral suspension under supervision and then further 2 PK blood samples will be taken up to 6 hrs post dose. Following the last scheduled PK sample on PK Day 1 (Visit 2), subjects will be reminded to take their dose twice daily until PK Day 2 (between Day 7-Day 10). On PK Day 2 (Visit 3) subjects should withhold their morning dose until attending their next PK assessments. Same procedure will be repeated for PK assessment as on PK Day 1.
    Following PK Day 2 subjects will continue on treatment until Week 12.
    Once the 12 subjects in each age subgroup (2 - 9 yrs, 10-17 yrs, respectively) have finished their PK visits, they will continue on treatment until week 12. They will not need to have further PK samples taken.
    Subjects randomised to ferrous sulfate oral liquid will not need to complete the PK period, they will remain on oral ferrous sulfate liquid until Week 12.

Ferrous sulfate 125 mg/ml (25 mg elemental iron) or equivalent dose will be used for all children/adolescents. To maximise the iron replenishment for subjects within this group as well; aged 2 - 17 yrs will be dosed 0.24ml (6mg elemental iron) per kg body weight per day, up to a maximum of 8ml given daily in two divided doses.

- Assigned treatment phase: 12 weeks open label treatment for ferric maltol children aged 1 month to less than 2 years

  Once the PK samples collected from the pre-assignment phase have been analysed for subjects aged 1 month to less than 2 years and confirm they can enrol in the randomisation phase, they will be assigned to receive ferric maltol oral suspension and start the 0.1ml/kg/dose, BID (Maximum 2.5ml BID) dose on Visit 2 and continue for 7-10 days. On Visit 3 (PK Day 2), following baseline pre-dose blood sample and urine sample, subjects will take a single dose of 0.1 ml/kg ferric maltol suspension under supervision. Further three PK blood and urine samples will be collected up to 12 hours post dose. Subjects will continue until week 12.

  - End of study: Week 12 visit
- Post-treatment safety follow-up: 10-14 days following study completion of the treatment period or premature discontinuation

Number of Subjects

Approximately 110 male and female children from 1 month to 17 years of age, with iron deficiency anaemia.

Subjects aged 2 to 17 years will be 1:1 randomised to ferric maltol and ferrous sulfate, with 49 subjects in each arm. Subjects then will be further divided into 2 age groups: 2 yrs – 9 yrs and 10 yrs -17 yrs. A minimum of 18 subjects must be recruited into the 2 yrs - 9 yrs and 10 yrs – 17 yrs age groups and a minimum of 25% of either sex must be recruited.

A maximum of 12 subjects will be recruited in the 1 month to less than 2 years age group. If less than 91 subjects in total have been randomized when 32 ferric maltol subjects have completed, then an interim analysis analysis of the primary effectiveness endpoint (change in Hb concentration from baseline to Week 12) will be conducted. If significant, the study will stop recruitment. If not significant, the study will continue (all subjects will be assigned to

ferric maltol) until 54 subjects have been recruited in the ferric maltol arm.

Inclusion Criteria

1. Patient is 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 provide informed consent and the patient should provide assent per local and national requirements.
2. Age ≥1 month and ≤17 years at the time of informed consent
3. Subjects must have iron deficiency anaemia defined by the following criteria, as measured by the central laboratory at the screening visit

   Haemoglobin thresholds define anaemia by age and gender:

   Children (1 m – < 5 yrs) <11.0 g/dl

   Children (5 yrs – < 12 yrs) <11.5 g/dl

   Children (12 yrs) <12.0 g/dl

   Female child (≥13 yrs) <12.0 g/dl

   Male child (≥13 yrs) <13.0 g/dl

   and

   Ferritin thresholds define anaemia by:

   ferritin <30 μg/L,

   or ferritin <50 μg/L with transferrin saturation (TSAT) <20%,
4. Female subjects of childbearing potential must agree to use a highly effective method of contraception (which includes complete abstinence) until study completion and for at least 4 weeks following their final study visit. Highly effective contraception is defined as a method which results in a low failure rate, i.e., less than 1% per year when used consistently and correctly, such as implants, injectables, some intrauterine contraceptive devices (IUDs), a vasectomised partner and oral contraceptive medications.
   The need for contraception and compliance with contraception requirements will be assessed at every visit for adolescent patients, and urine pregnancy testing will be performed at each visit for female subjects of

childbearing potential.

Exclusion Criteria

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

1. Subject with anaemia due to any cause other than iron deficiency, including, but not limited to,
    a. Untreated or untreatable severe malabsorption syndrome
2. Subjects who have received prior to Screening:
    a. Within 28 days intramuscular or intravenous (IV) injection or administration of depot iron preparation.
    b. Within 7 days single agent iron preparations and during the study.
    c. Within 12 weeks of blood transfusion or is scheduled to have blood transfusion or donation during the study period
    d. Within 28 days erythropoiesis stimulating agents and during the study period
    e. Within 14 days COVID-19 vaccination
3. Subjects with vitamin B12 or folic acid deficiency as determined by the central laboratory screening results. Subjects may start vitamin B12 or folate replacement and rescreen after at least 2 weeks.
4. Has concomitant disease that would significantly compromise iron absorption or absorbed iron utilization such as swallowing disorders and/or extensive small bowel resection.
5. History of active peptic ulcer
6. Has chronic renal disease (eGFR <60 mL/min/m^2), as assessed at Screening based on serum creatinine.
7. Known hypersensitivity or allergy to either the active substance or excipients of ferric maltol or ferrous sulfate.
8. Has a known contraindication for treatment with iron preparations, e.g. haemochromatosis, chronic haemolytic disease, sideroblastic anaemia, thalassemia, or lead intoxication induced anaemia.
9. Impaired liver function as indicated by alanine aminotransferase (ALT) or aspartate transaminase (AST)>2.0

times upper normal limit as measured at the Screening visit.

10. Active acute inflammatory disease, including IBD flare or disease exacerbation, which in the opinion of the Investigator, is clinically significant.
11. Active chronic or acute infectious diseases requiring antibiotic treatment.
12. Pregnant or breast feeding.
13. Concomitant medical conditions with extensive active bleeding, other than menstrual cycles; subjects who suffer from menorrhagia may be included at the Investigator's discretion.
14. Scheduled or expected hospitalisation and/or surgery during the course of the study
15. Participation in any other interventional clinical study within 28 days prior to Screening.
16. Diagnosed to be COVID-19 positive by (SARS-CoV-2-RT-PCR positive) within 28 days prior to screening.
17. Cardiovascular, liver, renal, hematologic, psychiatric, neurologic, gastrointestinal, immunologic, endocrine, metabolic, respiratory or central nervous system disease that, in the opinion of the Investigator, may adversely affect the safety of the subject and/or objectives of the study drug or severely limit the lifespan of the subject.
18. Any other unspecified reason that, in the opinion of the Investigator or the Sponsor make the subject unsuitable for enrolment.

Concomitant Medication

Not Permitted:

- Treatment with other single agent oral iron preparations (prescription and non-prescription) within 7 days prior to screening and throughout the study period.
- Treatment with parenteral iron preparations within 28 days prior to screening and throughout the study period.
- Blood transfusions within 12 weeks before screening and during the study.
- Erythropoiesis stimulating agents within 28 days before screening and during the study.

Permitted:

- Immunosuppressants.

- Vitamin B12 and folic acid supplements/replacement are allowed during the study
- Over the Counter (OTC) oral supplements/multivitamin type preparations (including those that contain iron) may be taken, however subjects should keep the same dose during the study
- Oral contraceptives are allowed during the study
- All other concomitant medications must remain stable from Screening and throughout the study

Discontinuation Criteria

Subjects may be discontinued prematurely during the study for the following reasons:

- Withdrawal of informed consent
- >1 g/dl Hb drop from baseline
- Unwillingness or inability to comply with protocol requirements
- Pregnancy or not using a reliable method of birth control (female subject of childbearing potential)
- Use of prohibited concomitant medications
- Serious adverse events that are judged by the Investigator to be related to study treatment
- Blood transfusions for any cause during the study treatment period
- Use of any other single agent prescribed iron medications

The reason for study drug discontinuation and the date of last dose should be recorded in the eCRF. Subjects who discontinue treatment prematurely must return for the Post-treatment safety visit, unless informed consent is withdrawn (and the subject and/or their parent or guardian do not agree to attend this follow-up visit). A subject who meets discontinuation criteria should be discussed on an individual basis with the Medical Monitor.

Investigational Medicinal Product	Ferric maltol oral suspension: oral suspension containing 30 mg elemental iron, in the form of 231.5 mg ferric maltol, in 5 ml suspension. **Ferric maltol** oral suspension will be taken every morning and evening at least 30 minutes after a meal. Dosing will be supervised by the parent/legal guardian for children/adolescents throughout the treatment period and recorded on a dosing diary. Ferric maltol bottles will be labelled for clinical trials use and each bottle will have a unique bottle number which will be utilised in the randomisation procedure. A final eligibility evaluation must be conducted immediately prior to randomisation. Reference safety information will be the Investigator Brochure.
Comparator Therapy	Ferrous sulfate 125 mg/ml (25 mg/ml elemental iron) oral liquid or equivalent dose will be administered under this protocol. Dosing will be supervised by the parent/legal guardian for children/adolescents throughout the treatment period and recorded on a dosing diary. Reference safety information will be the currently approved summary of product characteristics.
Statistical Methods	Safety and gastrointestinal tolerability will be compared between ferric maltol oral suspension and ferrous sulfate oral liquid via summaries of treatment emergent adverse events (TEAEs), treatment emergent serious AEs (TESAEs) and treatment-emergent AEs (TEAEs) leading to premature discontinuation of study drug. Efficacy of ferric maltol will be assessed via the change in Hb concentration from baseline to week 12. If no interim analysis is conducted it will be based on a 95% two-sided confidence interval; If an interim analysis is conducted, a Pocock spending function will be used; the interim analysis will be based on a (100 – 3.45)% two sided confidence interval; if the study does not stop after the interim analysis, the final analysis will be based on a (100 – 2.57)% two sided confidence interval. For the PK analysis, all analytes in serum will be summarised per PK day, for children and adolescents aged 1 month to 17 years receiving ferric maltol.

In addition, all analytes in urine will be summarised per PK day, for children aged 1 month to less than 2 years.

Full details of the statistical analysis, including the analysis of PK endpoints, will be specified in the statistical analysis plan (SAP).

5 BACKGROUND INFORMATION

5.1 OVERVIEW OF DISEASE

In children, iron deficiency anaemia (IDA) should be considered in the presence of tiredness, restlessness, attention-deficit/hyperactivity disorder, irritability, growth retardation, and cognitive and intellectual impairment.

The gold standard for diagnosing IDA is an iron stain of the bone marrow aspirate. Because bone marrow aspiration is too invasive to be used on a regular basis, the accepted and reliable method of diagnosis is based on a combination of parameters, including haematological and iron metabolism indices. Typically, decreased serum concentrations of haemoglobin (Hb) and iron, mean corpuscular volume, ferritin concentration and transferrin saturation are accompanied by increased total iron-binding capacity, transferrin concentration, red blood cell distribution width and erythrocyte protoporphyrin in comparison to age-appropriate reference ranges. Additionally, hypochromasia (meant by an excess of 10% of hypochromic cells) is noted on the peripheral blood smear (Thayu & Mamula, 2005; Mamula *et al*, 2002).

However, diagnosing IDA in the setting of inflammatory disease (e.g. Inflammatory Bowel Disease, IBD) may be complicated due to inflammation. In these circumstances, many of the laboratory measures of iron status may be unreliable, as inflammation influences parameters of iron metabolism (Thayu & Mamula, 2005). For instance, the elevation in transferrin levels typical of iron deficiency may not be found, as patients with low albumin tend also to have low transferrin concentrations. Similarly, serum iron, transferrin saturation (TSAT), total iron binding capacity (TIBC) and zinc protoporphyrin levels are often difficult to interpret in the presence of inflammation. Finally, circulating concentrations of the iron storage protein ferritin, the most accessible and well-known measure of stored iron and the most powerful test for iron deficiency, can be normal or even increased in response to inflammation, as it is an acute phase reactant, even in the presence of severe iron deficiency. Therefore, this parameter may not provide adequate information about the storage compartment in the setting of inflammatory conditions such as IBD, making it a less reliable marker because it adds confusion to the clinical picture.

Accordingly, it has been suggested that specific diagnostic criteria for IDA need to be adapted to the level of inflammation. Thus, in patients without biochemical (C-reactive protein, *etc.*) or clinical (diarrhoea, endoscopic findings, *etc.*) evidence of inflammation, the cut-off point for defining a low level of serum ferritin is <30 µg/L; however, in the presence of inflammation, the lower limit of this parameter consistent with normal iron stores should be increased up to 100 µg/L.

The soluble transferrin receptor, a cell surface glycoprotein, is a truncated fragment of the membrane receptor whose levels are increased when the availability of bone marrow iron stores for erythropoiesis are low, as in IDA. As the circulating concentration is not affected by anaemia of chronic disease, increased concentration of soluble transferrin receptor and the

ratio of soluble transferrin receptor/log ferritin has been proposed for reliable differential diagnosis of these overlapping conditions (Gasche *et al*, 2004). However, this assay is used primarily as a secondary measure, because it is not yet widely available and published data exist only for paediatric IBD (Weiss & Gasche, 2010).

Other aids to the differentiation between IDA and anaemia of chronic disease, essential in order to provide the appropriate treatment, include quantification of reticulocyte haemoglobin and the percentage of hypochromic red cells, which indicate the availability of iron for erythroid progenitors, as well as determination of hepcidin in serum (Weiss & Gasche, 2010). While anaemia of chronic disease is mostly normochromic and normocytic, IDA more frequently presents as microcytic and hypochromic anaemia.

5.2 CURRENT TREATMENT OF DISEASE

There is a clear unmet medical need for an alternative oral treatment for anaemic children, particularly those who are intolerant to ferrous products, to avoid the need for IV iron therapy, regardless of the cause of the iron deficiency. The proposed paediatric indication to be developed for ferric maltol is the treatment of iron deficiency anaemia (IDA).

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 that containing the better-absorbed haem iron), and by increasing the absorption of iron by avoiding concomitant intake of tea (for example) or by concomitant ingestion of vitamin C. Introduction of iron-rich food/formula should be considered for asymptomatic infants aged 6-12 months who are at increased risk of IDA, but infants and toddlers with suspected or proven IDA should begin oral iron treatment (British Columbia Guidelines, 2010). The ultimate goal of dietary changes or pharmacological treatment is the return of haemoglobin concentrations to the age-appropriate reference range. The duration of treatment should be sufficient to normalise not only the haemoglobin value but also the iron stores. In the case of individuals with underlying diseases associated with IDA, the primary disease must also be addressed, of course.

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 two to three intakes and up to a maximum daily dose of 180 mg (British Columbia Guidelines, 2010) or 200 mg (BNF for Children, 2012).

