CLINICAL STUDY PROTOCOL: A Phase 1, Open-Label, Randomised, Repeat Dose, Parallel Group Study to Evaluate the Pharmacokinetics, Safety and Tolerability of Ferric Maltol at Three Dosage Levels in Paediatric Subjects Aged 10-17 Years of Age with Iron Deficiency (with or without Anaemia)

Protocol Number: ST10-01-103

Test Drug: Ferric Maltol

EudraCT Number: 2016-002192-10

NCT Number: **NCT03181451**

Study Name: AEGIS Kids PK

Sponsor: Shield TX (UK) Limited, Northern Design Centre, Baltic Business Quarter, Gateshead Quays, NE8 3DF United Kingdom

Version/Date: Version 3.0, Final, 08 February 2017

Confidentiality Statement

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1 PROTOCOL APPROVALS

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3 ABBREVIATION INDEX

AE	Adverse Event
ALT	Alanine Aminotransferase
ANCOVA	Analysis of Covariance
AST	Aspartate Aminotransferase
AUC	Area Under the Plasma Concentration Curve
$AUC_{(0\text{-}6h)}$	Area Under the Plasma Concentration Curve for 0-6h
$AUC_{(0\text{-}inf)}$	Area Under the Plasma Concentration Curve for 0-infinity
BID	Twice Daily
BUN	Blood Urea Nitrogen
C	Celsius
CA	Competent Authority
$C_{ave(0\text{-}6h)}$	Average Steady State Plasma Concentration from 0-6h
CD	Crohn's Disease
CHr	Reticulocyte Haemoglobin Concentration
C_{max}	Maximum Plasma Concentration
CL/F	Apparent Systemic Clearance
CRF	Case Report Form
CRO	Contract Research Organisation
CRP	C-Reactive Protein
CS	Clinically Significant
CSR	Clinical Study Report
C_{trough}	Minimum Plasma Concentration
ECG	Electrocardiogram
eGFR	Estimated Glomerular Filtration Rate
ESA	Erythropoiesis Stimulating Agent
FOCE	First Order Conditional Estimation
FO	First Order Estimation
GCP	Good Clinical Practice
GGT	Gamma-Glutamyl Transpeptidase
GI	Gastrointestinal
GMP	Good Manufacturing Practice
h	Hour
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
IRB	Institutional Review Board

ITT	Intention-To-Treat
IV	Intravenous
MCH	Mean Cell Haemoglobin
MCHC	Mean Cell Haemoglobin Concentration
MCV	Mean Cell Volume
NCS	Non-Clinically Significant
NTBI	Non-Transferrin Bound Iron
OFP	Oral Ferrous Product
PHI	Protected Health Information
PK	Pharmacokinetics
PPK	Population Pharmacokinetics
PP	Per Protocol
PR	Electrocardiogram PR Interval
QRS	Electrocardiogram QRS Duration
QT	Electrocardiogram QT Interval
RR	Electrocardiogram RR Interval
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
$t_{1/2}$	Half-life
TIBC	Total Iron Binding Capacity
T_{max}	Time to Maximum Plasma Concentration
TNFα	Tumor necrosis factor alpha
TSAT	Transferrin Saturation
UC	Ulcerative Colitis
UIBC	Unsaturated Iron Binding Capacity
V/F	Apparent Volume of Distribution
WHO	World Health Organisation
yrs	Years

4 SYNOPSIS

Title	A Phase 1, Open-Label, Randomised, Repeat Dose, Parallel Group Study to Evaluate the Pharmacokinetics, Safety and Tolerability of Ferric Maltol at Three Dosage Levels in Paediatric Subjects Aged 10-17 Years of Age with Iron Deficiency (with or without Anaemia)
Protocol Number	ST10-01-103
Study Name	AEGIS Kids-PK
Test Drug	Ferric Maltol (ST10)
Comparator	Not Applicable
Phase	Phase 1
Sites	Approximately 4-6 sites in the UK
Study Rationale	The existing scientific and clinical experience with ferric maltol in the treatment of IDA in patients with inflammatory bowel disorder (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-PIP01-11). This trial is the initial PIP specified clinical study, designed to establish the PK and iron uptake of Ferric Maltol in children and adolescents aged 10-17 years using two (2) lower dose strengths in comparison to the approved 30mg BID dose in adults with IDA in IBD. The data from this study will be used to select the dose(s) for a subsequent Phase 3 paediatric study of Ferric Maltol in the treatment of IDA (per the EU PIP). Doses chosen for this paediatric pharmacokinetic study (ages 10 to 17 years) are based on the daily elemental iron requirements of the study subjects and the broad range of weights likely to enrolled, with an aim of finding a minimum effective dose in this age group. With the 30mg BID adult dose chosen as the highest exposure, 16.6mg BID and 7.8mg BID were chosen as approximately ½ and ¼ of the adult dose. The exact doses coincide with full fill of available capsule shell sizes. The lower strength formulations will be identical to the 30mg capsule formulation.
Objectives	**Primary objective:** To assess the pharmacokinetics (PK) and iron uptake of Ferric Maltol (ST10) in children and adolescents (aged 10-17 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.

Secondary objectives:

1. To assess the effect of 7.8 mg, 16.6 mg or 30 mg Ferric Maltol in children and adolescents (aged 10-17 years) after twice daily oral doses for 9 days (Days 1 to 9) and a single morning dose on Day 10, on serum transferrin, total and unsaturated iron binding capacity (TIBC, UIBC), ferritin, non-transferrin bound iron (NTBI); routine haematology indices, including absolute reticulocyte count, in blood.

2. To assess the safety and tolerability of 7.8 mg, 16.6 mg or 30 mg Ferric Maltol in children and adolescents (aged 10-17 years) after twice daily oral doses for 9 days (Days 1 to 9) and a single morning dose on Day 10, based upon vital signs, adverse events, concomitant medications, 12-lead ECG and clinical laboratory safety blood tests.

Endpoints

Primary endpoints:

1. Population PK analysis of maltol and maltol glucuronide in plasma from PK samples collected on Day 1 (after first morning dose) and Day 10 (after last morning dose). Parameters to be derived and reported for each Ferric Maltol dose will be:

   C_{max}, $C_{ave(0\text{-}6h)}$, $AUC_{(0\text{-}6h)}$, $AUC_{(0\text{-}inf)}$ on Day 1 and Day 10, and ratios of Day 10/Day 1 for these parameters.

   T_{max}, half-life ($t_{1/2}$).

   Apparent systemic clearance (CL/F), apparent volume of distribution (V/F)

   Descriptive statistics for plasma concentrations of maltol and maltol glucuronide by time of collection on Day 1 and Day 10 will also be presented, including C_{trough}.

2. Descriptive and population PK analysis of serum iron and TSAT from PK samples collected on Day 1 and Day 10. Parameters to be derived and reported for each Ferric Maltol dose will be:

   Change from pre-dose (C_{trough}) to maximum post-dose (C_{max}) value for serum iron and TSAT; $C_{ave(0\text{-}6h)}$.

   Pre-dose adjusted Incremental $AUC_{(0\text{-}6h)}$ on Day 1 and Day 10 from a population PK analysis approach, and percentage change from Day 1 to Day 10.

   Apparent systemic clearance (CL/F), apparent volume of distribution (V/F).

   Descriptive statistics for serum iron and TSAT by time of collection on Day 1 and Day 10 will also be presented.