A wide range of iron supplements is available, both on prescription and over-the-counter. Table 1 displays examples of oral iron compounds that are indicated for the treatment of iron-deficiency anaemia in paediatric patients.

Table 1. Example of oral liquid ferrous sulfate for treatment of iron-deficiency states in paediatrics

Product	Iron content	Indication(s)	Paediatric dose
Ironorm® Drops	1 ml of syrup contains the active ingredient Ferrous Sulfate 125 mg (equivalent to 25 mg Iron per ml).	Prevention and treatment of iron deficiency anaemia.	Paediatric: 0.12 ml to 0.24 ml (3 mg – 6 mg elemental iron) per kg body weight, up to a maximum of 8 ml (200 mg elemental iron) given daily in two or three divided doses.
Ferrous sulfate 75 mg/ml (Iron 15 mg/ml) (US OTC Monograph)	Iron 15 mg/ml (as sulfate 75 mg/ 1 ml	Prevention and treatment of iron deficiency anaemia.	Paediatric: 3-6 mg/kg daily in 3 divided doses.

Data sourced from: http://www.medicines.org.uk/EMC/ , Iron Preparations, Oral Monograph for Professionals - Drugs.com

Intramuscular iron compounds are not widely used due to the multiple side effects and the existence of intravenous agents.

Intravenous iron preparations are considered treatment options after the failure of oral therapy or in specific cases in which iron stores and the degree of anaemia warrant acute therapy. They sometimes become necessary in the case of active IBD (flare-ups), for example, because chronic inflammation inhibits iron absorption in the duodenum because of the combined actions of hepcidin and TNF-α (Weiss & Gasche, 2010). The major drawback concerning intravenous iron is that tight physiological regulation of iron absorption is bypassed, so there is an important risk for potential iron overload and associated toxicity.

Blood transfusions are widely used as an immediate intervention for rapid correction of severe or life-threatening anaemia. However, such transfusions do not correct the underlying pathology and do not have a lasting effect. The decision on whether to administer blood should not, therefore, be based only on the haemoglobin level, but should also take clinical symptoms and co-morbidity into account (Weiss & Gasche, 2010).

5.3 OVERVIEW OF TEST PRODUCT

In an effort to overcome the significant challenges of iron substitution with oral ferrous products (OFP), ferric maltol, a chemically stable complex formed between ferric iron (Fe3+) and maltol (3-hydroxy-2-methyl-4-pyrone) was developed. Ferric maltol makes iron available in the GI tract, providing the iron in a biologically labile form for uptake onto transferrin and ferritin and ultimately haematopoiesis and storage on ferritin. European Commission marketing authorisation was granted for ferric maltol in February 2016 and FDA approval was granted on 25 July 2019. The currently approved dose and indication is 30 mg capsule twice daily (BID), taken in the morning and evening on an empty stomach for the treatment of ID in adults.

5.4 RESULTS OF PREVIOUS CLINICAL STUDIES

5.4.1 Phase 3 studies in adults

ST10-01-301/302 study

A Phase 3 study has been completed in adult subjects with IDA and IBD, who are intolerant of oral iron products or are unsuitable for treatment with them (ST10-01-301 and ST10-01-302; Gasche, 2015; Schmidt, 2016), using a dose of 30 mg BID ferric maltol, or 60 mg elemental iron total daily dose. 128 subjects were randomised to 12 weeks of blinded medication (30 mg BID ferric maltol or matched placebo capsule) followed by a 52-week open-label extension period; during which all available subjects received ferric maltol at the same dose. 87% and 82% Ferric Maltol and placebo treated subjects, respectively, completed the 12-week double blind period. The difference between the treatment groups in mean Hb from baseline to week 12 was 2.25 g/dL (ANCOVA $p<0.0001$). Hb increased to normal values at week 12 in 65% of ferric maltol group and 10% of placebo subjects. When the placebo subjects were transferred to ferric maltol treatment in the open-label phase, there was a sharp rise in Hb levels that mirrored the response in the ferric maltol group in the double-blind phase. There were further increases in Hb up to 48 weeks of treatment and no indication of any reduction in efficacy over the full 64-week treatment period.

ST10-01-303 study

A double-blind, randomised, placebo-controlled study in 167 patients with Iron Deficiency Anaemia in Chronic Kidney Disease was performed in a 2:1 randomisation. Ferric maltol 30 mg capsules or matching placebo were administered bid for 16 weeks followed by open-label treatment with ferric maltol 30 mg capsules for up to an additional 36 weeks.

167 patients with IDA in Chronic Kidney Disease (CKD) over 16-week double blind phase and an open label 36-week treatment in 125 subjects demonstrated positive safety, efficacy and tolerability. Changes in TSAT, ferritin, and serum iron concentrations indicated an

improvement in all iron parameters in the ferric maltol group compared to the placebo group and through the open-label 36-week treatment period to Week 52.

The efficacy parameters in subjects originally in the placebo group moving to the ferric maltol group during the open-label 36-week treatment period mirrored the changes seen in the ferric maltol group patients during the double-blind 16-week treatment period. No clinically significant accumulation was observed for either plasma maltol or plasma maltol glucuronide. The results indicated that subjects with eGFR >30 mL/min/1.73 m^2 may experience a greater treatment effect. Indeed, this would be expected due to a likely lower erythropoietin response to anaemia in the subjects with more severe renal impairment.

The most common system organ class of study drug related TEAEs during the double-blind and open-label period was GI disorders. Only three subjects experienced study drug-related adverse events that led to discontinuation in the double-blind phase and 5 subjects in the open-label phase. Changes in laboratory values were mainly consistent with the disease progression and all of them were considered as not related to study drug.

In general, ferric maltol was well tolerated with only minor differences in the safety profile and overall GI side effects compared to placebo.

5.4.2 Phase I studies in adults

ST10-01-101 study

Another open-label, randomised Phase 1 study evaluated the pharmacokinetics of ferric maltol and its effect on iron indices in patients with iron deficiency (with or without anaemia). 24 subjects received ferric maltol 30, 60, or 90 mg BID over an 8-day period. PK and iron uptake were assessed on Days 1 and 8. Ferric maltol showed predictable pharmacokinetics, no accumulation over 7 days, and improvements in iron uptake across the dose range 30–90 mg BID (Bokemeyer, 2016).

The PK data from this study are consistent with previous data indicating that maltol is rapidly glucuronidated and renally excreted after ferric maltol dosing, while iron is independently absorbed. Across the three dosing regimens investigated, exposure to maltol glucuronide increased dose proportionally. Serum iron concentrations and TSAT values generally increased with higher doses, but there was no clear relationship between these parameters and exposure to maltol or maltol glucuronide. Higher NTBI levels were detected in the higher dosing regimens. Although the frequency of AEs was also higher with these dosing regimens, there is no evidence that this was a consequence of elevated NTBI in these subjects. The reported AEs were consistent with the established safety profile of ST10.

ST10-01-102 study

The pharmacokinetics (PK) and iron uptake of 30 mg ferric maltol BID were confirmed in a cohort of 15 IBD patients participating in the open-label phase of studies ST10-01-301 and ST10-01-302 (Shield TX, data on file for sub-study ST10-01-102). Plasma concentrations of

maltol above the limit of assay detection were transiently observed between 15 min and 4 h after dosing (mean C_{max} 67.3 ng/mL; median T_{max} 1.0 h; mean AUC 136 h*ng/mL; mean t 1/2 term 0.8 h). However, consistent with earlier studies of ferric maltol, maltol glucuronide predominated in plasma (mean C_{max} 4677 ng/mL; median T_{max} 1.0 h; mean AUC 9651h*ng/mL and mean t ½ term 1.1 h). Maximal change in serum iron and TSAT was observed 2 h after dosing, however in many subjects it was apparent from the TSAT rises that iron uptake was occurring from 30 minutes. The inter-subject variability for AUC of both maltol and maltol-glucuronide in this cohort was low (approximately 27%).

ST10-01-104 study

An open-label, Phase I, randomised, 4-way crossover study was completed to evaluate the PK and iron absorption after a single 30 mg dose of ferric maltol administered as a capsule or oral suspension (fasted and fed condition) via primary parameters C_{max} and AUC_{last}.

Both capsule and suspension of ferric maltol in fasted and fed conditions were readily absorbed with mean serum iron concentrations returning to baseline or slightly below at 24 hours.

For the fasted condition, comparing the suspension versus the capsule, the ratios of C_{max}, AUC_{last}, and AUC_{inf} geometric LS means (90% Confidence Interval (CI)) for serum iron findings indicated that, in the fasted condition, ferric maltol capsule and suspension had different PK with respect to C_{max} but a definitive difference in PK was not observed with respect to AUC_{last} and AUC_{inf}.

For the suspension formulation comparing fasted versus fed conditions, the ratios of C_{max}, AUC_{last}, and AUC_{inf} geometric LS means (90% CI) findings indicate that the ferric maltol suspension had similar PK when administered in fasted or fed conditions with respect to C_{max} and AUC_{last}.

For the fed condition, comparing the suspension versus capsule the ratios of C_{max}, AUC_{last}, and AUC_{inf} geometric LS means (90% CI) for serum iron indicate that, in the fed condition, ferric maltol capsule and suspension had similar PK with respect to C_{max} and AUC_{last} and a definitive difference in PK was not observed for AUC_{inf}.

The baseline corrected serum iron and TSAT, were consistent with the primary endpoint findings, although the formulation effect and capsule food effect differences were more marked with baseline corrected serum iron.

It is noted that the overall exposure of maltol and maltol glucuronide are less influenced by physiological iron status compared to the iron PK parameters.

There were no apparent differences between the formulations (suspension versus capsule) in the number of AEs and no study drug-related TEAEs were reported for either formulation.

5.4.3 Phase I study in children and adolescents

ST10-01-103 study

An open-label, randomised, Phase I study was completed in 37 children and adolescents (aged 10-17) after BID oral doses of 7.8 mg, 16.6 mg or 30 mg ferric maltol (ST10) over a 10 days treatment period. Of the 37 subjects, there were 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 primary objective of the study was to assess the PK and iron uptake of these 3 doses, through measurement of serum iron, TSAT and plasma concentrations of maltol and maltol glucuronide.

A one-compartment model with first order absorption with TLAG and first order elimination kinetics describes plasma maltol glucuronide PK for ferric maltol according to the current data. No covariates tested in this analysis had an effect on KA, TLAG, CL/F, and Vz/F of maltol glucuronide. The exposure of maltol glucuronide (C_{max} and 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 C_{max} of plasma maltol glucuronide on Day 10 slightly deviated from dose proportionality.

The exposure of iron (C_{max} and AUCs) was estimated using the NCA 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. The 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.

A direct effect linear model without intercept fit serum TSAT according to the current data. The predicted response parameters of TSAT (C_{max}, AUC_{Above_B}, etc) were estimated using the NCA method with the predicted TSAT. The response-time profile had a similar pattern with iron-time profile.

Safety was assessed by evaluating TEAEs, SAEs, physical examinations, vital signs, 12-lead ECGs, and laboratory parameters. In total, 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. One (7.7%) subject in the 16.6 mg dose group experienced a TEAE of tonsillitis that led to withdrawal of study drug and study discontinuation; this event was considered by the Investigator to be moderate in severity and not related to study drug. No subjects died or experienced an SAE during the study.

No clinically meaningful differences in mean changes from baseline in haematology or clinical chemistry parameters were noted between dose groups. Overall, individual shifts from

normal to abnormal in haematology and clinical chemistry laboratory parameters were considered as not related to study drug and not clinically significant.

No subjects had laboratory abnormalities that were considered as TEAEs, SAEs, or led to withdrawal of study drug or study discontinuation. There were no clinically meaningful mean changes from baseline in vital signs results or ECG parameters, and no subjects had clinically significant abnormal ECG results. There was 1 abnormal, clinically significant physical examination finding for the subject who had a TEAE of tonsillitis that led to withdrawal of study drug and study discontinuation.

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

Refer to the Investigator Brochure for further information.

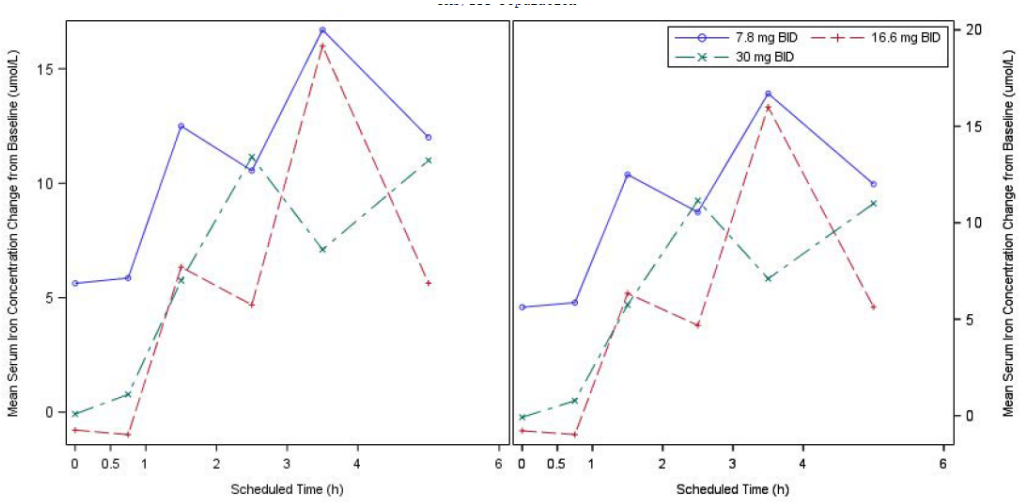
5.5 DOSE SELECTION AND RATIONALE FOR THE STUDY

Clinical studies conducted to date provide evidence for the therapeutic potential of ferric maltol in adult patients with IDA in IBD, CKD and other causes of IDA. The performed Phase 1 and Phase 3 studies demonstrate that ferric maltol is effective and well-tolerated in patients who are intolerant of OFPs or are unsuitable for other treatments as well at a dose of 30 mg (elemental iron) BID in adults aged 18 and over. Additional data has shown increased absorption from 60 mg dosing, but no additional increase at 90 mg, suggesting a saturable absorption mechanism. (Study ST10-01-101).

The existing scientific and clinical experience with ferric maltol in the treatment of IDA in patients with IBD supports its further investigation in the treatment of iron deficiency/IDA in children and adolescents, in line with the Paediatric Investigation Plan (PIP) for ferric maltol that has been reviewed and approved by the European Medicines Agency (PIP reference: EMEA-001195-PIP 01-11) and FDA (IND 114832).

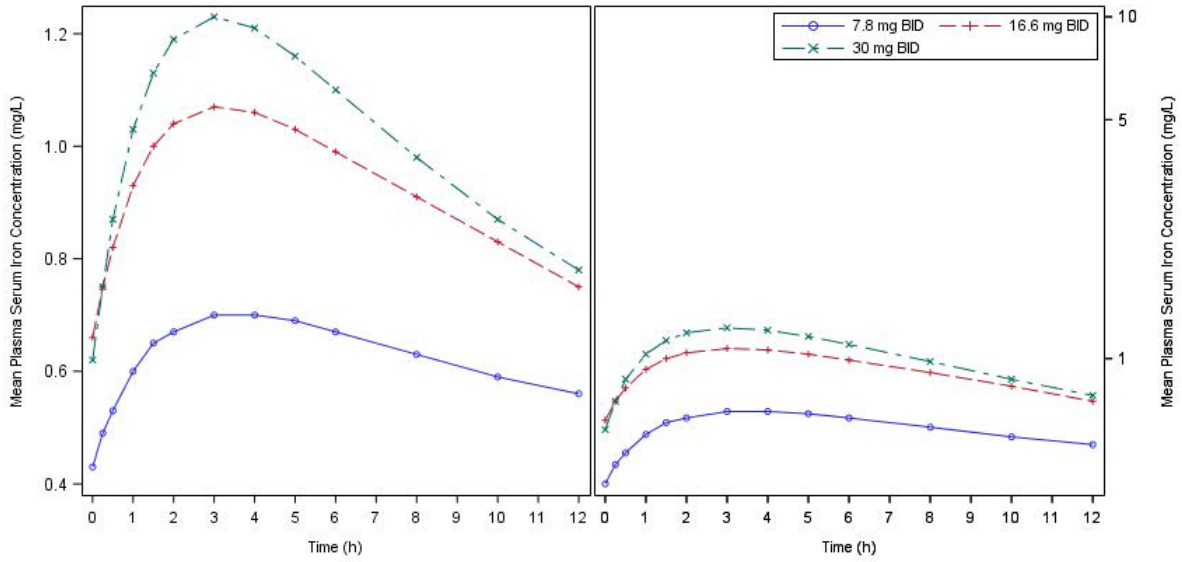
The initial PIP specified clinical study ST10-01-103 assessed the pharmacokinetics (PK) and iron uptake of ferric maltol (ST10) in children and adolescents (aged 10 to 17 years) after twice daily (BID) oral doses of 7.8 mg, 16.6 mg, or 30 mg for 9 days (Days 1 to 9) and a single morning dose on Day 10 through measurement of serum iron, transferrin saturation (TSAT), and plasma concentrations of maltol and maltol glucuronide.

Figure 1. presents a plot of mean serum iron concentrations change from baseline by dose group on linear and semi-logarithmic scales on Day 10 for the FAS/ITT Population



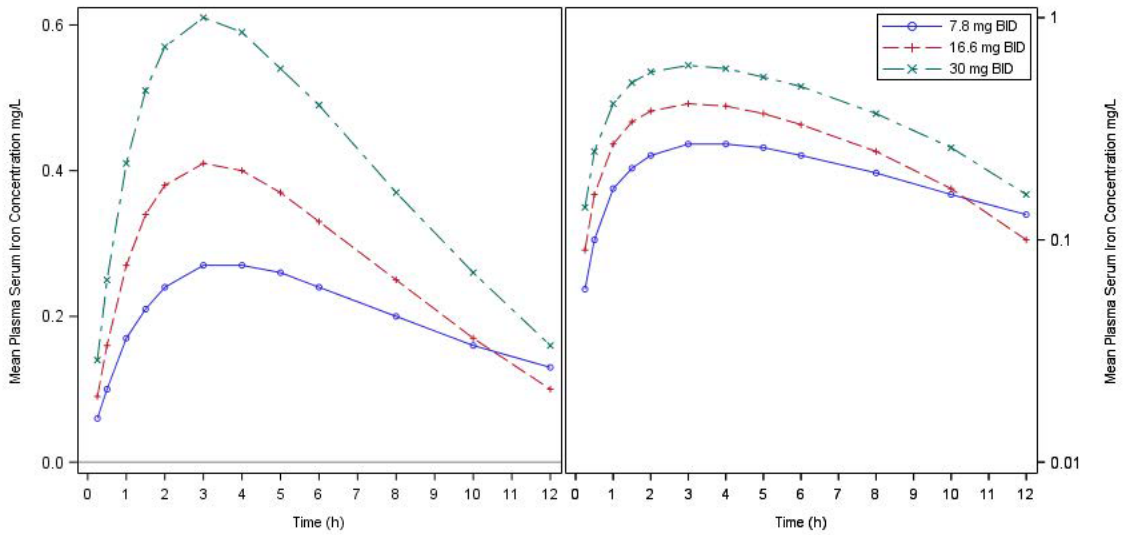
The scheduled time was chosen from the intermediate time point of the particular window. For example, pre-dose was deemed as 0 h, and '0.5 - 1 h' was deemed as 0.75 h. Baseline was defined as the last value observed before the first dose.Lower limit of quantitation for serum iron = 1.8 µmol/L.

Figure 2. 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

Figure 3. 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



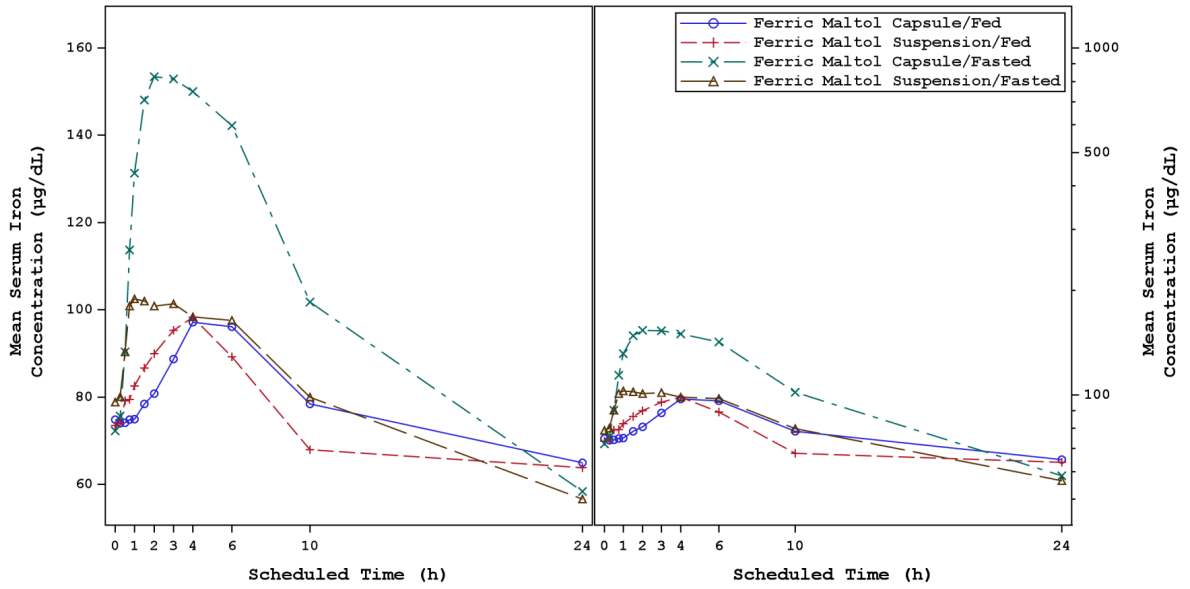
Baseline was defined as the predicted Day 1 pre-dose concentration.

Lower limit of quantitation for serum iron = 0.1 mg/L

The predicted iron concentration PK parameters showed that iron uptake increases with dosage but under proportionally at Day 1, while the predicted maltol glucuronide PK parameter results showed dose proportionality exists. The dissociation of ferric maltol complexes may explain the different PK profiles of iron and maltol glucuronide.

The most recent PK study has shown comparing the ferric maltol suspension and capsule in fed and fasted that serum iron concentration has returned to baseline or slightly below at 24 hours. After 2 hours post-dose, the mean serum iron concentration of the ferric maltol capsule/fasted condition was higher than all other treatments studied,

Figure 4 Plot of Mean Serum Iron Concentration (µg/dL) by Formulation/Condition Group on Linear Scale and Semi-Log Scale – FAS Population



To assess the impact of formulation of ferric maltol on the PK of serum iron, an 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), and period as fixed effects, and subjects nested within a sequence as a random effect.

For the fasted condition, the ratios of C_{max}, AUC_{last}, and AUC_{inf} geometric LS means (90% CI) for serum iron were 69.94% (61.75, 79.23), 77.54% (70.38, 85.42), and 78.16% (65.64, 93.06), respectively, comparing the suspension versus capsule. The geometric LS mean of C_{max} in the ferric maltol suspension/fasted group was lower than in the ferric maltol capsule/fasted group and the 90% CI was below 80%. These findings indicate that, in the fasted condition, ferric maltol capsule and suspension had different PK with respect to C_{max} but a definitive difference in PK was not observed with respect to $AUCl_{ast}$ and AUC_{inf}.

For the fed condition, the ratios of C_{max}, AUC_{last}, and AUC_{inf} geometric LS means (90% CI) for serum iron were 99.11% (87.50, 112.27), 96.99% (88.04, 106.86), and 111.86% (87.36, 143.23), respectively, comparing the suspension versus capsule. These findings indicate that, in the fed condition, ferric maltol capsule and suspension had similar PK with respect to C_{max} and AUC_{last} and a definitive difference in PK was not observed for AUC_{inf}.

To assess the impact of a test meal on the PK of ferric maltol, an 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), and period as fixed effects, and subjects nested within a sequence as a random effect.

For the capsule formulation, the ratios of C_{max}, AUC_{last}, and AUC_{inf} geometric LS means (90% CI) were 147.27% (130.01, 166.81), 134.25% (121.86, 147.91), and 137.53% (114.45, 165.26), respectively, comparing fasted versus fed conditions. These findings indicate that a food effect was observed for ferric maltol capsule with respect to C_{max} but a definitive food effect was not observed with respect to AUC_{last} and AUC_{inf}.

For the suspension formulation, the ratios of C_{max}, AUC_{last}, and AUC_{inf} geometric LS means (90% CI) were 103.93% (91.75, 117.72), 107.32% (97.41, 118.24), and 96.10% (76.45, 120.79), respectively, comparing fasted versus fed conditions. These findings indicate that the ferric maltol suspension had similar PK when administered in fasted or fed conditions with respect to C_{max} and AUC_{last}.

This Phase 3 open-label, comparative study is in the Paediatric Investigational Plan (PIP), designed to evaluate the safety, efficacy and tolerability of ferric maltol oral suspension compared to ferrous sulfate oral liquid over a 12 weeks treatment period in children and adolescents aged between 2 and 17 years. In order to comply with the iPSP agreed with FDA, children from 1 month to less than 2 years will be included in only the ferric maltol group. Due to the isoform of the glucuronidation enzyme, infants will initially receive only a single dose of ferric maltol. If the data from the single dose in this age group shows evidence of absorption of serum iron and elimination of maltol, subjects will enter a Treatment phase and be assigned to the ferric maltol arm. Subjects will be eligible to enter the treatment phase if the maltol level returns to baseline, or to a low level, confirming there is no accumulation of maltol or maltol glucuronide and there is evidence of iron absorption.

During early infancy, iron requirements are met by the little iron contained in the human milk. (FAO/WHO, 2004). The need for iron rises markedly 4-6 months after birth and amounts to about 0.7-0.9 mg/day during the remaining part of the first year. Between 1 and 6 years of age, the body iron content is again doubled. Iron requirements are also very high in adolescents, particularly during the period of growth spurt. Girls usually have their growth spurt before menarche, but growth is not finished at that time. In boys there is a marked increase in haemoglobin mass and concentration during puberty. In this stage, iron requirements increase to a level above the average iron requirements in menstruating women.

Age/sex	mg/day[b]
4–12 months	0.96
13–24 months	0.61
2–5 years	0.70
6–11 years	1.17
12–16 years (girls)	2.02
12–16 years (boys)	1.82
Adult males	
Pregnant women[c]	1.14
First trimester	0.8
Second and third trimester	6.3
Lactating women	1.31
Menstruating women	2.38
Postmenopausal women	0.96

[a] Absorbed iron is the fraction that passes from the gastrointestinal tract into the body for further use. [b] Calculated on the basis of median weight for age. [c] Requirements during pregnancy depend on the woman's iron status prior to pregnancy

Iron requirements of 97.5% of individuals in terms of absorbed iron, by age group and sex (World Health Organization, 1989).

The average adult stores about 1-3 g of iron in his or her body. A fine balance between dietary uptake and loss maintains this balance. About 1 mg of iron is lost each day through sloughing of cells from skin and mucosal surfaces, including the lining of the gastrointestinal tract (Cook et al, 1986). Menstruation increases the average daily iron loss to about 2 mg per day in premenopausal female adults (Bothwell, 1982). The augmentation of body mass during neonatal and childhood growth spurts transiently and boosts iron requirements (Gibson, 1988). Many disease states increase the daily iron requirement by causing increased blood loss, reduced iron absorption or by affecting iron utilization.

Physiologically, iron stores are managed through active absorption of dietary iron that matches loss. Any additional iron in the gastrointestinal tract that is not required is passed in the faeces. This ensures that there is no iron overload, which can be potentially toxic.

As the physiological mechanisms of absorption of iron ensure that only the required amount of iron is absorbed and the fact that this required amount changes with disease state and level of iron deficiency, the principles of dosing choice are to ensure sufficient iron levels to address the physiological need and to minimise the gastrointestinal effects that are frequently a challenge to adherence.

Available iron salts for children are dosed at up to 200 mg of elemental iron from 1 year of age up to 17 years (BNF for Children, 2012) with higher exposure than in adults. However, the

availability of iron salt preparations can be less than 10% of the ingested dose (Harvey *et al*, 1998).

As the basal iron requirement for adolescents/children are raised, it is proposed that ferric maltol is dosed at the adult dose level of 30 mg BID from ages 12 to 17 years. For those aged 2 - 11 years, a lower dose of 15 mg BID will provide approximately 7.2 mg of potential iron available for absorption (based on 24% availability) which will ensure that the basal requirements plus additional disease related needs are available.

For infants under 2 years of age, dosing by weight is proposed at a level of 0.6 mg of elemental iron per kg BID.

Ferrous sulfate oral liquid 125 mg/ml (25 mg/ml elemental iron) or equivalent dose will be administered under this protocol. To maximise the iron replenishment for subjects within the ferrous sulfate group as well; aged 2-17 years will be dosed 0.24ml (6mg elemental iron) per kg body weight, up to a maximum of 8ml given daily in two divided doses.

This Phase 3 study will generate data to provide an alternative to existing oral ferrous products in treating children with IDA both from a patient/physician perspective but also wider healthcare decision making.

5.5.1 Study Population

The study population will be males and females, aged 1 month - 17 years at time of screening.