Secondary endpoints:

1. Descriptive analysis of transferrin, TIBC, UIBC and ferritin concentrations from PK samples collected on Day 1 and Day 10.
2. Descriptive analysis of non-transferrin bound iron (NTBI) concentrations from PK samples collected on Day 1 and Day 10.
3. Descriptive analysis of haemoglobin concentration and absolute reticulocyte count from haematology samples collected at Screening and Day 10.
4. Treatment-emergent Adverse Events (AEs) will be summarised.
5. Treatment-emergent Serious Adverse Events (SAEs) will be summarised.
6. Treatment-emergent Adverse Events leading to premature discontinuation of study drug/PK assessments will be summarised.
7. Clinical laboratory safety blood results at Screening and Day 10 will be summarised.
8. Changes in vital signs and 12-lead ECG will be summarised.
9. Concomitant medications will be summarised.

Design

The study will comprise of the following stages:

- Screening: to determine subject eligibility for the study (within 14 days prior to the planned Ferric Maltol dosing period for each subject).
- Randomised, Parallel Group, Open-Label Treatment Period: A treatment period of 10 days with 2 visits on Day 1 and Day 10 for PK blood sampling.

  Eligible subjects will be randomly allocated to one of the three Ferric Maltol dose groups according to a centralised treatment allocation scheme, as follows:

  1. Group 1 – 12 subjects will receive 30 mg Ferric Maltol twice daily for 9 days (Days 1-9) plus a final 30mg dose on the morning of Day 10. PK study Day 1 & Day 10.
  2. Group 2 – 12 subjects will receive 16.6 mg Ferric Maltol twice daily for 9 days (Days 1-9) plus a final 16.6mg dose on the morning of Day 10. PK study Day 1 & Day 10.
  3. Group 3 – 12 subjects will receive 7.8 mg Ferric Maltol twice daily for 9 days (Days 1-9) plus a final 7.8mg dose on the morning of Day 10. PK study Day 1 & Day 10.

- Post-treatment Safety Follow-up: 3-10 days following completion of the treatment period or premature discontinuation of study medication.

Number of Subjects

Thirty-six (36) eligible subjects aged 10-17 years will be randomised at a ratio of 1:1:1 to one of three doses of Ferric Maltol (7.8 mg, 16.6 mg or 30 mg twice daily [BID]) for 9 days (Days 1 to 9); a final single dose will then be administered on the morning of Day 10.

The randomisation scheme will be stratified by co-variates for age (10-14y, 15-17y) and sex (M/F). This will ensure that a minimum of 25% of each gender and at least 3 children per age group (15-17 yrs and 10 to 14 yrs) are enrolled in each Ferric Maltol dose group.

Inclusion Criteria

1. Ability to understand the information given in the Independent Ethics Committee (IEC) approved Information Sheet and Consent form. The parent or guardian of the study subject must sign and date the informed consent and authorisation to use protected health information (PHI) in accordance with national and local subject privacy regulations prior to any study mandated procedure. The study participant will be asked to provide their assent to participate in the study using the IEC approved Assent form.
2. Willing and able to comply with study requirements.
3. Age ≥10 to ≤17 years at the time of informed consent and throughout duration of the study.
4. A current diagnosis of iron deficiency (with or without anaemia); iron deficiency defined by ferritin <30 μg/L, or ferritin <50 μg/L with transferrin saturation (TSAT) <20%, as measured by the central laboratory at the Screening visit (subjects with or without anaemia may be enrolled providing Hb is ≥8.5 g/dL as measured at the Screening visit).
5. Where appropriate, female subjects of childbearing potential must agree to use a reliable method of contraception until study completion and for at least 4 weeks following their final study visit. Reliable contraception is defined as a method which results in a low failure rate, i.e., less than 1% per year when used consistently and correctly, such as implants, injectables, some intrauterine contraceptive devices (IUDs), complete sexual abstinence, a vasectomized partner and oral contraceptive medications.

Exclusion Criteria

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

1. Has untreated or untreatable severe malabsorption syndrome e.g., untreated coeliac disease
2. Has received within 28 days prior to Screening intramuscular or intravenous (IV) injection or administration of depot iron preparation.
3. Has received oral iron supplementation within 7 days prior to Screening
4. Has received blood transfusion within 12 weeks prior to Screening or is scheduled to have blood transfusion or donations during the

study period.

5. Has concomitant disease that would significantly compromise iron absorption or absorbed iron utilisation such as swallowing disorders and/or extensive small bowel resection.
6. Has chronic renal disease (eGFR <30mL/min), as assessed at Screening based on serum creatinine.
7. Known hypersensitivity or allergy to either the active substance or excipients of Ferric Maltol capsules.
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. 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.
17. 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 oral iron preparations (prescription and non-prescription) within 7 days prior to Screening and throughout the study period. Over the Counter (OTC) multivitamins containing iron are permitted provided the dose remains stable throughout the study (from Screening to Post-Study visit).
- Treatment with parenteral iron preparations within 28 days prior to Screening and throughout the study period.
- Antibiotics, which are prohibited at screening and during the study.
- 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 taken at a stable dose for 12 weeks prior to randomisation and likely to stay stable throughout the study treatment period are permitted so long as there is no clinical evidence or suspicion of the immunosuppressant contributing to the subject's anaemia (if relevant).
- Vitamin B12 and folic acid supplements/replacement are allowed during the study
- Over the Counter (OTC) oral supplements/multivitamin type preparations may be taken, however subjects are encouraged to keep the same dose during the course of the study.
- Oral contraceptives are permitted, provided that the subject has been on a stable dose for at least 12 weeks prior to the Screening visit and dosage changes are not anticipated 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.
- 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 Ferric Maltol.

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-study visit, unless informed

consent is withdrawn (and the subject and/or their parent or guardian do not agree to attend this visit follow-up visit).

Investigational Medicinal Product

Ferric Maltol, presented as hard, gelatine, red capsules. For the purposes of this study capsules containing three different doses of iron and associated excipients will be provided:

- 30 mg capsule: Each capsule contains 30 mg iron and the following excipient(s) with known effect: lactose, Allura Red AC (E129) and Sunset Yellow FCF (E110).
- 16.6 mg capsule: Each capsule contains 16.6 mg iron and the following excipient(s) with known effect: lactose, Allura Red AC (E129) and Sunset Yellow FCF (E110).
- 7.8 mg capsule: Each capsule contains 7.8 mg iron and the following excipient(s) with known effect: lactose, Allura Red AC (E129) and Sunset Yellow FCF (E110).

Eligible subjects will be randomly allocated to one of the three Ferric Maltol dose groups according to a centralised treatment allocation scheme using the eCRF, and treated as follows:

1. Group 1 – 12 subjects will receive 30 mg Ferric Maltol twice daily for 9 days (Days 1-9) plus a final 30mg dose on the morning of Day 10. PK study Day 1 & Day 10.
2. Group 2 – 12 subjects will receive 16.6 mg Ferric Maltol twice daily for 9 days (Days 1-9) plus a final 16.6mg dose on the morning of Day 10. PK study Day 1 & Day 10.
3. Group 3 – 12 subjects will receive 7.8 mg Ferric Maltol twice daily for 9 days (Days 1-9) plus a final 7.8mg dose on the morning of Day 10. PK study Day 1 & Day 10.

Subjects will be instructed to take Ferric Maltol with a glass of water on an empty stomach (one hour before eating, or two hours after eating), as the absorption of iron is reduced when taken with food. The capsules should be swallowed whole only. The first capsule of Ferric Maltol will be administered in the presence of the site staff on Day 1. For subsequent doses, depending upon the age of the subject, capsules may need to be administered under the supervision of the child's parent or guardian. Subjects will be instructed to withhold their final dose of Ferric Maltol on the morning of Day 10 until pre-dose PK blood samples have first been collected at the site.

Statistical Methods

The primary endpoints for this study are PK parameters, which will be analysed using a Population PK (PPK) approach. PPK models will be built using a nonlinear mixed effects modelling technique with NONMEM® software. It is planned that the first order conditional estimation (FOCE) method will be used for model development. If this is not feasible (i.e. the model will fail to converge), the first order (FO) method will be used instead. Different models will be attempted to fit

the PK concentration-time data. The models will include but not limited to one-compartment linear model, one-compartment linear model with first order absorption, two-compartment linear mammillary model, two-compartment linear mammillary model with first order absorption, three- compartment linear model, and three-compartment linear model with first order absorption.