5.5.2 Study Treatment and Duration

Ferric maltol group:

Subjects aged 1 month to 17 years randomised or assigned to oral ferric maltol will receive the following dosing for the duration of the study (12 weeks), including 2 PK days:

Age	Dose	Suspension equivalent
1 month to < 2 years	0.6 mg/kg/dose, BID	0.1 ml/kg/dose, BID
2 years to 11 years	15 mg per dose, BID	2.5 ml per dose, BID
12 years to 17 years	30 mg per dose, BID	5 ml per dose, BID

In the event of an administered dose not being consumed or partially consumed by the patient this will be noted as a missed dose and will not be repeated. Clear instructions will be provided to the parents/guardians who are supervising the drug administration and dosing diary.

To give the right dose of study treatment to the infant, the adaptor and oral syringe provided must be used. The parents/guardians should be instructed to gently invert the bottle (maximum 5 times) prior to preparing the dose.

After drawing up the required dose from the bottle using the oral syringe, the parents/guardians should put the tip of the syringe into the infant's mouth and push the plunger to slowly push small amounts of the study product into the infant's mouth at a time.

The parents/guardians should allow the infant to swallow the study product before they push the syringe again. This step should be repeated until the whole dose has been administered.

Patient weight should be recorded at each clinic visit and drug dosing administered as per last clinic visit weight.

Ferrous sulfate group:

Subjects aged 2 years to 17 years randomised to oral ferrous sulfate will receive the following dosing for the duration of the study (12 weeks):

- 2 yrs -17 yrs: 0.24ml per kg body weight, up to a maximum of 8ml given daily in two divided doses.

Age	Dose	Liquid equivalent
2 years to 17 years	3 mg/kg/dose, BID	0.12 ml/kg/dose, BID

In the event of an administered dose not being consumed or partially consumed by the patient this will be noted as a missed dose and will not be repeated. Clear instructions will be provided to the parents/guardians who are supervising the drug administration and dosing diary.

Patient weight should be recorded at each clinic visit and drug dosing administered as per last clinic visit weight.

5.6 RISK-BENEFIT EVALUATION

The safety of ferric maltol in adult subjects with IDA and IBD has been established in a well-controlled Phase 3 clinical study with data having been collected over 12 weeks on 128 subjects in the double-blind phase and for over 12 months in some subjects in open-label follow-up (Gasche, 2015; Schmidt, 2016). IBD patients are reported as being very sensitive and largely intolerant to oral ferrous products, and so if non-IBD paediatric subjects are recruited into this Phase 3 study, it is anticipated their tolerability to ferric maltol will be comparable to the existing adult data. The safety and tolerability of ferric maltol in adults with IDA in IBD study was positive, with the overall AE rate in ferric maltol being comparable to the placebo group over a 12-week period; 87% of ferric maltol subjects remained in the study. This data is supported by smaller published clinical studies using higher doses of ferric maltol and by preclinical studies testing ferric maltol in rodents (see Investigator's Brochure).

The safety and tolerability study with ferric maltol in 167 subjects with CKD and IDA have been positive with data collected over the 52 weeks period. The most common system organ class of study drug related TEAEs during the double-blind and open-label period was GI disorders. Only three subjects experienced study drug-related adverse events that led to discontinuation in the double-blind phase and 5 subjects in the open-label phase. Changes in laboratory values were mainly consistent with the disease progression and all of them were considered as not related to study drug. In general, ferric maltol was well tolerated with only minor differences in the safety profile and overall GI side effects compared to placebo.

In the Phase 1 paediatric PK study, children and adolescents aged 10 to 17 years were administered up to the adult dose of 30 mg BID. Given physiological control of intestinal absorption of iron uptake through the hepcidin pathway and considering a total daily dose of 60 mg iron is within the approved dosage regimen for oral ferrous products in older children, iron overload in a 10-day exposure was considered not to be a risk. Furthermore, in children the metabolism of maltol through glucuronidation in the liver was similar to adults. There was not any great individual clinical benefit over 10 days of ferric maltol therapy, although the information gathered was very important in establishing the doses to be studied in this subsequent Phase 3 paediatric efficacy and safety study in IDA subjects.

Doses chosen for this phase 3 study were based on the first Paediatric PK study and a new age-appropriate formulation has been developed. The study population will recruit subjects with iron deficiency anaemia who are otherwise generally well. The study population will include both female and male subjects aged 1 month - 17 years age range.

From the Phase I PK adult study comparing the ferric maltol suspension and ferric maltol capsule under fed and fasted condition, information was gathered that in the fed condition, ferric maltol capsule and suspension had similar PK with respect to serum iron C_{max} and AUC_{last}.

The C_{max} data suggest that there might be a formulation effect in the fasted state in favor of the capsule with respect to serum iron levels but this was not definitively supported by AUC_{last} and AUCinf comparisons, nor was this supported by the maltol and maltol glucuronide PK.

Ferric maltol suspension had similar PK when administered in fasted or fed conditions with respect to Cmax and AUClast. Nevertheless, we advise ferric maltol should be taken at least 30 mins after meal.

PK assessments will take place for the first 12 subjects in age group 2 yrs -17 yrs) and all 1 m - < 2 yrs assigned to ferric maltol to assess the efficacy, the safety and tolerability of ferric maltol.

This study`s procedures risks are related to IV cannulation and blood sampling, with fainting, minor bleeding and bruising regarded as the main risks. Total blood loss as a result of phlebotomy will be approximately 33.8 ml in subject group 1 m to less than 2 years and 40 ml in the 2 to 17 yrs age group.

There is no appreciable risk from urine collection.

If the subject`s Hb drops by >1 g/dl from baseline, each individual case will be discussed with the Medical Monitor prior to study discontinuation.

Pregnancy testing will ensure that pregnant female subjects do not enter the study, and that any subjects who become pregnant during the study are detected.

The comparator product, ferrous sulfate liquid, is available as various proprietary and generic formulations in the EU, UK and US for the treatment of ID/IDA. The proposed dosage is in accordance with the US OTC monograph and UK Prescribing Information for oral iron preparations. According to UK Prescribing Information and the US OTC monograph, the recommended dosage for the therapeutic use of ferrous sulfate is 3-6 mg/kg with maximum daily dose of up to 8 ml.

Assessment of Patient Safety and Benefit conducting this study during coronavirus (COVID-19) Pandemic

The start of this study will be after the vaccination programme for COVID-19 has started in all countries being considered for clinical study investigational sites. Patients with a significant underlying health condition that could also be eligible for this study will be prioritised to receive a vaccination; as have healthcare staff. For patients that are unable to be vaccinated for health or other reasons, we would expect the Investigator to make a judgement with the patient/carer about the benefits and added risks of participation. Mandating COVID-19 vaccination as an eligibility criteria could act to systematically exclude some groups of patients from this study. Visits by patients and carers to healthcare facilities should always have a purpose and benefit to the patient, and with the introduction of additional sanitation and infection control practices at study sites the risks of cross-infection have not been eliminated completely but are considered to be very low.

The oral iron replacement treatments in this study are not contraindicated or cautioned against in the prescribing information for currently available vaccines; however we do advise that a 14 day period has elapsed from the last COVID-19 vaccination before a patients starts participation in this study (to avoid side effects overlapping with study participation).

This is a randomised study, with two active treatments, both with known benefit and side-effect profile in adults and children; and monitoring of clinical effect on iron deficiency anaemia. As all participants in this study are receiving active treatment, the risk to the patient is that one treatment is less effective than correcting IDA compared to the other, or that rate and seriousness of side effects are not the same. Infection with COVID-19 during participation in this study would have minimal additional risk, compared to infection out with the study

The number and frequency of site visits in this study has been reviewed and reduced to what is considered a safe minimum; based on collection of clinical samples, clinical evaluation, collection of adverse events and distribution/collection of study drug. As this is also a PK

study it is unavoidable that patients have to visit the clinic for blood samples – phlebotomy in these paediatric subjects at home has been considered and was not thought appropriate. Some aspects of patient care are being managed through telephone calls (i.e. end of study visit/follow up).

Summary

There is considered to be a good balance of risks and potential benefits in either treatment arm, justifying randomisation of subjects within this open-label clinical study.

The risk to the subject related to study procedures has been assessed as very low and considered positive.

Refer to the Investigator's Brochure for further details on risk/benefit assessment.

6 STUDY OBJECTIVES AND ENDPOINTS

6.1 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 years to 17 years and assess the safety and tolerability of ferric maltol oral suspension in children 1 month to less than 2 years, in the treatment of iron deficiency anaemia during the 12 weeks treatment period.

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

6.2 SECONDARY OBJECTIVES:

1. 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), and after twice daily administration for at least 6 days, 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

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

3. To assess the PK, in children aged 1 month to less than 2 years of age after a single dose of ferric maltol oral suspension (Pre-assignment PK visit) and after twice daily administration for at least 6 days, on Visit 3 (PK Day 2), after a single morning dose, through measurement of serum iron, corrected serum iron, transferrin saturation (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 less than 2 years of age after twice daily administration for at least 6 days, on Visit 3 (PK Day 2) after a single morning dose, on serum transferrin, total and unsaturated iron binding capacity (TIBC, UIBC)

5. To assess the effect, in children aged 2 to 17 after a single dose of ferric maltol suspension Visit 2 (PK Day 1), and after twice daily administration for at least 6 days, on Visit 3 (PK Day 2) after a single morning dose, on serum transferrin, total and unsaturated iron binding capacity (TIBC, UIBC).

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

6.3 PRIMARY ENDPOINTS

- Safety and gastrointestinal tolerability
  - Treatment emergent Adverse Events (TEAE)
  - Treatment-emergent Serious Adverse Events (TESAEs) Treatment-emergent Adverse Events leading to premature discontinuation of study drug/PK assessments from baseline to Week 12
- - Change in Hb concentration from baseline to Week 12

6.4 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 12

- Achieving Hb concentration within normal range at Week 12

- Qualitative assessments from subject questionnaires that allow evaluation of the acceptability, palatability and ease of use

- Age 1 month to less than 2 years; maltol and maltol glucuronide in urine from both PK days in children aged 1 month to less than 2 years

6.5 EXPLORATORY ENDPOINTS

Not Applicable

7 INVESTIGATIONAL PLAN

7.1 STUDY OVERVIEW

This is a Phase 3, randomised, open-label, active controlled, multicentre, comparative study between ferric maltol oral suspension and ferrous sulfate oral liquid. 98 eligible subjects aged 2 to 17 years will be randomised at a ratio of 1:1 to ferric maltol or ferrous sulfate for a 12 weeks treatment period and a maximum of 12 subjects aged 1 month to < 2 years will be assigned to the ferric maltol group.

The study will comprise of the following stages:

- Screening: To determine subject eligibility for the study (within 21 days prior to the randomisation for each subject)
- Pre-assignment PK phase: only applicable for subjects aged 1 month to less than 2 years. Up to 28 days from Screening visit.

  All eligible subjects aged 1 month to less than 2 years will enter a Pre-assignment phase, 1-day Pharmacokinetic assessment day following a single dose of ferric maltol oral suspension. After a baseline pre-dose urine sample, subjects will take a single dose of 0.1 ml/kg ferric maltol suspension under supervision and then further urine samples from three timepoints up to 12 hours.

  The PK samples will be analysed and if evidence of metabolism and elimination of maltol is shown, these subjects will enter the treatment phase and be assigned to the ferric maltol arm. Subjects will be eligible to enter the treatment phase if the maltol level returns to baseline, or to a level confirming there is no accumulation of maltol or maltol glucuronide.
- Randomised treatment: 12 weeks open label treatment

  Subjects aged 2-17 will be randomised 1:1 to receive ferric maltol oral suspension or ferrous sulfate oral liquid. The first 12 subjects randomised to ferric maltol in each age sub-groups (2 – 9 yrs, 10 – 17 yrs, respectively) will enter a Pharmacokinetic phase from Visit 2 (PK Day 1) till Visit 3 (PK Day 2) with 2 PK days. Following baseline pre-dose blood sample, subjects will take a single dose of 2.5 ml (2 yrs -11 yrs) or 5 ml (12 yrs - 17 yrs) ferric maltol oral suspension under supervision and then a further 2 PK blood samples will be taken up to 6 hours. Following the last scheduled PK sample on PK Day 1 (Visit 2), subjects will be reminded to take their dose twice daily until PK Day 2 (between Day 7-Day 10). On PK Day 2 (Visit 3) subjects should withhold their morning dose until attending their second PK assessment day. Same procedure will be repeated for PK assessment as on PK Day 1. Following PK Day 2, subjects will continue treatment until Week 12.

Once the 12 subjects in each age subgroup (2 - 9 yrs, 10-17 yrs, respectively) have finished their PK visits, they will continue on treatment until week 12. Further subjects will not need to have PK samples taken.

Subjects randomised to ferrous sulfate oral liquid will not need to complete the PK period, they will remain on oral ferrous sulfate until Week 12. Ferrous sulfate 125 mg/ml (25 mg/ml elemental iron) or equivalent dose will be used for all children/adolescents. To maximise the iron replenishment for subjects within this group as well; aged 2 - 17 yrs will be dosed 0.24ml (6mg elemental iron) per kg body weight, up to a maximum of 8ml given daily in two divided doses.

- Assigned treatment phase: 12 weeks open label treatment for ferric maltol children aged 1 month to less than 2 years

  Once the PK samples have been analysed for subjects aged 1 month to less than 2 years and they can enrol in the randomisation phase, they will be assigned to receive ferric maltol oral suspension and start the 0.1 ml/kg/dose, BID on Visit 2 for 7-10 days. On Visit 3 (PK Day 2), following baseline pre-dose blood sample and urine sample, subjects will take a single dose of 0.1 ml/kg ferric maltol suspension under supervision and then a further three PK blood samples and urine samples will be taken at three timepoints up to 12 hours. Subjects will continue treatment until week 12.

- End of study: Week 12 visit

- Post-treatment safety follow-up: 10-14 days following study completion of the treatment period or premature discontinuation

The randomisation scheme will be stratified by co-variates for age (2 yrs – 9 yrs, 10 yrs – 17 yrs) and sex (M/F). A minimum of 18 subjects must be recruited into each age group with 25% of either sex.

A maximum of 12 subjects will be recruited in the 1 months to < 2 years age group and they will only be assigned to ferric maltol. Once there is evidence of metabolism and elimination of maltol from Pre-assignment PK samples, they will continue to the Treatment Phase and be assigned to the ferric maltol arm. Subjects will be eligible to enter the treatment phase if their maltol level returns to baseline, or to a level confirming there is no accumulation of maltol or maltol glucuronide.

Where applicable country and local regulations and infrastructure for home healthcare allow, home healthcare may take place at a location other than the clinical trial site to perform study

assessments, which may include but are not limited to collection of blood and urine samples, measurement of vital signs, length/height, and weight.

7.2 INVESTIGATIONAL SITES

Approximately 20 sites

7.3 INCLUSION AND EXCLUSION CRITERIA

No deviations to the inclusion or exclusion criteria are permitted.