For each individual model, model stability will be assessed with the following:

- Model parameter estimates not close to a boundary;
- Shrinkage for interindividual variability terms (ETA) and residual unknown variability (EPS) < 30%;
- Condition number (ratio of the largest to the smallest eigenvalues) <100; and
- Correlation less than 0.95 between any two parameter estimates.

For the final PPK model, diagnostic plots will be presented.

The plasma maltol and maltol glucuronide concentration-time profile at steady state will be predicted using the PPK parameters estimates in the final model.

The pre-dose adjusted incremental $AUC_{(0\text{-}6h)}$ on Day 1 and Day 10 in serum iron and TSAT will be calculated with non-compartmental methods using a population approach. Ratio between Day 10 and Day 1 will be calculated.

Full details of the planned primary and secondary endpoint analyses will be documented in the Statistical Analysis Plan (SAP) for the study prior to database lock.

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 sulphate, 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 (sulphate, 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 prophylaxis and/or treatment of iron-deficiency anaemia in paediatric patients.

Table 1. Examples of oral iron compounds for treatment of iron-deficiency states in paediatrics

Product	Iron content	Indication(s)	Paediatric dose
Ferrous gluconate tablets	300 mg ferrous gluconate	Prevention and treatment of iron deficiency states.	Children (aged 6-12 years) Prophylactic: 1 or 2 tablets daily. Therapeutic: 3 tablets daily in divided doses.
Ferrous sulphate tablets	Each 200mg ferrous sulphate tablet is equivalent to 65mg of ferrous iron.	Prevention and treatment of iron- deficiency anaemia	Children 6-12 years: Treatment: > 22kg – one tablet daily; < 44kg – one tablet twice daily; > 66kg – one tablet three times daily. A liquid preparation maybe more appropriate for children.
Fersamal (syrup)	Ferrous fumarate approx 140 mg/5 mL (45 mg elemental iron)	Prophylaxis and treatment of iron- deficiency states for prophylaxis during pregnancy, a combination of iron and folic acid is usually recommended.	Full-term infants and young children: half to one 5 mL spoonful twice a day. Premature infants: 0.6 mL/kg/day to 2.4 mL/kg/day.
Feospan Spansule Capsules	Dried ferrous sulphate 150 mg (elemental iron 47 mg)	Prevention and treatment of iron deficiency	Children over one year: one capsules a day. The capsule may be opened and the pellets mixed with soft, cool food, but they must not be chewed.

Product	Iron content	Indication(s)	Paediatric dose
Galfer capsules	Ferrous fumarate 305.0 mg (equivalent to 100 mg elemental iron)	Treatment and prophylaxis of uncomplicated iron-deficiency anaemia	Children over 12 years; prophylaxis = one capsule daily; treatment = one capsule twice daily.
Galfer syrup	Ferrous fumarate 150 mg/5 mL (equivalent to 45 mg elemental iron)	Prophylaxis and treatment of iron- deficiency anaemia	Full-term infants and young children> 0.5 mL/kg/day administered in 2-3 divided doses daily. Max total daily dose should not exceed 20 mL. Premature infants: 0.5 mL/day in infants weighting up to 3 kg. Iron supplementation in premature infants is only recommended in those of low birth weight who are solely breastfed and in these cases supplementation should be commenced 4-6 weeks after the birth and continued until mixed feeding is established,
Niferex100 mg gastro-resistant capsules, hard	Ferrous (II) glycine-sulphate complex equivalent to Fe 2+ 100 mg.	Iron deficiency	Adults and children from age 6: 1 capsule per day. In case of pronounced iron deficiency anaemia, adults and adolescents from age 15 or from at least 50 kg bodyweight can increase dosage to 1 capsule 2-3 times daily at the beginning of therapy. A daily dose of 5 mg Fe 2+ / kg should not be exceeded. Capsules contain gastro-resistant granules, which can be emptied from the capsule shell and swallowed together

Product	Iron content	Indication(s)	Paediatric dose
Sytron (oral solution)	Sodium feredetate 190 mg (equivalent to 27.5 mg of iron/5 mL	Iron-deficiency anaemias, notably in paediatrics In pregnancy when other forms of oral iron may not be well absorbed Anaemias secondary to rheumatoid arthritis	Infant (including premature infants) up to 1 year: 2.5 mL twice daily, somewhat smaller doses should be used initially 1 to 5 years: 2.5 mL three times daily 6 to 12 years 5 mL three times daily

Data sourced from: http://www.medicines.org.uk/EMC/ and http://www.drugs.com/uk/

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. The approved dose and indication is 30mg twice daily (BID), taken in the morning and evening on an empty stomach for the treatment of IDA in IBD in adults.

Unlike OFPs, which are often given with food in order to reduce side effects, Ferric Maltol should, be given on an empty stomach to maximise bioavailability. Oral ferric iron chelated

with maltol can be administered with improved tolerability and the total dose exposure of unabsorbed iron within the GI tract is significantly reduced.

In early human studies, maltol was not detected in the systemic circulation following oral intake of Ferric Maltol. This suggests that following absorption, maltol undergoes rapid and complete first pass metabolism, is bio transformed to maltol-glucuronide, and excreted in the urine. This is consistent with the known metabolism and excretion of maltol absorbed naturally from the diet (WHO, 1980; WHO, 2006; Barrand, 1991a,b).

5.4 DOSE SELECTION AND RESULTS OF PREVIOUS CLINICAL STUDIES

Ferric maltol is not absorbed systemically as an intact complex and traditional PK studies may not provide the relevant information (Barrand 1991a,b). Therefore, a model was developed to determine the optimal dose. Data from 6 previous studies of Ferric Maltol in subjects with IBD and IDA were used to estimate absorption rates in the study population. Using these data, the model suggested that in a compliant adult study population, 30 mg Ferric Maltol twice daily would result in correction of baseline anaemia in the majority of subjects.

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 (30mg 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 2.25g/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.

The pharmacokinetics (PK) and iron uptake of 30mg 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 15min and 4h after dosing (mean Cmax 67.3ng/mL; median Tmax 1.0h; mean AUC 136h*ng/mL; mean t1/2term 0.8h). However, consistent with earlier studies of Ferric Maltol, maltol glucuronide predominated in plasma (mean Cmax 4677ng/mL; median Tmax 1.0h; mean AUC 9651h*ng/mL and mean t1/2term 1.1h). Maximal change in serum iron and TSAT was observed 2h 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%).

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). Twenty-four subjects received Ferric Maltol 30, 60, or 90 mg BID over an 8-day period. Pharmacokinetics 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). Maximum serum concentrations of total iron were reached between 2 and 3 hours' post-dose. Initially a slight decline in serum total iron concentrations was observed, followed by an increase to on average 32.3, 49.1 and 48.7 µmol/L on Day 1 for the 30 mg, 60 mg and 90 mg BID dose groups, respectively. Serum total iron concentrations gradually declined after reaching Tmax and mean serum concentrations were 11.8, 33.0 and 24.3 µmol/L above baseline at 6 hours' post-dose on Day 1 for the 30 mg, 60 mg and 90 mg BID dose groups, respectively. Comparable serum concentrations were measured on Day 8. Plots comparing total iron and the exposure to maltol and maltol glucuronide showed no clear relationship.

Maximum serum values of TSAT were reached between 2 and 3 hours' post-dose. TSAT values gradually increased up to an average value of 45.6, 69.8 and 67.3% on Day 1 for the 30 mg, 60 mg and 90 mg BID dose groups, respectively. TSAT gradually declined after reaching Tmax and serum values were 17.0, 47.3 and 33.3% above baseline at 6 hours' post-dose on Day 1 for the 30 mg, 60 mg and 90 mg BID dose groups, respectively. Similar TSAT serum values were measured on Day 8. Plots comparing TSAT and the exposure to maltol and maltol glucuronide showed no clear relationship.

Both serum iron concentration and TSAT increased after dosing, with maximum values between 1.5 and 3 hours' post dose. Iron absorption appeared to plateau at 60mg BID. There was no clear relationship between either total serum iron or TSAT and exposure to maltol or maltol glucuronide. Total serum iron concentrations and TSAT values were generally higher with increasing ferric maltol doses and were comparable after a single dose and at steady-state.

Plasma concentrations of both maltol and maltol glucuronide increased rapidly after dosing, reaching Cmax in around 1 to 1.5 hours' post dose, before declining to baseline levels between 3 and 6 hours. Exposure to maltol glucuronide was considerably higher than exposure to maltol for all ferric maltol dosing regimens. The mean amount of unchanged maltol excreted in urine over 6 hours (Ae0-6h) on Day 1 was very low: 0.1, 0.2 and 0.4 mcg for the 30 mg, 60 mg and 90 mg dose groups, respectively, representing approximately 0.05, 0.04 and 0.07% of the administered dose. The mean renal clearance ranged between 2.5 and 15 L/hour. Urine PK parameters were generally comparable between Day 1 and Day 8. The mean amount of maltol glucuronide excreted in urine over 6 hours on Day 1 was 197, 403 and 870 mg for the 30 mg, 60 mg and 90 mg BID dose groups, respectively, representing approximately 40.8, 41.7 and 60.6% of the administered dose. The mean renal clearance ranged between approximately 20 to 27 L/hour for the different dose groups. Urine PK parameters were generally comparable between Day 1 and Day 8.

Unlike serum iron, maltol absorption appeared to be dose proportional. These data are consistent with the iron and maltol absorption profiles reported in the early unpublished/published clinical data and the published non-clinical data.

Refer to the Investigator Brochure for further information.

5.5 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 and other causes of IDA. A Phase 3 study in 128 subjects with IDA and IBD, who are intolerant of OFPs or are unsuitable for treatment with them (ST10-01-301 and ST10-01-302; Gasche, 2015) demonstrated ferric maltol to be effective and well-tolerated.

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-PIP01-11).

This trial is the initial PIP specified clinical study, designed to establish the PK and iron uptake of Ferric Maltol in children and adolescents aged 10-17 years using two (2) lower dose strengths in comparison to the approved 30mg BID dose in adults with IDA in IBD. The data from this study will be used to select the dose(s) for a subsequent Phase 3 paediatric study of Ferric Maltol in the treatment of IDA (per the agreed EU PIP).

Doses chosen for this paediatric pharmacokinetic study (in ages 10 to 17 years) are based on the daily elemental iron requirements of the study subjects and the broad range of weights likely to enrolled, with an aim of finding a minimum effective dose in this age group. With the 30mg BID adult dose chosen as the highest exposure, 16.6mg BID and 7.8mg BID were chosen as approximately ½ and ¼ of the adult dose. The exact doses coincide with full fill of available capsule shell sizes. The lower strength formulations will be based on the 30mg capsule formulation. Fixed dosing with 7.8, 16.6 or 30mg Ferric Maltol BID is considered sufficient to meet the objectives of this study for a population PK analysis approach.

5.5.1 Study Population

The study population (per the PIP) will be male and females, aged 10-17 years.

5.5.2 Study Treatment Duration

Subjects will receive twice daily (morning and evening) Ferric Maltol (7.8mg, 16.6mg or 30mg) for 9 days (Days 1 to 9) and final single dose on the morning of Day 10.

5.6 RISK-BENEFIT EVALUATION

The safety of Ferric Maltol in 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 PK 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).

In this paediatric PK study, children aged 10 to 17 years will be 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 is considered not to be a risk. Furthermore, the metabolism of maltol through glucuronidation in the liver will be similar to adults. There is unlikely to be any great individual clinical benefit over 10 days of Ferric Maltol therapy, although the information gathered will be very important in establishing the dose(s) to be studied in the subsequent Phase 3 paediatric efficacy and safety study in IDA subjects. The risk to the subject related to study procedures has been assessed as very low. The study population will recruit subjects with iron deficiency or low-normal iron and who are otherwise generally well. The study population will include both female and male children and adolescents aged 10-17 age range. 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 main study procedure risk is related to IV cannulation and blood sampling, with fainting, minor bleeding and bruising regarded as the main risks. Overall the benefit-risk of this study is considered positive.

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

6 STUDY OBJECTIVES AND ENDPOINTS

6.1 PRIMARY OBJECTIVE

- To assess the pharmacokinetics (PK) and iron uptake of Ferric Maltol (ST10) in children and adolescents (aged 10-17 years) after twice daily [BID] oral doses of 7.8 mg, 16.6 mg or 30 mg for 9 days (Days 1-9) and single morning dose on Day 10 through measurement of serum iron, transferrin saturation (TSAT) and plasma concentrations of maltol and maltol glucuronide.

6.2 SECONDARY OBJECTIVES

- To assess the effect of 7.8 mg, 16.6 mg or 30 mg Ferric Maltol in children and adolescents (aged 10-17 years) after twice daily oral doses for 9 days (Days 1 to 9) and a single morning dose on Day 10, on serum transferrin, total and unsaturated iron binding capacity (TIBC, UIBC), ferritin, non-transferrin bound iron (NTBI); routine haematology indices, including absolute reticulocyte count, in blood.
- To assess the safety and tolerability of 7.8 mg, 16.6 mg or 30 mg Ferric Maltol in children and adolescents (aged 10-17 years) after twice daily oral doses for 9 days (Days 1 to 9) and a single morning dose on Day 10, based upon vital signs, adverse events, concomitant medications, 12-lead ECG and clinical laboratory safety blood tests.

6.3 PRIMARY ENDPOINTS

1. Population PK analysis of maltol and maltol glucuronide in plasma from PK samples collected on Day 1 (after first morning dose) and Day 10 (after last morning dose). Parameters to be derived and reported for each Ferric Maltol dose will be:

   C_{max}, $C_{ave(0\text{-}6h)}$, $AUC_{(0\text{-}6h)}$, $AUC_{(0\text{-}inf)}$ on Day 1 and Day 10, and ratios of Day 10/Day 1 for these parameters.

   T_{max}, half-life ($t_{1/2}$).

   Apparent systemic clearance (CL/F), apparent volume of distribution (V/F).

   Descriptive statistics for plasma concentrations of maltol and maltol glucuronide by time of collection on Day 1 and Day 10 will also be presented, including C_{trough}.

2. Descriptive and population PK analysis of serum iron and TSAT from PK samples collected on Day 1 and Day 10. Parameters to be derived and reported for each Ferric Maltol dose will be:

   Change from pre-dose (C_{trough}) to maximum post-dose (C_{max}) value for serum iron and TSAT; $C_{ave(0\text{-}6h)}$.

   Pre-dose adjusted Incremental $AUC_{(0\text{-}6h)}$ on Day 1 and Day 10 from a population PK analysis approach, and percentage change from Day 1 to Day 10.

   Apparent systemic clearance (CL/F), apparent volume of distribution (V/F).

Descriptive statistics for serum iron and TSAT by time of collection on Day 1 and Day 10 will also be presented.