7.3.1 Inclusion Criteria

1. Patient is 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 provide informed consent and the patient should provide assent per local and national requirements.
2. Age ≥1 month and ≤17 years at the time of informed consent
3. Subjects must have iron deficiency anaemia defined by the following criteria, as measured by the central laboratory at the screening visit

   Haemoglobin thresholds define anaemia by age and gender:

   - Children (1 m – < 5 yrs) < 11.0 g/dl
   - Children (5 yrs – < 12 yrs) <11.5 g/dl
   - Children (12 yrs) <12.0 g/dl
   - Female child (≥13 yrs) <12.0 g/dl
   - Male child (≥13 yrs) <13.0 g/dl

   And

   Ferritin thresholds define anaemia by:

   - ferritin <30 μg/L,
   - or ferritin <50 μg/L with transferrin saturation (TSAT) <20%,
4. Female subjects of childbearing potential must agree to use a highly effective method of contraception (which includes complete abstinence) until study completion and for at least 4 weeks following their final study visit. Highly effective contraception is defined as a method which results in a low failure rate, i.e., less than 1% per year when used consistently and correctly, such as implants, injectables, some intrauterine contraceptive devices (IUDs), a vasectomised partner and oral contraceptive medications.
   The need for contraception and compliance with contraception requirements will be

assessed at every visit for adolescent patients, and urine pregnancy testing will be performed at each visit for female subjects of childbearing potential.

7.3.2 Exclusion criteria

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

1. Subject with anaemia due to any cause other than iron deficiency, including, but not limited to,
    a. Untreated or untreatable severe malabsorption syndrome
2. Subjects who have received prior to Screening:
    a. Within 28 days intramuscular or intravenous (IV) injection or administration of depot iron preparation.
    b. Within 7 days single agent iron preparations.
    c. Within 12 weeks of blood transfusion or is scheduled to have blood transfusion or donation during the study period
    d. Within 28 days erythropoiesis stimulating agents and during the study
    e. Within 14 days COVID-19 vaccination
3. Subjects with vitamin B12 or folic acid deficiency as determined by the central laboratory screening results. Subjects may start vitamin B12 or folate replacement and rescreen after at least 2 weeks.
4. Has concomitant disease that would significantly compromise iron absorption or absorbed iron utilization such as swallowing disorders and/or extensive small bowel resection.
5. History of active peptic ulcer
6. Has chronic renal disease (eGFR <60 mL/min/m^2), as assessed at Screening based on serum creatinine.
7. Known hypersensitivity or allergy to either the active substance or excipients of ferric maltol or ferrous sulfate.
8. Has a known contraindication for treatment with iron preparations, e.g., haemochromatosis, chronic haemolytic disease, sideroblastic anaemia, thalassemia, or lead intoxication induced anaemia.
9. Impaired liver function as indicated by alanine aminotransferase (ALT) or aspartate transaminase (AST)>2.0 times upper normal limit as measured at the Screening visit.
10. Active acute inflammatory disease, including IBD flare or disease exacerbation, which in the opinion of the Investigator, is clinically significant.

11. Active chronic or acute infectious diseases requiring antibiotic treatment.
12. Pregnant or breast feeding.
13. Concomitant medical conditions with extensive active bleeding, other than menstrual cycles; subjects who suffer from menorrhagia may be included at the Investigator's discretion.
14. Scheduled or expected hospitalization and/or surgery during the course of the study.
15. Participation in any other interventional clinical study within 28 days prior to Screening.
16. Diagnosed to be COVID-19 positive by (SARS-CoV-2-RT-PCR positive) within 28 days prior to screening.
17. Cardiovascular, liver, renal, hematologic, psychiatric, neurologic, gastrointestinal, immunologic, endocrine, metabolic, respiratory or central nervous system disease that, in the opinion of the Investigator, may adversely affect the safety of the subject and/or objectives of the study drug or severely limit the lifespan of the subject.
18. Any other unspecified reason that, in the opinion of the Investigator or the Sponsor make the subject unsuitable for enrolment.

7.4 CONCOMITANT MEDICATION

7.4.1 Not Permitted

- Treatment with single agent oral iron preparation (prescription and non-prescription) within 7 days prior to screening and throughout the study period.
- Treatment with parenteral iron preparations within 28 days prior to screening and throughout the study period.
- Blood transfusions within 12 weeks before screening and during the study.
- Erythropoiesis stimulating agents within 28 days before screening and during the study.

7.4.2 Permitted

- Immunosuppressants
- Vitamin B12 and folic acid supplements/replacement are allowed during the study.
- Over the Counter (OTC) oral supplements/multivitamin type preparations (including those that contain iron) may be taken, however subjects should keep the same dose during the study.
- Oral contraceptives are allowed during the study.

- All other concomitant medications must remain stable from Screening and throughout the study.

7.4.3 Potential Medication Interactions

Iron-drug interactions of clinical significance have been reported to occur with a large number of concomitant therapies. Concurrent ingestion of oral iron causes marked decrease in the bioavailability of a number of drugs due to the formation of iron-drug complexes (chelation or binding of iron by the second drug). Examples of affected drugs are: penicillamine, bisphosphonates, ciprofloxacin, entacapone, levodopa, levofloxacin, levothyroxine (thyroxine) moxifloxacin, mycophenolate, norfloxacin, ofloxacin, tetracyclines, calcium and magnesium salts, dimercaprol, chloramphenicol and methyldopa.

Based on the recent Phase I study finding, ferric maltol oral suspension can be taken at least 30 mins after a meal. To minimise the potential for drug interactions, patients should wait at least 4 hours before taking other concomitant medications and/or supplements. The exact timing of any concomitant medication and its iron content should be recorded in the eCRF.

7.5 INDIVIDUAL DISCONTINUATION CRITERIA

Subjects and/or their parents or guardians have the right to withdraw consent without prejudice at any time during the study. If a subject withdraws consent, the Investigator should make a reasonable effort to determine the cause. All withdrawn subjects should have a Post-Treatment Safety Visit within 10-14 days after the last dose of study drug (if the subject agrees in the case of withdrawn consent).

If there is any sign of accumulation of maltol or glucuronide in the pre-assignment phase PK day for subject population aged 1 month to less than 2 years, the recruitment to this age group will be suspended and they will not enter the treatment phase until the risk has been assessed and approved via a substantial amendment to the protocol.

Subjects may be discontinued prematurely during the study for the following reasons:

- Withdrawal of informed consent
- A drop of >1 g/dl in Hb from baseline
- Unwillingness or inability to comply with protocol requirements
- Pregnancy or not using a reliable method of birth control (female subject of childbearing potential)
- Use of prohibited concomitant medications
- Serious adverse events that are judged by the Investigator to be related to study treatment

- Blood transfusions for any cause during the study treatment period
- Use of any other single agent prescribed iron medications
- Occurrence of any condition that, in the opinion of the Investigator, significantly jeopardizes the wellbeing and safety of the patient, including any intolerable toxicity related to study treatment determined by the investigator to be unacceptable given the severity of the event

The reason for study drug discontinuation and the date of last dose should be recorded in the eCRF. Subjects who discontinue treatment prematurely must return for the Post-Treatment Safety Visit, unless informed consent is withdrawn (and the subject and/or their parents or guardians do not agree to attend this follow-up visit). A subject who meets discontinuation criteria should be discussed on an individual basis with the Medical Monitor.

7.6 STUDY TERMINATION

The Sponsor reserves the right to temporarily halt and/or terminate the study (or if appropriate, individual treatment dose groups) at any time for safety, scientific or ethical reasons including, but not limited to:

- Emerging safety concerns from this study, other ongoing studies with ferric maltol, or new and relevant scientific information, which result in the risk-benefit ratio for this study becoming unfavorable, in the Sponsor's opinion.
- If the total number of dropouts is so high or the number of included subjects is so low that completion of the trial will not realistically be expected within a reasonable timeframe.
- If the Sponsor determines the study will no longer reveal new knowledge and consequently is ethically no longer justifiable.

In case of an early termination of the study or temporary halt by the Sponsor, the IEC and CA will be notified within 15 calendar days, including a detailed written explanation of the reasons for the termination/halt.

In all circumstances connected with temporary halt and/or termination of the study, the following principles will apply:

- All affected parties (such as the IEC, CA, Investigators, heads of study centers /clinic directors) must be informed as applicable according to local law.
- All study materials and supplies (except documentation that should remain stored at site) must be returned to the Sponsor/designee.

8 TREATMENT OF SUBJECTS

Ferric maltol oral suspension will be supplied to study sites on behalf of Shield TX (UK) Ltd by Quay Pharma, Deeside Ind. Park, Flintshire. The drug substance and drug product are manufactured, tested and controlled in accordance with Good Manufacturing Practice (GMP). Full details are documented in the Investigational Medicinal Product Dossier (IMPD) and current Investigator's Brochure. Sites must arrange storage of Investigational Medicinal Product in a temperature monitored, secure location which is accessible to authorised individuals only.

Ferrous sulfate oral liquid 125 mg/ml (25 mg/ml elemental iron) or equivalent dose will be used for all children/adolescents randomised to this group.

8.1 INVESTIGATIONAL MEDICINAL PRODUCT (IMP) PRESENTATION

- 150 ml amber glass bottle with graduated syringe and adaptor. Oral suspension containing 30 mg elemental iron, in the form of 231.5 mg ferric maltol, in 5 ml suspension

A full list of excipients can be found in the Investigator's Brochure.

8.2 COMPARATOR

- Ferrous sulfate 125 mg/ml (25 mg/ml elemental iron) oral liquid or equivalent dose will be administered under this protocol.

8.3 PACKAGING

Oral suspension: Ferric maltol oral suspension will be supplied in an amber glass bottle with graduated syringes and adaptor.

8.4 STORAGE

IMP must be stored below 25 °C and must not be frozen. In the event that the drug is exposed to temperatures greater than or equal to 25°C, or to freezing, the CRA/Sponsor should be contacted for review and further instruction.

Ferrous sulfate oral liquid to be handled and stored according to SPC/PI.

8.5 LABELLING

All bottles will be identified by a unique Bottle ID number. Bottles will be clearly labelled as ferric maltol with the dose indicated. Labels of the IMP will contain information according to European Directives 2003/94/EC, 2001/20/EC and US 21 CFR 312.6.

Individual supplies packaging and labelling will be checked by the Investigator/designee before the subject (aged 2-17 yrs) takes their first dose of study medication at site on Day 1 (Visit 2).

Packaging and labelling will be checked by the Investigator/Designee before the subject (aged 1 m - < 2 yrs) takes their single dose on the Pre-assignment PK visit.

8.6 TREATMENT ASSIGNMENT AND BLINDING

At randomisation, the Interactive Response Technology (IRT) will assign children aged 2 yrs to 17 yrs to either the ferric maltol or ferrous sulfate treatment group. The site will dispense the appropriate number of open-label ferric maltol bottles or ferrous sulfate at each scheduled study visit according to the schedule of assessments. Study Treatment and duration is specified in section 5.5.2 of this protocol.

Children aged 1 m - < 2 yrs: all subjects will receive ferric maltol oral suspension following satisfactory completion of the pre-assignment phase.

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

8.6.1 TREATMENT ASSIGNMENT

Subjects aged 2 yrs to 17 yrs will be randomised 1:1 to either treatment. Randomisation will be centrally controlled and stratified by age and gender as well.

The subject will be instructed to administer the first dose of ferric maltol oral suspension in the presence of the site staff on Visit 2 (infant age group Pre-assignment PK Day). Subsequent doses may need to be administered under the supervision of the child's parent or legal guardian and recorded on a dosing diary. The first 12 subjects in each age group (2 yrs – 9 yrs, 10 yrs – 17 yrs, respectively) will be instructed to withhold their morning dose of ferric maltol on PK Day 2 until pre-dose PK blood samples have been collected at the site.

If a subject forgets to take a dose, he/she should take the next dose as normal. The subject should not take a double dose to make up for a forgotten dose.

In the event of an administered dose not being consumed or partially consumed by the patient this will be noted as a missed dose and will not be repeated. Clear instructions will be provided by the Investigator to the parents/guardians who are supervising the drug administration and dosing diary.

Patient weight should be recorded at each clinic visit and drug dosing administered as per last clinic visit weight.

During the PK days:

- if the administered dose is not consumed or partially consumed by the patient this will be noted as a missed dose and will not be repeated. The PK sampling will be cancelled.

-the site staff will record the timing of each meal, concomitant medication and its iron content within the eCRF.

8.7 TREATMENT COMPLIANCE

Subjects will be instructed to take the study drug as described in detail on the drug labels and by the Investigator/designee.

Subjects (ferric maltol and ferrous sulfate) will be instructed on Visit 2 to complete a dosing diary from the evening of Visit 2 until the next visit, in order to document the day and time that they took their morning and evening doses on those treatment days whilst at home. Subjects will be instructed to return all unused supplies medication packaging on their visits, having withheld their dose of ferric maltol on PK Day 2 morning. Compliance will be assessed from the dosing diary entries and reconciled using the drug accountability form.

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

If the subject discontinues the study due to intolerance to either ferrous sulfate or ferric maltol, this should be documented in the eCRF.

Subjects who do not attend their visits may be withdrawn from the study. A copy of the relevant local SPC/PI for ferrous sulfate will be available in the Investigator Site File (ISF). Special safety information and warnings/precautions relating to the drug will be highlighted to the Investigator during the Site Initiation Visit (SIV).

The delivery of medication to the site, its use and return, as well as subject-specific compliance, will be reconciled and documented using a Drug Accountability Form in order to monitor compliance with the medication schedule. All opened containers, together with remaining contents, and unopened containers will be kept by the Investigator in a secure, locked area until return to the drug supplier by the monitor or destruction by the site if agreed with the Sponsor/designee. The Investigator will use the IMP only within the framework of this clinical study and in accordance with the current, approved study protocol.

8.8 CONTINUATION OF TREATMENT

No further provisions are made for access to the study treatment under this protocol following Day 84/Visit 6.

9 ENROLMENT AND RANDOMISATION PROCEDURES

Full details of procedures will be provided in the Investigator Site File and eCRF Completion Guidelines.

9.1 SCREENING (Visit 1)

Subjects will be evaluated according to the inclusion and exclusion criteria (Sections 7.3.1 and 7.3.2). Subjects will be deemed eligible for randomisation if all inclusion criteria and no exclusion criteria are met. The Investigator is required to document all screened candidates considered for inclusion in this study. If excluded prior to enrolment, the reasons for exclusion will be documented in the subject's eCRF, medical notes and on the study screening log.

A subject may be retested once for screening laboratory criteria that do not meet protocol in/exclusion criteria initially, so long as randomisation occurs no more than 21 days from the initial Screening visit date (if eligible based on retest results).