6.4 SECONDARY ENDPOINTS

1. Descriptive analysis of transferrin, TIBC, UIBC and ferritin concentrations from PK samples collected on Day 1 and Day 10.
2. Descriptive analysis of non-transferrin bound iron (NTBI) concentrations from PK samples collected on Day 1 and Day 10.
3. Descriptive analysis of haemoglobin concentration and absolute reticulocyte count from haematology samples collected at Screening and Day 10.
4. Treatment-emergent Adverse Events (AEs) will be summarised.
5. Treatment-emergent Serious Adverse Events (SAEs) will be summarised.
6. Treatment-emergent Adverse Events leading to premature discontinuation of study drug/PK assessments will be summarised.
7. Clinical laboratory safety blood results at Screening and Day 10 will be summarised.
8. Changes in vital signs and 12-lead ECG will be summarised.
9. Concomitant medications will be summarised.

6.5 EXPLORATORY ENDPOINTS

Not Applicable

7 INVESTIGATIONAL PLAN

7.1 STUDY OVERVIEW

This is a Phase 1, randomised, open-label, parallel group, multicentre paediatrics pharmacokinetic (PK) study. Thirty-six (36) eligible subjects aged 10-17 years will be randomised at a ratio of 1:1:1 to one of three doses of Ferric Maltol (7.8 mg, 16.6 mg or 30 mg twice daily [BID]) for 9 days (Days 1 to 9); a final dose will then be administered on the morning of Day 10. During the treatment period (Days 1 to 10) subjects will visit the centre for two PK blood sampling sessions, Day 1 and Day 10. On those days, sparse PK blood sampling will be performed at baseline (pre-morning dose) and then at two (2) additional post-dose times up to 6 hours after the morning dose of Ferric Maltol (see Section 10.7.2).

The study will comprise of the following stages:

- Screening: to determine subject eligibility for the study (within 14 days prior to the planned Ferric Maltol dosing period for each subject).
- Randomised, Parallel Group, Open-Label Treatment Period: A treatment period of 10 days with 2 visits on Day 1 and Day 10 for PK blood sampling.

  Eligible subjects will be randomly allocated to one of the three Ferric Maltol dose groups according to a centralised treatment allocation scheme, as follows:

  1. Group 1 – 12 subjects will receive 30 mg Ferric Maltol twice daily for 9 days (Days 1-9) plus a final 30mg dose on the morning of Day 10. PK study Day 1 & Day 10.
  2. Group 2 – 12 subjects will receive 16.6 mg Ferric Maltol twice daily for 9 days (Days 1-9) plus a final 16.6mg dose on the morning of Day 10. PK study Day 1 & Day 10.
  3. Group 3 – 12 subjects will receive 7.8 mg Ferric Maltol twice daily for 9 days (Days 1-9) plus a final 7.8mg dose on the morning of Day 10. PK study Day 1 & Day 10.

- Post-treatment Safety Follow-up: 3-10 days following completion of the treatment period or premature discontinuation of study medication.

Refer to Section 10.1 for a schematic of the study design and Section 10.2 for a detailed schedule of assessments.

The randomisation scheme will be stratified by co-variates for age (10-14y, 15-17y) and sex (M/F). This will ensure that a minimum of 25% of each gender and at least 3 children per age group (15-17 yrs and 10 to 14 yrs) are enrolled in each Ferric Maltol dose group.

7.2 INVESTIGATIONAL SITES

Approximately 4-6 sites in the UK will participate in the study.

7.3 INCLUSION AND EXCLUSION CRITERIA

No deviations to the inclusion or exclusion criteria are permitted.

7.3.1 Inclusion Criteria

1. Ability to understand the information given in the Independent Ethics Committee (IEC) approved Information Sheet and Consent form. The parent or legal guardian of the study subject must sign and date the informed consent and authorisation to use protected health information (PHI) in accordance with national and local subject privacy regulations prior to any study mandated procedure. The study participant will be asked to provide their assent to participate in the study using the IEC approved Assent form.
2. Willing and able to comply with study requirements.
3. Age ≥10 to ≤17 years at the time of informed consent and throughout duration of the study.
4. A current diagnosis of iron deficiency (with or without anaemia); iron deficiency defined by ferritin <30 μg/L, or ferritin <50 μg/L with transferrin saturation (TSAT) <20%, as measured by the central laboratory at the Screening visit (subjects with or without anaemia may be enrolled providing Hb is ≥8.5 g/dL as measured at the Screening visit).
5. Where appropriate, female subjects of childbearing potential must agree to use a reliable method of contraception until study completion and for at least 4 weeks following their final study visit. Reliable contraception is defined as a method which results in a low failure rate, i.e., less than 1% per year when used consistently and correctly, such as implants, injectables, some intrauterine contraceptive devices (IUDs), complete sexual abstinence, a vasectomized partner and oral contraceptive medications.

7.3.2 Exclusion criteria

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

1. Has untreated or untreatable severe malabsorption syndrome e.g., untreated coeliac disease
2. Has received within 28 days prior to Screening intramuscular or intravenous (IV) injection or administration of depot iron preparation.
3. Has received oral iron supplementation within 7 days prior to Screening
4. Has received blood transfusion within 12 weeks prior to Screening or is scheduled to have blood transfusion or donations during the study period.
5. Has concomitant disease that would significantly compromise iron absorption or absorbed iron utilisation such as swallowing disorders and/or extensive small bowel resection.

6. Has chronic renal disease (eGFR <30mL/min), as assessed at Screening based on serum creatinine.
7. Known hypersensitivity or allergy to either the active substance or excipients of Ferric Maltol capsules.
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. 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.
17. 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 other oral iron preparations (prescription and non-prescription) within 7 days prior to Screening and throughout the study period. Over the Counter (OTC) multivitamins containing iron are permitted provided the dose remains stable throughout the study (from Screening to Post-Study visit).
- Treatment with parenteral iron preparations within 28 days prior to Screening and throughout the study period.
- Antibiotics, which are prohibited at screening and during the study.
- 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 taken at a stable dose for 12 weeks prior to randomisation and likely to stay stable throughout the study treatment period are permitted so long as there is no clinical evidence or suspicion of the immunosuppressant contributing to the subject's anaemia (if relevant).
- Vitamin B12 and folic acid supplements/replacement are allowed during the study
- Over the Counter (OTC) oral supplements/multivitamin type preparations may be taken, however subjects are encouraged to keep the same dose during the course of the study.
- Oral contraceptives are permitted, provided that the subject has been on a stable dose for at least 12 weeks prior to the Screening visit and dosage changes are not anticipated 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: quinolone or tetracycline antibiotics, bisphosphonates, angiotensin-converting enzyme inhibitors, folic acid, methyldopa, levodopa, carbidopa, levothyroxine, and mycophenolate.

To minimise the potential for drug interactions, Ferric Maltol should be taken on an empty stomach at least 2 hours prior to other concomitant medications and/or supplements.

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-Study Visit within 3-10 days after the last dose of study drug (if the subject agrees in the case of withdrawn consent).

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

- Withdrawal of informed consent.
- Unwillingness or inability to comply with protocol requirements.
- Pregnancy or not using a reliable method of birth control (female subject of childbearing potential, if applicable).
- Use of prohibited concomitant medications.
- Serious adverse events that are judged by the Investigator to be related to Ferric

Maltol.

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-study visit, unless informed consent is withdrawn (and the subject and/or their parents or guardians do not agree to attend this visit follow-up visit).

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 centres/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 will be supplied to study sites on behalf of Shield TX (UK) Ltd by Piramal Healthcare UK Limited, Whalton Close, Morpeth Northumberland, UK. 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.

8.1 INVESTIGATIONAL MEDICINAL PRODUCT (IMP) PRESENTATION

Ferric Maltol is presented as a hard, gelatine, red capsule. For the purposes of this study capsules containing three different doses of iron and associated excipients will be provided:

- 30 mg capsule: Each capsule contains 30 mg iron and the following excipient(s) with known effect: lactose, Allura Red AC (E129) and Sunset Yellow FCF (E110).
- 16.6 mg capsule: Each capsule contains 16.6 mg iron and the following excipient(s) with known effect: lactose, Allura Red AC (E129) and Sunset Yellow FCF (E110).
- 7.8 mg capsule: Each capsule contains 7.8 mg iron and the following excipient(s) with known effect: lactose, Allura Red AC (E129) and Sunset Yellow FCF (E110).