A subject may be re-screened after an initial screening and screening failure once it is assessed by the investigator the reason for the screening failure was resolved e.g.: Subject screening failure due to folates outside of protocol range, receives folates replacement therapy can be re-screened.

9.2 RANDOMISATION (Visit 2)

Subjects will be registered into the study at the Screening visit and assigned a unique subject identification number in the IRT. Subjects will be categorised during the screening process based upon their age (2 to ≤ 9 years of age and 10 to ≤ 17 years of age) and their gender. Age and gender will be incorporated into the randomisation as stratification factors. A minimum of 18 subjects must be recruited into the 2-9 and 10-17 age group and a minimum of 25% of either sex must be recruited. Maximum of 12 subjects will be recruited in the 1 m – 2 yrs cohort. In the event of a subject having a birthday whilst on study and they move to a different age cohort -they will remain in the baseline cohort for the duration of the study.

A final eligibility evaluation must be conducted by the Investigator/designee prior to randomisation/pre-assignment PK visit via IRT, once the results of all Screening assessments are available.

<u>Subjects aged 1 month to < 2 years:</u>

Following the eligibility evaluation, a maximum of 12 subjects will enter a Pre-assignment phase: 1-day Pharmacokinetic assessment day following a single dose of 0.1 ml/kg ferric maltol oral suspension. Once the PK samples have been analysed and evidence is showing metabolism and elimination of maltol, subjects will be assigned to ferric maltol oral suspension treatment phase. Subjects will be eligible to enter the treatment phase if their maltol level returns to baseline, or to a level confirming there is no accumulation of maltol

or maltol glucuronide. The sample results will be analysed on an individual basis. The Sponsor's Medical Monitor will make a recommendation to the investigator based on pre-assignment results. The investigator will make the final decision if subjects aged 1 month to < 2 years are eligible to enter the treatment phase.

Subjects aged 2 years to 17 years:

No subject may begin treatment prior to being randomised in the IRT. The randomisation procedure (created using a computer-generated random permutation procedure) will assign the subject to one of the treatment arms.

Initial dosing with ferric maltol and ferrous sulfate must occur on the same day of randomisation. The date of Visit 2 is the date of first dose with ferric maltol or ferrous sulfate.

9.3 REPLACEMENT POLICY

Discontinuations after randomisation due to adverse events will not be replaced. Discontinuations after randomisation for any other reasons may be replaced at the discretion of the Sponsor, in order to reach the agreed number of evaluable subjects for pharmacokinetic endpoints.

9.4 BLINDING PROCEDURES

Not applicable as this is an open label study.

9.5 EMERGENCY UNBLINDING

Not applicable as this is an open label study.

10 STUDY PROCEDURES

10.1 COVID-19 IMPLICATIONS ON THE TRIAL

All efforts will be made by the Investigational sites to avoid screenings of any subjects who might have a known exposure to SARS-CoV-2 or any symptoms suggestive of any infection with it by following the local guidelines provided for evaluating patients for COVID-19.

If there is a confirmed COVID-19 positive case (SARS-CoV-2-RT-PCR) in a subject after randomization, the subject will be assessed by the investigator to determine if their participation in the trial is suitable. Positive cases will be recorded as an adverse event in the CRF, and authorised medication will be recorded as concomitant medication in the CRF.

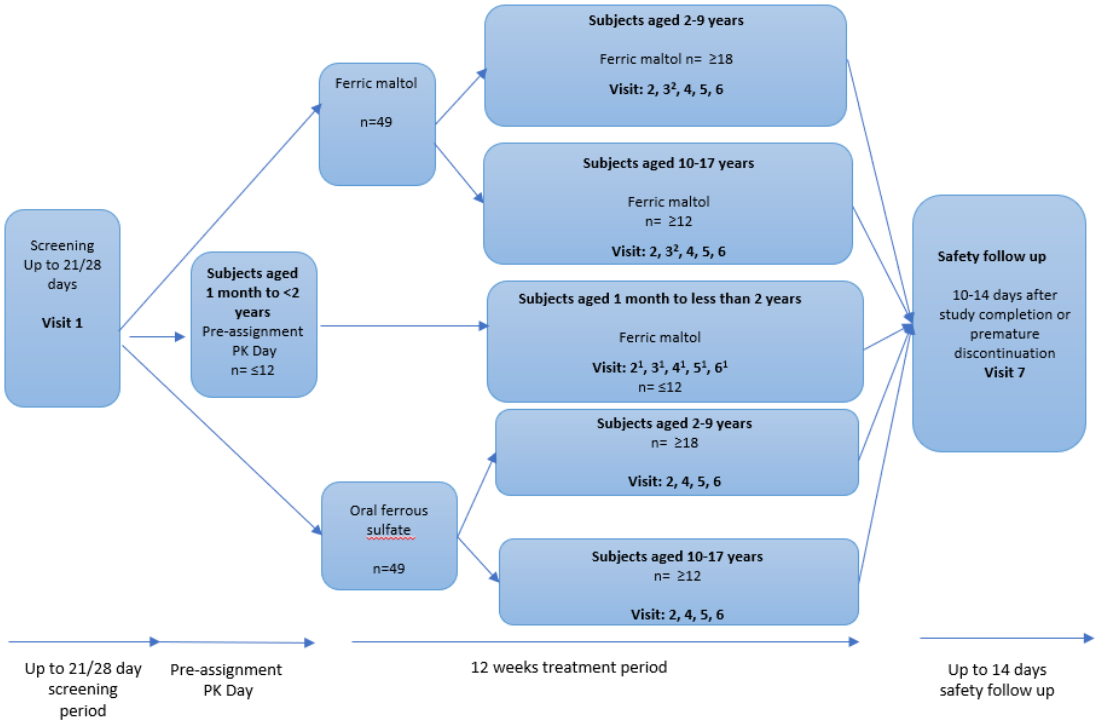
Every attempt will be made to follow up with the adverse events via phone call to the subject until known resolution or stabilization of the disease.

During periods of time when a pandemic impedes the ability of patients to travel to the study site

- Study assessments and visit window may be expanded up to 14 days (Visit 4, 5, 6)
- Study assessments by a healthcare professional may occur at an offsite location such as the patient`s home.

Where applicable country and local regulations and infrastructure for home healthcare allow, home healthcare may take place at a location other than the clinical trial site to perform study assessments, which may include but are not limited to collection of blood and urine samples, measurement of vital signs, length/height, and weight.

10.2 DESIGN SCHEMATICS



[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 12 subjects in age group 2-17 years

10.3 SCHEDULE OF ASSESSMENTS FOR SUBJECTS AGED 2 YEARS-17 YEARS

	SCREENING	TREATMENT					FOLLOW-UP
Duration	**Up to 21 days**	**12 WEEKS (equivalent of 84 days)**					**10-14 days**
Day		**1**	**7-10**	**28**	**56**	**84**	**94-98**
Visit [11]	**1**	**2**	**3[3]**	**4**	**5**	**6**	**7[9,10]**
Informed Consent	X						
Eligibility [1,8]	X	X					
Demographics	X						
Medical History	X						
Physical Examination	X					X	
Vital Signs [2]	X	X	X	X	X	X	
Urine Pregnancy Test [4]	X	X	X	X	X	X	
Clinical Laboratory tests [5]	X					X	
Haematology [6]	X			X		X	
Iron markers [6]	X			X		X	
PK assessment –PK Blood Sampling for maltol/maltol glucuronide and iron markers [7]		X	X				
Randomisation [8]		X					
Dispense Study Drug		X	X	X	X		
Return Study Drug for Accountability			X	X	X	X	
Palatability questionnaire		X		X			
Adverse Events		X	X	X	X	X	X
Concomitant Medications and Procedures	X	X	X	X	X	X	X
Compliance reminder		X	X	X	X	X	
Compliance assessment			X	X	X	X	

1. *A subject may be retested once for laboratory criteria that do not meet protocol criteria so long as randomisation occurs no more than 21 days from the initial screening visit date (if eligible).*
2. *Vital Signs – body weight, height, systolic/diastolic blood pressure, pulse, and body temperature at each visit. Patient weight should be recorded at each clinic visit and drug dosing administered as per last clinic visit weight.*
3. *Visit 3 (PK Day 2) only applicable for the first 12 subjects randomised to ferric maltol group in each age group (2 yrs -9 yrs, 10 yrs-17 yrs).*
4. *Urine pregnancy test for female subjects of childbearing potential only.*
5. *Clinical Laboratory tests including:*
    a. *Clinical Chemistry: Vitamin B12, folate, ALT, AST, alkaline phosphatase, gamma-glutamyl transpeptidase (GGT), total bilirubin, creatinine, amylase, blood urea nitrogen (BUN), phosphorous, sodium, potassium, chloride, calcium, total cholesterol, uric acid, glucose, total protein, albumin*
6. *Haematology and Iron markers:*
    a. *Haematology: Red blood cell count, haemoglobin, haematocrit, mean cell volume (MCV), white blood cell count (total and differential (% and absolute), absolute reticulocyte count and platelet count.*
    b. *Iron Markers: serum iron, transferrin, transferrin saturation (TSAT), total and unsaturated iron binding capacity (TIBC, UIBC) and ferritin.*
7. *On PK study Day 1 (Visit 2) and PK study Day 2 (Visit 3) for the first 12 subjects in each age group (2 yrs – 9 yrs, 10 yrs-17 yrs, respectively) who have been randomised to ferric maltol groups have baseline PK blood samples collected immediately prior to ferric maltol dosing (0 hr). Subjects will then have further PK blood samples collected at two (2) additional times between 0.5 hr and 6 hrs after dosing on Visit 2 and 3; the post-dose PK sample time collection windows will be 0.5-1h, 1.0-2.0 hrs, 2.0-3.0 hrs, 3.0-4.0 hrs and 4.0-6.0 hrs. For each individual subject, the post-dose PK blood sampling schedule will be the same on PK Day 1 and PK Day 2. Post-dose blood samples should be collected within the time windows allocated only. N.B: samples should be taken at least 1.0 hr apart.*

    In the event of an administered dose not being consumed or partially consumed by the patient this will be noted as a missed dose and will not be repeated.
8. *Eligibility laboratory sampling/assessments must be completed before the subject is randomised and before the first dose of study treatment taken. A minimum number of 18 subjects must be recruited into each age group (2 yrs -9 yrs, 10 yrs-17 yrs) and a minimum of 25% of either sex must be recruited and at least 49 subjects per arm.*
9. *Subjects who have at least one dose of study medication and withdraw earlier from the study undergo Visit 7 (Day 94-98) assessments (excluding those who have withdrawn consent).*
10. *Visit 7 is conducted by telephone, unless the Subject has an ongoing AE that requires physical examination or investigations for assessment/management. Visit 7 will take place 10-14 days after Visit 6 (Week 12) unless subject discontinued treatment early. All withdrawn subjects should undergo Visit 7 within 10-14 days after the last dose of study drug (if the subject agrees in the case of withdrawn consent).*
11. *Visit Windows: Maximum of 21 days between screening and randomisation. The Subject must visit to complete:*

a. *Visit 2 and Visit 3: must be 6-9 days between the scheduled PK days.*

b. *Visit 4: +/- 5 days relative to date of Visit 2/first dose administered*

c. *Visits 5 to 6: +/- 5 days relative to date of Visit 2/first dose administered*

d. *Visit 7: 10-14 days after Visit 6 (unless subject discontinued treatment early - see Note 10*

10.4 SCHEDULE OF ASSESSMENTS FOR SUBJECTS AGED 1 MONTH - < 2 YEARS

	SCREENING	PRE-ASSIGNMENT	TREATMENT					FOLLOW-UP
Duration	**Up to 21 days**	**Up to 28 days from Screening**	**12 WEEKS (equivalent of 84 days)**					**10-14 days**
Day			**1**	**7-10**	**28**	**56**	**84**	**94-98**
Visit[9]	**1**	**Pre-assigned[6]**	**2**	**3[3]**	**4**	**5**	**6**	**7[8,9]**
Informed Consent	X							
Eligibility [1,7]	X	X	X					
Demographics	X							
Medical History	X							
Physical Examination	X						X	
Vital Signs [2]	X	X	X	X	X	X	X	
Clinical Laboratory tests [4]	X						X	
Haematology, Iron markers [5]	X		X[10]				X	
PK assessment: Blood Sampling for iron markers, maltol and maltol glucuronide[6]				X[6]				
PK assessment: Urine sampling for maltol/maltol glucuronide[6]		X[6]		X[6]				
Treatment Assignment [7]			X					
Dispense Study Drug		X	X	X	X	X		
Return Study Drug for Accountability				X	X	X	X	
Adverse Events		X	X	X	X	X	X	X
Concomitant Medications and Procedures	X	X	X	X	X	X	X	X
Compliance reminder			X	X	X	X	X	
Compliance assessment				X	X	X	X	

1. *A subject may be retested once for laboratory criteria that do not meet protocol criteria so long as pre-assignment visit occurs no more than 28 days from the initial screening visit date (if eligible).*
2. *Vital Signs – body weight, length, systolic/diastolic blood pressure, pulse, and body temperature at each visit. Patient weight should be recorded at each clinic visit and drug dosing administered as per last clinic visit weight.*
3. *Visit 3 (PK Day 2) this visit will be the second PK day following the pre-assignment PK assessment.*
4. *Clinical Laboratory tests: including*
    a. *Clinical Chemistry: Vitamin B12, folate, ALT, AST, alkaline phosphatase, gamma-glutamyl transpeptidase (GGT), total bilirubin, creatinine, amylase, blood urea nitrogen (BUN), phosphorous, sodium, potassium, chloride, calcium, total cholesterol, uric acid, glucose, total protein, albumin*
5. *Haematology and Iron markers:*
    a. *Haematology: Red blood cell count, haemoglobin, haematocrit, mean cell volume (MCV), white blood cell count (total and differential (% and absolute), absolute reticulocyte count and platelet count.*
    b. *Iron Markers: serum iron, transferrin, transferrin saturation (TSAT), total and unsaturated iron binding capacity (TIBC, UIBC) and ferritin.*
6. *Pre-assignment phase: All subjects in 1 m-< 2 yrs age group will enter a 1-day PK assessment day prior to entering the treatment phase. Pre-assignment PK Day, each subject has baseline PK urine samples collected immediately prior to ferric maltol dosing (0 h). Following this, subjects will take a single dose of 0.1 ml/kg ferric maltol under supervision. Three (3) PK urine samples will be taken between 0.5 hr -3 hrs, 3 hrs -6 hrs, and 7 hrs -12 hrs post dose. N.B: samples should be taken at least 1.0 h apart. Urine collections instructions are detailed in the study's Laboratory Manual.*

    PK Day 2 (Visit 3), each subject has baseline PK blood and urine samples collected immediately prior to ferric maltol dosing (0 h). Following this, subjects will take a single dose of 0.1 ml/kg ferric maltol under supervision. Three PK Post-dose blood samples will be collected at the following windows 1.0-2.0 hrs, 3.0-4.0 hrs and 10.0-12.0 hrs; post-dose urine samples will be taken between 0.5 hr -3 hrs, 3 hrs -6 hrs and 7 hrs -12hrs post dose.