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

8.2 PACKAGING

Ferric Maltol capsules will be supplied in white polypropylene securitainer with a tamper evident standard securitainer cap of white medium density polyethylene. A single bottle containing 56 capsules will be provided to cover the entire 10-day treatment duration of the study for each subject. Each bottle will be uniquely numbered to facilitate allocation to an individual subject at randomisation.

8.3 STORAGE

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

8.4 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 Annex 13.

Individual supplies packaging and labelling will be checked by the Investigator/designee before the subject takes their first dose of study medication at site on Day 1, after which subjects will take their medication home and continue dosing from Day 1 evening, then

morning and evening from Days 2 to 9. The subject should withhold their morning dose on Day 10 until attending the site for PK assessments. The final single dose will be taken under supervision at the study site on the morning of Day 10, after pre-dose PK blood samples have been collected.

8.5 DISPENSATION

A specific strength bottle will be allocated to each subject according to the Ferric Maltol treatment randomly allocated for the 10-day dosing period using the eCRF system. Sites will dispense the next available bottle ID number for the corresponding Ferric Maltol dose group to each individual subject. Full details will be provided to sites in the Pharmacy File for the study.

8.6 ADMINISTRATION

Eligible subjects will be randomly allocated to one of the three Ferric Maltol dose groups according to a centralised treatment allocation scheme in the eCRF, as follows:

1. Group 1 – 12 subjects will receive 30 mg Ferric Maltol twice daily for 9 days (Days 1-9) plus a final 30mg dose on the morning of Day 10. PK study Day 1 & Day 10.
2. Group 2 – 12 subjects will receive 16.6 mg Ferric Maltol twice daily for 9 days (Days 1-9) plus a final 16.6mg dose on the morning of Day 10. PK study Day 1 & Day 10.
3. Group 3 – 12 subjects will receive 7.8 mg Ferric Maltol twice daily for 9 days (Days 1-9) plus a final 7.8mg dose on the morning of Day 10. PK study Day 1 & Day 10.

Subjects should be instructed to take Ferric Maltol on an empty stomach (one hour before eating, or two hours after eating) with a glass of water, as the absorption of iron is reduced when taken with food. The capsules should be swallowed whole only.

The first capsule of Ferric Maltol will be administered in the presence of the site staff on Day 1. For subsequent doses, depending upon the age of the subject, capsules may need to be administered under the supervision of the child's parent or guardian. Subjects will be instructed to withhold their final dose of Ferric Maltol on the morning of Day 10 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 capsule.

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 will be given a Diary Card on Day 1 after first dosing with Ferric Maltol at the study site and will be instructed to complete this card daily from the evening of Day 1 until the evening of Day 9, in order to document the day and time that they

took their morning and evening doses of Ferric Maltol on those treatment days whilst at home. Subjects will be instructed to return all unused supplies and all clinical study medication packaging on the morning of Day 10, having withheld their dose of Ferric Maltol that morning. Compliance will be assessed from the Diary Card entries and unused capsule count.

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 Visit 3, Day 10.

9 ENROLMENT AND RANDOMISATION PROCEDURES

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

9.1 SCREENING

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 randomisation, 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 14 days from the initial Screening visit date (if eligible based on retest results).

9.2 RANDOMISATION

Subjects will be registered into the study at the Screening visit and assigned a unique subject identification number in the eCRF. Subjects will be categorised during the screening process based upon their age (10 to 14 years of age and 15 to ≤ 17 years of age) and their gender. Age and gender will be incorporated into the randomisation as stratification factors. This will ensure that a minimum of 25% of each gender and at least 3 children per age group (15-17 yrs and 10 to 14 yrs) are enrolled and treated in each Ferric Maltol dose group.

A final eligibility evaluation must be conducted by the Investigator/designee prior to randomisation in the eCRF system, once the results of all Screening assessments are available. No subject may begin Ferric Maltol treatment prior to being randomised in the eCRF system. The randomisation procedure (created using a computer generated random permutation procedure) will assign the subject to one of the three study treatment groups (Ferric Maltol 30 mg, 16.6 mg or 7.8 mg BID). The randomisation process will also specify which PK blood sampling schedule should be followed for an individual subject on Day 1 and Day 10, in order to ensure that the minimum of three subjects per age group and Ferric Maltol dose group have PK samples collected at each of the required time point windows (see Section 10.7.2).

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

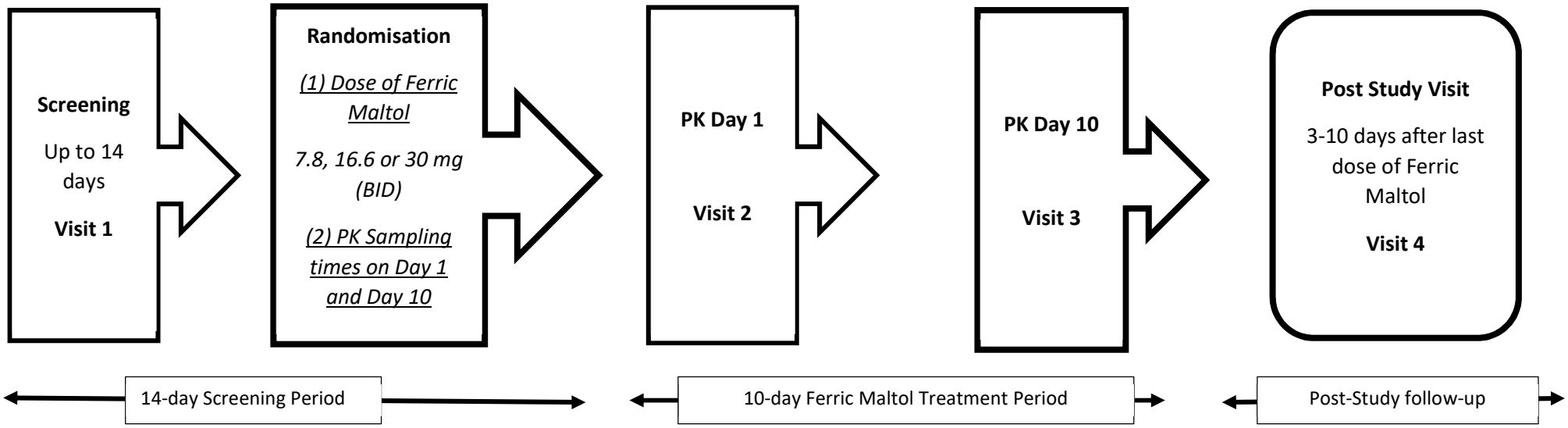
Not applicable as this is an open label study.

9.5 EMERGENCY UNBLINDING

Not applicable as this is an open label study

10 STUDY PROCEDURES

10.1 DESIGN SCHEMATIC



10.2 SCHEDULE OF ASSESSMENTS

PERIOD	SCREENING	TREATMENT		POST-STUDY FOLLOW-UP
Visit Number	**1**	**2**	**3**	**4**
Visit Name	**Screening Period[1]**	**PK Day 1**	**PK Day 2**	**Post-Study Safety Follow-up[4]**
Visit Day/Duration	**Up to 14 days**	**Day 1**	**Day 10**	**3-10 days after treatment discontinuation**
Informed Consent	**X**			
Demographics[7]	**X**			
Medical History	**X**			
Concomitant Medications and Procedures	**X**	**X**	**X**	**X**
Physical Examination	**X**			**X**
Vital Signs[2]	**X**	**X**	**X**	**X**
12-lead ECG[2]	**X**		**X**	
Urine Pregnancy Test[3]	**X**	**X**	**X**	**X**
Haematology, Clinical Chemistry and screening Iron markers blood sampling[3]	**X**		**X[6]**	
Eligibility Confirmation and Randomisation	**X**	**X[3]**		
Dispense Study Drug		**X**		
Supervised morning dosing with Ferric Maltol		**X**	**X**	
Sparse PK Blood Sampling for Iron markers, maltol/maltol glucuronide and NTBI[5, 6]		**X**	**X**	
Issue and Review of Subject Study Dosing Diary		**X**	**X**	
Subject to Return Study Drug for Accountability			**X**	
Adverse Events		**X**	**X**	**X**

1. A subject may be retested once for screening laboratory criteria that do not meet protocol in/exclusion criteria, so long as randomisation occurs no more than 14 days from the initial screening date (if eligible based on retest results).

2. Vital Signs – supine systolic/diastolic blood pressure, pulse rate and body temperature at each visit; 12-lead ECG at Screening and Day 10 (between 1h and 4h post-dose) - machine reported routine ECG parameters (heart rate, PR interval, RR interval, QRS duration, QT interval) and overall clinical ECG interpretation will be recorded in the eCRF.

3. Eligibility central laboratory sampling/assessments must be completed at Screening (Visit 1), before the subject is randomised and before the first dose of Ferric Maltol study treatment is taken. Screening parameters to be tested will be:

Haematology: red blood cell count, haemoglobin, haematocrit, mean cell volume (MCV), mean corpuscular haemoglobin (MCH), mean corpuscular haemoglobin (MCHC), white blood cell count (total and differential (% and absolute), absolute reticulocyte count and platelet count.

Clinical Chemistry: 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.

Urine pregnancy test for female subjects of childbearing potential.

On Day 10 (Visit 3), haematology and clinical chemistry blood samples will be collected at one of the PK sampling times between 1h to 4h post dose). Female subjects of childbearing potential will undergo urine pregnancy tests pre-dose on Day 1 and Day 10 and at the Post-study visit.

4. Subjects who discontinue from the study prematurely should have final assessments conducted per Visit 4/Post-study Safety Follow Up, unless consent is withdrawn.

5. On PK study Days 1 and 10, all subjects will have baseline PK blood samples collected immediately prior to Ferric Maltol dosing (0h). Subjects will then have further PK blood samples collected at two (2) additional times between 0.5h and 6h after dosing on Days 1 and 10; the post-dose PK sample time collection windows will be 0.5-1h, 1.0-2.0h, 2.0-3.0h, 3.0-4.0h and 4.0-6.0h. 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. For each individual subject, the post-dose PK blood sampling schedule will be the same on Day 1 and Day 10. Post-dose blood samples should be collected within the time windows allocated only. N.B: For those subjects in PK Sample Schedule Group 1 (see summary table in Section 10.7.4), the PK blood samples for the 0.5-1h timepoint window should be taken at least 30 minutes before the PK blood samples for the 1-2h timepoint window on Day 1 and Day 10. Further details are provided in Section 10.7.2 and Section 10.7.4. After the required post-dose PK blood sampling is completed on Day 1 and Day 10, an individual subject can be discharged from the site, providing the Investigator has no ongoing safety concerns.

6. Iron markers to be tested from PK blood samples on Days 1 and 10 will be: serum iron, total and unsaturated iron binding capacity (TIBC, UIBC), transferrin, transferrin saturation (TSAT), ferritin and non-transferrin bound iron (NTBI).

7. A minimum of 25% of each gender and at least 3 subjects per age category (10 to 14y and 15-17yr) are to be enrolled in each Ferric Maltol dose group. Height (m) and body weight (Kg) will be measured at Screening (Visit 1) only.

10.3 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 diagnosis regardless of onset, all clinically significant medical history from the past 5 years including all malignancies, sterilisations, hospitalisations and surgeries; the method of contraception for female subjects of childbearing potential, if applicable. Body weight (Kg), height (m) will be measured at the Screening visit only.

10.4 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.

10.5 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 with 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).

10.6 VITAL SIGNS AND 12-LEAD ECG

Body temperature (°C), blood pressure and pulse rate will be assessed at Screening, pre-dose on Days 1 and 10 and at Post-study; blood pressure and pulse rate should be measured after the subject has been supine for at least 5 minutes.

A 12-lead ECG will be recorded at Screening and again on Day 10 (between 1h and 4h post-dose). Machine reported standard ECG parameters (heart rate, PR interval, RR interval, QRS duration, QT interval) and overall clinical ECG interpretation will be recorded in the eCRF.

10.7 LABORATORY ASSESSMENTS

10.7.1 Haematology and Clinical Chemistry

Routine clinical laboratory safety bloods for haematology (1mL) and clinical chemistry/iron markers (5mL) evaluations will be collected at Screening to assess eligibility. Haematology (1mL) and clinical chemistry (2.5mL) will be repeated on Day 10 (at one of the PK sampling times between 1h to 4h post dose). 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.

10.7.1.1 Haematology test parameters

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

10.7.1.2 Clinical Chemistry and Screening Iron Markers test parameters

Clinical Chemistry: 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.

10.7.2 Pharmacokinetics

Blood samples for maltol and maltol glucuronide on Day 1 and Day 2 (Visits 2 and 3)

3mL venous blood samples will be collected in lithium-heparin tubes by indwelling cannula or venepuncture at the required times on the PK assessment days (Days 1 & 10), relative to the time of Ferric Maltol morning dosing: pre-dose then two further times between 0.5-6 hours post-dose (see Section 10.7.4).

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 and Non-Transferrin Bound Iron (NTBI) on Day 1 and Day 10 (Visits 2 and 3)

5mL venous blood samples will be collected in serum separator tubes (SST) by indwelling cannula or venepuncture at the following times on the PK assessment days (Days 1 & 10), relative to the time of Ferric Maltol dosing: pre-dose then then two further times between 0.5-6 hours post-dose (same times as blood samples for maltol/maltol glucuronide for each individual, see Section 10.7.4).

Following collection and mixing, blood samples will be centrifuged and the resultant serum samples separated and split into 1 primary (ambient) and 2 frozen (-20°C) 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) and ferritin. Frozen serum aliquots will be stored at site for later onward shipping on dry ice to the central laboratory. One (1) aliquot of frozen serum from each sampling timepoint on Day 1 and Day 10 will be assayed for serum concentrations of NTBI using an appropriately validated method; the second serum aliquot per timepoint will stored as a backup sample at 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.

10.7.3 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 with Ferric Maltol on Day 1; the result of this test must be negative for dosing with Ferric Maltol to commence on Day 1. Repeat urine pregnancy testing will also be conducted on Day 10 and at the Post-study visit.

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

10.7.4 Summary table of sparse PK blood sampling schedule on Day 1 and Day 10

On PK study Days 1 and 10, all subjects will have baseline (pre-dose) PK blood samples collected immediately prior to Ferric Maltol dosing (0h). Subjects will then have further PK blood samples collected at two (2) additional times between 0.5h and 6h after dosing on Days 1 and 10; within each Ferric Maltol dose group (7.8mg 16.6mg or 30mg BID), the post-dose PK sample time collection windows will be 0.5-1h, 1.0-2.0h, 2.0-3.0h, 3.0-4.0h and 4.0-6.0h. The twelve (12) subjects within each Ferric Maltol dose group 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. This is summarised in the following table:

PK Sample Schedule Day 1 and Day 10	PK Sample Schedule Group 1 (N=3/12)	PK Sample Schedule Group 2 (N=3/12)	PK Sample Schedule Group 3 (N=3/12)	PK Sample Schedule Group 4 (N=3/12)
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

For each individual subject, the post-dose PK blood sampling schedule will be the same on Day 1 and Day 10. Post-dose samples for each subject must be collected within the allocated time-windows (e.g. Between 0.5-1h or 1-2h); the exact time of sample collection will be recorded in the eCRF. For those subjects in PK Sample Schedule Group 1 (see above table), the PK blood samples for the 0.5-1h timepoint window should be taken at 30 minutes before the PK blood samples for the 1-2h timepoint window on Day 1 and Day 10, to provide an adequate spread of actual sampling times for the population PK analysis.