In the event of an administered dose not being consumed or partially consumed by the patient this will be noted as a missed dose and will not be repeated.

7. *Eligibility laboratory sampling/assessments must be completed before the subject is assigned to ferric maltol. The PK samples will be analysed and if evidence of metabolism and elimination of maltol is shown, these subjects will enter the ferric maltol treatment phase Visit 2.*
8. *Subjects who have at least one dose of study medication and withdraw early from the study undergo Visit 7 (Day 94-98) assessments (excluding those who have withdrawn consent).*
9. *Visit 7 is conducted by telephone, unless the subject has an ongoing AE that requires physical examination or investigations for assessment/management. Visit 7 will take place 10-14 days after Visit 6 (Week 12) unless subject discontinued treatment early. All withdrawn subjects should undergo Visit 7 within 10-14 days after the last dose of study drug (if the subject agrees in the case of withdrawn consent).*
10. *Visit Windows: Maximum of 28 days between screening and pre-assignment phase. The Subject must visit to complete:*
    a. *Visit 3: must be 7-10 days from Visit 2*
    b. *Visit 4: +/- 5 days relative to date of Visit 2/first dose administered*
    c. *Visits 5 to 6: +/- 5 days relative to date of Visit 2/first dose administered*
    d. *Visit 7: 10-14 days after Visit 6 (unless subject discontinued treatment - see Note 10*
11. *Baseline Haematology and Iron markers: to be performed after urine PK assessment and prior to assignment*
    a. *Haematology: haemoglobin*
    b. *Iron Markers: serum iron, transferrin, transferrin saturation (TSAT), total and unsaturated iron binding capacity (TIBC, UIBC), ferritin*

10.5 DEMOGRAPHICS AND MEDICAL HISTORY

The following will be documented at Screening and updated (if required) prior to randomisation: Date of Birth, race and ethnicity, gender, all current medical conditions, all medical history relevant to iron deficiency anaemia diagnosis regardless of onset, all clinically significant medical history from the past 5 years (age dependant) including all malignancies, sterilisations, hospitalisations and surgeries; the method of contraception for female subjects of childbearing potential, if applicable. Body weight (Kg), height/length (m/cm) should be recorded at each clinic visit and drug dosing administered as per last clinic visit weight.

PHYSICAL EXAMINATION

A brief physical examination is to be conducted to assess safety. The examination should include an assessment of general appearance, skin, head, eyes, ears, nose and throat, cardiovascular, respiratory, abdominal, gastrointestinal, and musculoskeletal systems.

10.6 CONCOMITANT MEDICATIONS AND PROCEDURES

The following will be documented at Screening and updated (if required) prior to randomisation: all current medications at the time of Screening or stopped within 3 months of screening and any medical procedure performed within 3 months prior to Screening.

The following will be documented throughout the study: any medications initiated stopped or dose and/or frequency changes throughout the study. Any medical procedure performed throughout the study.

Medical procedures to be documented are any therapeutic intervention such as surgery/biopsy, physical therapy or diagnostic assessment (e.g. blood gas measurement).

The exact timing and iron content of any concomitant medications taken on any PK days will be recorded in the eCRF.

10.7 VITAL SIGNS

Body temperature (°C), blood pressure, body weight (Kg), height/length (m/cm) and pulse rate will be assessed. Blood pressure and pulse rate should be measured after the subject has been sitting for at least 5 minutes.

10.8 LABORATORY ASSESSMENTS

10.8.1 Haematology and Clinical Chemistry

Routine clinical laboratory safety bloods for haematology and clinical chemistry/iron markers evaluations will be collected at Screening to assess eligibility. Additional testing may be required if any abnormal value is reported and this must be followed until it is resolved (other

than iron indices and low haemoglobin due to ongoing iron deficiency/anaemia, or abnormal results due to other pre-existing conditions).

All analyses will be conducted by a central laboratory. Procedures for the collection, processing, storing, and transporting of samples to the laboratory will be fully described in the study-specific Laboratory Manual.

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

The signed paper copy of the laboratory report is retained at the investigational site. The electronic data transferred from the central laboratory database to the clinical study database will be considered source data for the derivation of summary data and listings presented in the clinical study report.

10.8.1.1 Haematology test parameters

Red blood cell count, haemoglobin, haematocrit, mean cell volume (MCV), white blood cell count (total and differential (% and absolute), absolute reticulocyte count and platelet count.

10.8.1.2 Clinical Chemistry and Screening Iron Markers test parameters

Clinical Chemistry: Vitamin B12, folate, ALT, AST, alkaline phosphatase, gamma-glutamyl transpeptidase (GGT), total bilirubin, creatinine, amylase, blood urea nitrogen (BUN), phosphorous, sodium, potassium, chloride, calcium, total cholesterol, uric acid, glucose, total protein, albumin

Iron Markers: serum iron, transferrin, transferrin saturation (TSAT), total and unsaturated iron binding capacity (TIBC, UIBC) and ferritin.

10.8.2 Pharmacokinetics

Blood samples for maltol and maltol glucuronide on each PK day

Blood samples will be collected at the required times on the PK assessment days relative to the time of ferric maltol morning dosing: pre-dose then two further times between 0.5-10 hours post-dose in the 2-17 years age group and pre-dose then three further times between 1-12 hours post-dose in the 1 m to less than 2 years age group (see Section 10.3 and section 10.4).

Following collection and mixing, blood samples will be centrifuged, and the resultant plasma samples separated and stored at -20°C at the study site, prior to collection and onward shipping to the central laboratory on dry ice for subsequent assay of maltol and maltol glucuronide plasma concentrations using appropriately validated bioanalytical methods. Full

details of the required sample collection, processing and handling logistics will be specified in the study specific Laboratory Manual. Samples will be destroyed at the end of the study, once all analyses are complete.

Blood samples for iron markers on each PK day

Blood samples will be collected at the required times on the PK assessment days, relative to the time of ferric maltol dosing: pre-dose then two further times between 0.5-6 hours post-dose in the 2-17 yrs age group. Same times as blood samples for maltol/maltol glucuronide for each individual (see Section 10.3 and section 10.4.).

Following collection and mixing, blood samples will be centrifuged, and the resultant serum samples separated and split into 2 aliquots at each timepoint. Ambient serum samples will be shipped to the central laboratory for subsequent assay of serum iron, transferrin, transferrin saturation (TSAT), total and unsaturated iron binding capacity (TIBC, UIBC. Frozen serum aliquot will be stored at site (-20°C) for later onward shipping on dry ice to the central laboratory. Full details of the required sample collection, processing and handling logistics will be specified in the study specific Laboratory Manual. Samples will be destroyed at the end of the study, once all analyses are complete.

PK blood sample scheduling in the 2-17 yrs age groups:

3 subjects will be assigned to the required post dose PK blood sampling schedule in sequential order at the time of randomisation, based on current subject enrolment across all study sites. The PK sampling schedule is not the same for each patient, the scheme in the table below has been produced to reduce sampling burden.

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 (0h)	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

PK blood sample scheduling in the 1 m - < 2 yrs age groups:

Pre-assignment PK Day, each subject has baseline PK urine samples collected immediately prior to ferric maltol dosing (0 h). Following this, subjects will take a single dose of 0.1 ml/kg ferric maltol under supervision. Three PK urine samples will be taken between 0.5 hr -3 hrs, 3 hrs -6 hrs and 7 hrs -12hrs post dose.

Note: samples should be taken at least 1.0 h apart. The PK samples will be analysed and if evidence of metabolism and elimination of maltol is shown, these subjects will enter the treatment phase and be assigned to the ferric maltol arm.

PK Day 2 (Visit 3), each subject has baseline PK blood and urine samples collected immediately prior to ferric maltol dosing (0 h). Following this, subjects will take a single dose of 0.1 ml/kg ferric maltol under supervision. Three PK Post-dose blood samples will be collected at the following windows 1.0-2.0 hrs, 3.0-4.0 hrs and 10.0-12.0 hrs; post-dose urine samples will be taken between 0.5 hr -3 hrs, 3 hrs -6 hrs and 7 hrs -12hrs post dose.

Urine samples for maltol and maltol glucuronide

Urine samples will only be collected from subjects aged 1 month to less than 2 years.

Full details of the required sample collection, processing and handling logistics will be specified in the study specific Laboratory Manual. Samples will be destroyed at the end of the study, once all analyses are complete.

10.8.3 Urine Pregnancy Test

Females of childbearing potential only. A urine pregnancy test should be conducted at the Screening visit to assess eligibility using the test kits provided by the central laboratory. A repeat urine pregnancy test will be conducted prior to first dosing on Day 1; the result of this test must be negative for dosing with ferric maltol or ferrous sulfate to commence on Day 1. Repeat urine pregnancy testing will also be conducted at Visit 2, Visit 3, Visit 4, Visit 5, Visit 6.

Full details of the required sample collection and processing procedures will be described in the study-specific Laboratory Manual.

10.8.4 Palatability and acceptability scoring

Subjects aged 2 yrs to 17 yrs on Visit 2 and Visit 4 will receive a 5-point Facial Hedonic scale which will be completed immediately after the administration of ferric maltol oral suspension or ferrous sulfate oral liquid. Subjects are free to ask for support in completing the questionnaires from parents/legal guardian and site staff.

Subjects will complete Visit 2 Facial Hedonic Scale on site, immediately after dosing.

Subjects can complete Visit 4 Facial Hedonic Scale on site or at home after visit on site and dispensation of Visit 4 treatment, immediately after dosing. If subjects require support in completing the questionnaires from site staff, it is recommended the dosing and subsequent questionnaire completion occur on site.

Questionnaires should be completed immediately after dosing, once a day (morning or evening dose).

Hedonic expression will be converted to scores of 1-5 with 1 being the most positive expression and 5 the most negative. The data from the scales will be transformed into numbers for descriptive statistics.

10.8.5 PK Days food intake

On each PK day: the approximate amount of iron content for any food consumed after ferric maltol and before the end of the PK sampling will be recorded in the eCRF.

10.8.6 Overall blood volume

The individual volume of blood collected throughout the study will be:

- Subjects aged 1 m to less than 2 yrs: up to 24ml (including PK days)
- First 12 subjects aged 2 yrs to 17 yrs in the ferric maltol oral suspension group: up to 27 ml (including PK days)
- ferric maltol oral suspension group without PK sampling (2-17 years): 13 ml
- ferrous sulfate oral liquid group: 13 ml

<u>Blood samples on PK days</u>

Subjects aged 2 yrs to 17 yrs; total number of blood samples on each PK day: 3 timepoints, 1 pre-dose and 2 post doses. Total blood volume at each PK timepoint: 4.5 ml.

Subjects aged 1 month to less than 2 yrs: total number of blood samples on PK blood day: 4 timepoints, 1 pre-dose and 3 post doses. The total blood volume at each PK timepoint: 3.2 ml.

11 SAFETY

11.1 DEFINITIONS

11.1.1 ADVERSE EVENT (AE)

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

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

AEs include:

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

AEs do not include:

- Medical or surgical procedure, e.g., surgery, appendectomy, endoscopy, tooth extraction, transfusion (as these are treatments for an AE). However, the event resulting in the procedure is the AE (e.g. appendicitis, abdominal pain).

- Pre-existing disease or medical condition documented at baseline that does not worsen.
- Situations in which an adverse change did not occur, e.g., hospitalisations for cosmetic elective surgery or for social and/or convenience reasons.
- Anticipated day-to-day fluctuations or seasonal fluctuations (e.g. allergic rhinitis) of pre-existing disease(s) or condition(s) documented at baseline.
- The disease/disorder being studied, or the expected progression, signs or symptoms (including laboratory values) of the disease/disorder being studied, unless it is more severe than expected for the subject's condition.
- Overdose of either study drug or concomitant medication without any signs or symptoms.

11.1.2 SERIOUS ADVERSE EVENT (SAE)

An SAE is any untoward medical occurrence between the time of consent and the subject's final visit that:

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

The following guidelines should be used:

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

Inpatient hospitalisation: Subject has to stay in hospital at least overnight. The following reasons for hospitalisations are not considered AEs, and therefore not SAEs:

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

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

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

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

SAE related to study-mandated procedures: Such SAEs are defined as SAEs that appear to have a reasonable possibility of causal relationship (i.e., a relationship cannot be ruled out) to study-mandated procedures (excluding administration of study drug) or complication of a mandated invasive procedure (e.g., blood sampling, heart catheterisation), or car accident on the way to the hospital for a study visit, etc.

11.2 REPORTING AND DOCUMENTATION

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

Any pre-existing conditions or signs and/or symptoms present in a subject prior to the start of the study should be recorded on the Medical History CRF.

All SAEs that occur after informed consent through to study completion (Follow-up visit) or premature discontinuation must be reported on the SAE form in the CRF and reported within 24 hours to the Sponsor using the Shield SAE form. All AEs occurring from the time of the first dose of study treatment through study completion (Follow-up visit) or premature

discontinuation must be reported on the AE form in the CRF. For AEs related to COVID-19 testing, see section 10.1.

Any SAE that occurs during the clinical study or within two weeks of receiving the last dose of study drug, whether or not related to the study drug, must be reported to the Sponsor.

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

At each visit AEs will be solicited. The nature of each event should be established. Details of changes to study drug dosing or any subsequent treatment should be recorded on the appropriate pages of the CRF.

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

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

11.2.1 Immediate Reporting

The following AEs must be reported within 24 hours to the Sponsor or designee:

- SAEs
- Pregnancy (not considered as an AE, but must be reported immediately)

For immediate reporting, the Investigator must fill out the SAE form or the Pregnancy form for pregnancies and send to the Sponsor within 24 hours after awareness.

SAFETY CONTACT DETAILS

Primevigilance Limited has been contracted by the Sponsor for safety reporting

Email SAE reports to shieldpv@primevigilance.com or fax to +44 800 781 6187

Contact details for safety questions will be provided in the Investigator Site File

If the site obtains relevant follow-up information, this information needs to be forwarded to the Sponsor within 24 h of awareness using a new SAE form.

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

As soon as the Sponsor is informed about an SAE, an evaluation and potential reporting to central IRBs/IECs, Competent Authorities (CA) and other concerned parties will occur as required. The Investigator will be responsible for reporting to any local IRB/IEC as required.

11.2.2 Non-Immediate Reporting

AEs that do not qualify for immediate reporting will be documented in the eCRF and reported in the Clinical Study Report (CSR).

11.3 EVALUATION

AEs and the corresponding entries in the eCRF will be reviewed by the Investigator or qualified member of the study staff. Adverse events, toxicities and medical surgery/history will be categorized by primary system organ class (SOC) and preferred term using the MedDRA dictionary. Toxicities will also be graded as mild, moderate or severe.