After the required post-dose PK blood sampling is completed on Day 1 and Day 10, an individual subject can be discharged from the site, providing the Investigator has no ongoing safety concerns for the subject.

10.7.5 Overall blood volume

The individual volume of blood collected throughout the study (Screening and PK assessment days) will be 57.5mL.

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/symptoms 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, ECG 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 an 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 subjects 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) such as discontinuation of subject's previous treatment during a washout period, 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 is obtained through study completion or premature discontinuation must be reported on the AE form in the CRF and reported within 24 hours to the Sponsor. All AEs occurring from the time of the first dose of study treatment through study completion or premature discontinuation must be reported on the AE form in the CRF.

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 (also 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 1483431831

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 and the updated AE form if appropriate.

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.

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). However, a severe event may be of relatively minor medical significance (such as severe headache) and is not necessarily serious. For example, nausea lasting several hours may be rated as severe, but may not meet the definition of seriousness. Fever of 39 °C that is not considered severe may become serious if it prolongs hospitalisation.

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.

11.5 SAFETY ENDPOINTS

During the study, safety endpoints will be treatment-emergent AEs and SAEs, including clinically significant changes from baseline in vital signs, physical examination, routine clinical laboratory abnormalities (other than iron deficiency/anaemia indices) and ECG wave interval, waveform or rhythm.

12 STATISTICAL CONSIDERATIONS

12.1 SAMPLE SIZE AND POWER CALCULATIONS

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

In sub-study ST10-01-102, with 15 IBD patients participating in the open-label phase of studies ST10-01-301 and ST10-01-302, plasma concentrations of maltol above the limit of assay detection were transiently observed between 15min and 4h after dosing (mean Cmax 67.3ng/mL; median Tmax 1.0h; mean AUC 136h*ng/mL; mean $t_{½term}$ 0.8h). However, consistent with earlier studies of ST10, maltol glucuronide predominated in plasma (mean Cmax 4677ng/mL; median Tmax 1.0h; mean AUC 9651h*ng/mL and mean $t_{½term}$ 1.1h). Maximal change in serum iron and TSAT was observed 2h 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%).

Therefore, as agreed with the EU CAs in the PIP, the inclusion of 36 subjects aged 10-17 years (12 per treatment group) in this study is considered to be adequate to characterise the iron uptake and PK parameters for the range of Ferric Maltol doses in an iron deficient adolescent population (with or without anaemia).

12.2 STATISTICAL METHODS

The following provides a summary of the statistical data analysis methods to be used. Full details of the planned PK and statistical analysis will be specified in the Statistical Analysis Plan (SAP) for the study prior to database lock.

12.2.1 Primary Endpoint Analysis

The primary endpoints for the study are pharmacokinetic parameters

1. Population PK analysis (PPK) of maltol and maltol glucuronide in plasma from PK samples collected on Day 1 (after first morning dose) and Day 10 (after last morning dose). Parameters to be derived and reported for each Ferric Maltol dose will be:

C_{max}, $C_{ave(0-6h)}$, $AUC_{(0-6h)}$, $AUC_{(0-inf)}$ on Day 1 and Day 10, and ratios of Day 10/Day 1 for these parameters.

T_{max}, half-life ($t_{1/2}$).

Apparent systemic clearance (CL/F), apparent volume of distribution (V/F).

Descriptive statistics for plasma concentrations of maltol and maltol glucuronide by time of collection on Day 1 and Day 10 will also be presented, including C_{trough}.

2. Descriptive and population PK analysis of serum iron and TSAT from PK samples collected on Day 1 and Day 10. Parameters to be derived and reported for each Ferric Maltol dose will be:

   Change from pre-dose (C_{trough}) to maximum post-dose (C_{max}) value for serum iron and TSAT; $C_{ave(0-6h)}$.

   Pre-dose adjusted Incremental $AUC_{(0-6h)}$ on Day 1 and Day 10 from a population PK analysis approach, and percentage change from Day 1 to Day 10.

   Apparent systemic clearance (CL/F), apparent volume of distribution (V/F).

   Descriptive statistics for serum iron and TSAT by time of collection on Day 1 and Day 10 will also be presented.

Population PK models will be built using a nonlinear mixed effects modelling technique with NONMEM® software. It is planned that the first order conditional estimation (FOCE) method will be used for model development. If this is not feasible (i.e. the model will fail to converge), the first order (FO) method will be used instead. Different models will be attempted to fit the PK concentration-time data. The models will include but not limited to one-compartment linear model, one-compartment linear model with first order absorption, two-compartment linear mammillary model, two-compartment linear mammillary model with first order absorption, three- compartment linear model, and three-compartment linear model with first order absorption.

For each individual model, model stability will be assessed with the following:

- Model parameter estimates not close to a boundary;
- Shrinkage for interindividual variability terms (ETA) and residual unknown variability (EPS) < 30%;
- Condition number (ratio of the largest to the smallest eigenvalues) <100; and
- Correlation less than 0.95 between any two parameter estimates.

For the final PPK model, diagnostic plots will be presented.

The plasma maltol and maltol glucuronide concentration-time profile at steady state will be predicted using the PPK parameters estimates in the final model.

The pre-dose adjusted incremental $AUC_{(0-6h)}$ on Day 1 and Day 10 in serum iron and TSAT will be calculated with non-compartmental methods using a population approach. Ratio between Day 10 and Day 1 will be calculated.

12.2.2 Secondary Endpoint Analyses

Secondary endpoints are:

1. Descriptive analysis of transferrin, TIBC, UIBC and ferritin concentrations from PK samples collected on Day 1 and Day 10.
2. Descriptive analysis of non-transferrin bound iron (NTBI) concentrations from PK samples collected on Day 1 and Day 10.
3. Descriptive analysis of haemoglobin concentration and absolute reticulocyte count from haematology samples collected at Screening and Day 10.
4. Treatment-emergent Adverse Events (AEs) will be summarised.
5. Treatment-emergent Serious Adverse Events (SAEs) will be summarised.
6. Treatment-emergent Adverse Events leading to premature discontinuation of study drug/PK assessments will be summarised.
7. Clinical laboratory safety blood results at Screening and Day 10 will be summarised.
8. Changes in vital signs and 12-lead ECG will be summarised.
9. Concomitant medications will be summarised.

In general, data for these secondary endpoints will be listed and summarised by dose group, as described in the SAP.

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.

Vital signs, body weight and height will be evaluated and summarised with appropriate descriptive statistics.

Abnormal findings on physical examination and 12-lead ECG clinical interpretation will be described by shift tables with description of shift from baseline categories of normal to abnormal. 12-lead ECG parameters will be listed and summarised descriptively.

Screening clinical laboratory data will be listed and summarised with appropriate descriptive statistics and for Day 10 results, changes from Screening will be summarised.

Concomitant medications will be listed and summarised by WHO preferred term.

12.2.3 Sensitivity Analyses

Any planned sensitivity analyses will be documented in the SAP prior to database lock.

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

All subjects who are randomised.

12.3.2 Safety Population

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

12.3.3 Intention- To-Treat (ITT) Population (Full Analysis Set)

For PPK, all subjects who have had at least one dose of study drug and who have at least one evaluable post-dose PK sample will be included in the ITT analysis. The ITT analysis will be used in the PPK 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 (e.g. EU Data Protection Directive 95/46/EC). 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 ECGs and 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.

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.

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

The Sponsor 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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