11.3.1 Intensity

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

Mild: Symptoms barely noticeable to the subject or does not make the subject uncomfortable; does not influence performance or functioning.

Moderate: Symptoms of a sufficient severity to make the subject uncomfortable; performance of daily activity is influenced; subject is able to continue in study.

Severe: Symptoms cause significant discomfort; incapacitation or significant impact on the subject's daily life; may cause cessation of study treatment.

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

11.3.2 Causality

The following should be considered when evaluating the relationship of AEs and SAEs to the study treatment:

Not related: There is not a possibility that the event has been caused by the product under investigation. Consideration should be given to factors, including but not limited to, a lack of reasonable temporal relationship between administration of the drug and the event, the

presence of a biologically implausible relationship between the product and the AE (e.g. the event occurred before administration of drug), or the presence of a more likely alternative explanation for the AE.

Related: There is a possibility that the event may have been caused by the product under investigation. Consideration should be given to factors, including but not limited to a positive re-challenge, a reasonable temporal sequence between administration of the drug and the event, a known response pattern of the suspected drug, improvement following discontinuation or dose reduction, a biologically plausible relationship between the drug and the AE or a lack of an alternative explanation for the AE.

11.3.3 Outcome

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

- Fatal: The AE resulted in death ("Death" is recorded as an outcome, not as the AE)
- Ongoing/Not resolved: The AE has not resolved
- Recovered with sequelae: Resolution of the AE has occurred, but the subject retains some sequelae
- Recovered: The AE fully resolved with no observable residual effects
- Unknown: The outcome of the AE is not known as the subject did not return for follow-up and attempts to locate the subject and/or to obtain follow-up information were unsuccessful (lost to follow-up).

11.4 RE-EXPOSURE

If an AE requires discontinuation of IMP and is judged to be treatment-related by the Investigator or by the Sponsor, re-exposure is not allowed. If an AE requires dose reduction or discontinuation of IMP and is judged by the Investigator or by the Sponsor to be unrelated to investigational products, the decision to re-introduce the medication or to increase the dose of the medication requires prior approval of the Sponsor or designee.

12 STATISTICAL CONSIDERATIONS

12.1 POWER CALCULATIONS

The study will be analysed by descriptive statistics only. As such, there is no formal power calculation.

The aim is to recruit up to 49 subjects in each treatment group in the 2 – 17 years cohort. At least 12 subjects in each age group (i.e. 36 subjects in total) will be included in the PK model in the ferric maltol oral suspension group. A sample size of 49 in the Ferric Maltol group provides at least 80% power to demonstrate that the lower bound of the 95% confidence interval for increase in Hb at 12 weeks, compared with baseline, is above zero. This assumes that the SD of the change from baseline is 1.2 g/dL or lower and the true mean change is at least 0.5 g/dL.

Every effort will be made to recruit up to 12 subjects in the under 2`s age group but in case of reasons of feasibility it cannot be completed, then the study may be completed without that cohort.

If less than 91 subjects in total have been randomized when 32 ferric maltol subjects have completed, then an interim analysis of the primary effectiveness endpoint (change in Hb concentration from baseline to Week 12) will be conducted. Less than 91 subjects recruited would indicate that the study will not complete in the near future.

The interim analysis will test for significance of the increase in Hb in the ferric maltol arm (from Baseline to Week 12). If significant, the study will stop recruitment. If not significant, the study will continue (all subjects will be assigned to ferric maltol) until 54 subjects have been recruited in the ferric maltol arm.

12.2 STATISTICAL METHODS

Full details of the statistical analysis, including the analysis of PK endpoints, will be specified in the statistical analysis plan.

12.2.1 Primary Endpoint Analysis

- Safety and gastrointestinal tolerability will be compared between ferric maltol oral suspension and ferrous sulfate oral liquid via the incidence of treatment emergent adverse events (TEAEs), treatment emergent serious AEs (TESAEs) and treatment-emergent AEs (TEAEs) leading to premature discontinuation of study drug, estimated as the number of subjects with at least one event divided by the number of subjects in the safety population.

- AEs will be categorised by primary system organ class and MedDRA preferred term as coded using the MedDRA dictionary. The number, intensity, relation to study medication and action taken will be described by incidence tables. SAEs will be discussed separately.
- Efficacy of ferric maltol will be assessed via the change in Hb concentration from baseline to week 12.
    - If no interim analysis is conducted it will be based on a 95% two-sided confidence interval;
    - If an interim analysis is conducted, a Pocock spending function will be used; the interim analysis will be based on a (100 – 3.45) % two sided confidence interval;
    - if the study does not stop after the interim analysis, the final analysis will be based on a (100 – 2.57)% two sided confidence interval

12.2.2 Secondary Endpoint Analyses

The following endpoints will be reported for each treatment group using descriptive statistics summarised by mean, median, and range, and 95% CIs where applicable, split by age group:

- PK analysis of serum iron, TSAT, transferrin, TIBC, 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 12
- Achieving Hb concentration within normal range at Week 12
- Qualitative assessments from subject questionnaires that allow evaluation of the acceptability, palatability and ease of use
- For subjects aged 1 month to < 2 years; Maltol and maltol glucuronide in urine: $Ae_{0\text{-}6h}$, $Ae_{0\text{-}3h}$, $Ae_{3\text{-}6h}$, $D_{urine0\text{-}6h}$, $D_{urine0\text{-}3h}$, $D_{urine3\text{-}6h}$, CL_R; Pre-assignment and PK Day 2

Categorical variables will be summarised for each treatment group via number and percentage in each category, split by age group:

- Achieving Hb concentration within normal range at Week 12

Qualitative assessments from subject questionnaires that allow evaluation of the acceptability, palatability and ease of use will be summarised appropriately.

12.2.3 Sensitivity Analyses

Change in Hb concentration from baseline to Week 12, will be summarized for subjects randomized when the endpoint was designated as secondary and for subjects randomized after the endpoint was changed to a primary endpoint.

12.2.4 Imputation of Missing Data

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

12.3 DEFINITION OF POPULATIONS

12.3.1 Randomised Population/ Intention to treat (ITT)

All subjects who are randomised/assigned to treatment arms.

12.3.2 Safety Population

All subjects who have had at least one dose of study drug will be analysed for safety.

12.3.3 Per Protocol Population (PP)

The PP population will consist of those randomised/assigned subjects who do not have major protocol deviation during the study.

12.3.4 Pharmacokinetic (PK) Population (Full Analysis Set)

All subjects who have had at least one dose of study drug and who have at least one evaluable post-dose PK sample (applicable only for ferric maltol group) will be included in the PK analysis.

13 ETHICAL CONSIDERATIONS

The Sponsor and Investigator must comply with this protocol, all applicable national and local regulations including International Conference on Harmonisation (ICH) and Good Clinical Practice (GCP).

13.1 DECLARATION OF HELSINKI

The Sponsor and the Investigator must comply with the principles set forth by the Declaration of Helsinki dated October 2008.

13.2 INSTITUTIONAL REVIEW BOARD / INDEPENDENT ETHICS COMMITTEE

The Investigator must ensure that the IRB/IEC has approved the protocol, the Information Sheet and Consent/Assent Form and any other required study documents prior to starting the study. The Sponsor must approve any changes to the Information Sheet and Consent/Assent Form before submission to the IRB/IEC.

Prior to activation of a site and provision of IMP, the Sponsor must receive documentation to demonstrate IRB/IEC approval of the required study documents and must have completed a comprehensive site initiation training with the Investigator and site staff.

A progress report must be submitted to the IRB/IEC at least annually and more frequently if required by the IRB/IEC.

On completion or termination of the study the Investigator or Sponsor must submit a closeout letter to the IRB/IEC (as required). A copy of the CSR synopsis will also be sent in accordance with local laws.

13.3 SUBJECT INFORMATION AND INFORMED CONSENT

IRB/IEC approval of the written information sheet and consent/assent form must be obtained prior to use. The Information Sheet will provide the subject/legal guardian with a complete and comprehensive explanation of the study including the study rationale, the procedures, the benefits and risks, that participation is voluntary and that the subject may withdraw from the study at any time without any negative consequences. In addition, a physician will discuss this information with the subject/legal guardian who will be given sufficient time and opportunity to have any questions answered and to make a decision of whether to participate in the study.

Written informed consent must be obtained from the subject/legal guardian in accordance with local practice and regulations prior to any study assessment or test being conducted. Written consent will be obtained by signing and dating the IRB/EC approved consent/assent forms.

Each consent form must also contain an authorisation for the Sponsor and Investigators to use and disclose Protected Health Information (PHI) in compliance with local law.

No study assessments or procedures should be conducted until written informed consent/assent has been provided.

A copy of the information sheet and consent/assent form signed and dated by the subject/legal guardian must be given to the subject/legal guardian. The signed consent and assent form(s) will be retained with the study records at site. A description of the consent/assent process must be documented in the subject's medical record.

13.4 SUBJECT DATA PROTECTION

Prior to any study test being conducted, including Screening tests, the subject/legal guardian must provide authorisation as required by local law to use and disclose PHI. Subjects will not be identified by name (or initials) in the eCRF or any study reports. Data will be used for research purposes only. Every effort will be made to keep the subject's personal medical data confidential. All data will be used for research purposes only.

13.5 SUBJECT INSURANCE

The Sponsor maintains appropriate insurance coverage for clinical trials and will follow applicable local compensation laws.

13.6 CONFLICT OF INTEREST

Investigators should address any potential conflicts of interest (e.g. financial interest in the Sponsor) with the subject before the subject makes a decision to participate in the study.

13.7 REGISTRATION OF STUDY AND DISCLOSURE OF RESULTS

The Sponsor will register the study on all required registries (e.g. clinicaltrials.gov) and will post study results regardless of outcome on publicly accessible websites in accordance with the applicable laws and regulations.

14 STUDY MANAGEMENT

14.1 SOURCE DATA

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

The Investigator should ensure clear records are maintained that demonstrate the integrity of the data reported to the Sponsor via the eCRF. This includes all original records, certified copies of clinical findings, observations or other activities necessary for reconstruction and evaluation of the study. This includes, but is not limited to, Investigator signed/dated laboratory reports and medical notes. Source data must not be changed without clear and documented rationale. Any changes should be confirmed with the originator. A full audit trail should always be available to identify the person making the entry and/or amendments, the original entry/result, the amendment and rationale. The Investigator must ensure that source data is always attributable, legible, contemporaneous, original and accurate.

For this study, key data reported on eCRFs will be verified against source documents. The eCRF will not act as source except in the instance of laboratory data which will be transferred directly to the Sponsor/designee responsible to Data Management.

14.2 QUALITY ASSURANCE

During and/or after study completion, Sponsor quality assurance officers, IRB/IEC or regulatory authorities may perform on-site audits. The Investigator will be expected to cooperate with any audit by providing assistance and access to all requested study-related records.

14.3 MONITORING

The Investigator must permit study-related monitoring by providing direct access to source data and to the subjects' medical records. The Monitor(s) will visit the Investigator at regular intervals during the course of the study and after completion of the study if needed.

During the monitoring visits, eCRFs, source records and other documentation relating to the study will be made available for review. The Investigator will ensure any discrepancies or omissions are resolved.

Monitoring visits must be conducted according to the applicable ICH and GCP guidelines to ensure protocol adherence, data quality, IMP accountability, compliance with IRB/IEC/regulatory requirements and continued adequacy of the investigational site, resources and its facilities to conduct the study.

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

14.4 STUDY FUNDING

Shield TX (UK) Limited is the Sponsor and provides funding for the conduct of this study. All financial details are provided in clinical trial agreements between the institution, Investigator and Sponsor.

14.5 CONTRACT RESEARCH ORGANISATION (CRO)

A CRO (Medpace Inc.) will be contracted to be responsible for administrative aspects of the study including, but not limited to, site selection and qualification, study set-up, site initiation, monitoring, data management including clinical database and electronic CRF provisioning, statistics and programming and study reporting. Vendors will also be contracted to cover supportive services such as a central laboratory, bioanalysis of PK samples and IMP production/labelling, distribution.

14.6 AMENDMENTS TO THE STUDY PROTOCOL

The study will be conducted in compliance with this Protocol, as approved by all relevant parties. Should any amendments to the protocol be deemed necessary, this will be resolved by mutual written agreement between the Principal Investigator and the Sponsor.

Any significant changes to the protocol shall be submitted to the IRB/IEC and Regulatory Authorities and must be approved prior to implementation as required by local law.

However, the Sponsor may, at any time, amend this protocol to eliminate an apparent immediate hazard to a subject. In this case, appropriate communications and notifications to the IRB/IEC and Regulatory Authorities will occur as required by local law.

Amendments to the Information Sheet and Consent/Assent Form will be made if impacted by an amendment to the study protocol which will also be submitted and approved to the IRB/IEC as required by local law.

14.7 STUDY STOPPING RULES

The Sponsor may terminate this study at any time. In consultation with the Investigator, it is normal procedure to review the emerging clinical and safety data (see Section 7.6). As a result of this review, it may be necessary to stop the study before all subjects have completed the study. In this case, all subjects will be followed-up for safety assessments.

If less than 91 subjects in total have been randomized when 32 ferric maltol subjects have completed, then an interim analysis will be conducted. The interim analysis will test for significance of the increase in Hb in the ferric maltol arm. If significant, the study will stop recruitment. If not significant, the study will continue until 54 subjects have been recruited in the ferric maltol arm.

The Sponsor will notify the IRB/IEC of discontinuation of the study and the reason for doing so.

14.8 END OF STUDY

The end of study is the date of the last subject, last visit for final collection of data.

14.9 RETENTION OF RECORDS

The Investigator must retain the informed consent/assent documentation, disposition of the IMP, hard-copy eCRFs, medical records and other source data at least 25 years after completion or discontinuation of the trial or for at least 2 years after the granting of the last marketing authorisation in the EC (when there are no pending or contemplated marketing applications in the EC) or for at least 2 years after formal discontinuation of clinical development of the investigational product. Prior to proceeding with destruction of records, the Investigator must notify the Sponsor in writing and receive written authorisation from the Sponsor to destroy study records.

The Investigator must also notify the Sponsor of any changes in the archival arrangements including, but not limited to, archival at an off-site facility or transfer of ownership if the Investigator leaves the site.

In addition, the Sponsor will retain copies / originals (as appropriate) of any study-related documents in the Trial Master File for at least 25 years after completion or discontinuation of the trial or for at least 2 years after the last approval of a marketing application in an ICH region, until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product.

14.10 SECURITY AND PUBLICATIONS

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

The Sponsor ensures that substances used in the manufacture of the IMP are generally known in pharmaceutical science and have been released by the appropriate national authorities for use in medications, cosmetics or food.

Publication rights will be described in the Investigator contract. The study site's agreement is not required for using the study results for discussions with regulatory/governmental authorities or for other purposes such as presentation at conferences, discussion with potential licencing partners or specialist groups.

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