CLINICAL STUDY PROTOCOL

A randomized, open-label, single dose, four-way crossover, Phase I study to compare the pharmacokinetics of ferric maltol capsules and oral suspension under fasted and fed conditions in adult healthy volunteers

Protocol Number:	ST10-01-104
Test Drug:	Ferric Maltol (ST10)
EudraCT Number:	2018-000079-34
Study Name:	Phase 1 crossover study of the PK of ferric maltol capsules and suspension
Sponsor:	Shield TX (UK) Limited, Northern Design Center, Baltic Business Quarter, Gateshead Quays, NE8 3DF United Kingdom
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Confidentiality Statement

1 PROTOCOL APPROVALS

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AE	Adverse Event
ALT	Alanine Aminotransferase
ANCOVA	Analysis of Covariance
AST	Aspartate Aminotransferase
AUC	Area Under the Plasma Concentration Curve
$AUC_{(0\text{-}inf)}$	Area Under the Plasma Concentration Curve for 0-infinity
AUC_{last}	Area Under the Plasma Concentration Curve from 0 up to the last measurable concentration (non-below) quantification limit after dosing
BID	Twice Daily
BUN	Blood Urea Nitrogen
BP	Blood pressure
C	Celsius
CA	Competent Authority
CD	Crohn's Disease
CI	Confidence Interval
CKD	Chronic Kidney Disease
C_{max}	Maximum Observed Concentration
COVID-19	Coronavirus Disease 2019
CRA	Clinical Research Associate
CRF/eCRF	Case Report Form/electronic Case Report Form
CRO	Contract Research Organization
CS	Clinically Significant
CSR	Clinical Study Report
CV	Coefficient Variation
ECG	Electrocardiogram
eGFR	Estimated Glomerular Filtration Rate
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	Gamma-Glutamyl Transpeptidase
GI	Gastrointestinal
hr	Hour
Hb	Hemoglobin
HIV	Human Immunodeficiency Virus
IBD	Inflammatory Bowel Disease
ICH	International Conference on Harmonization
ID	Iron Deficiency
IDA	Iron Deficiency Anemia

IEC	Independent Ethics Committee
IMP	Investigational Medical Product
IRB	Institutional Review Board
IRT	Interactive Response Technology
IUD	Intrauterine Contraceptive Devices
IV	Intravenous
MAA	Marketing Authorization Application
NCS	Non-Clinically Significant
NTBI	Non-Transferrin Bound Iron
OFP	Oral Ferrous Product
PHI	Protected Health Information
PIP	Pediatric Investigational Plan
PK	Pharmacokinetics
PSP	Pediatric Study Plan
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SARS-CoV-2-RT-PCR	Severe Acute Respiratory Syndrome–associated Coronavirus Real-Time Reverse Transcriptase–Polymerase Chain Reaction
SD	Standard Deviation
TEAE	Treatment-emergent Adverse event
TESAE	Treatment-emergent Serious Adverse event
TIBC	Total Iron Binding Capacity
TLAG	The delay between the time of dosing and time of appearance of concentration in the sampling compartment.
T_{max}	Time to Maximum Plasma Concentration
TNF-a	Tumor Necrosis Factor alpha
TSAT	Transferrin Saturation
$T_{1/2}$	Apparent terminal elimination half-life
UC	Ulcerative Colitis
UIBC	Unsaturated Iron Binding Capacity
WHO	World Health Organization
yrs	Years
λz	Apparent terminal elimination rate constant, determined by linear regression of the terminal points of the ln-linear plasma concentration-time curve.

4 SYNOPSIS

Title	A randomized, open-label, single dose, four-way crossover, Phase I study to compare the pharmacokinetics of ferric maltol capsules and oral suspension under fasted and fed conditions in adult healthy volunteers
Protocol Number	ST10-01-104
Study Name	Phase 1 crossover study of the PK of ferric maltol capsules and suspension
Test Drug	Ferric Maltol (ST10)
Comparator	Not Applicable
Phase	Phase I
Sites	Approximately 1-2 sites
Study Rationale	The existing scientific and clinical experience with ferric maltol in the treatment of IDA in patients with inflammatory bowel disease (IBD) and chronic kidney disease (CKD) supports its further investigation in the treatment of iron deficiency/IDA in children and adolescents, in line with the Pediatric Investigation Plan (PIP) for Ferric Maltol that has been reviewed and approved by the European Medicines Agency (PIP reference: EMEA-001195-PIP 01-11) and the Pediatric Study Plan (PSP) agreed with the US FDA (IND 114832). Ferric Maltol makes iron available in the gastrointestinal tract, providing the iron in a biologically labile form for uptake across duodenal mucosal cells and ultimately hematopoiesis and storage on ferritin. Randomized Phase III studies (ST10-01-301/302) have demonstrated that Ferric Maltol over a 12-week period effectively increases Hb by over 2 g/dL compared to baseline in iron deficiency anemia patients with inflammatory bowel disease (IBD). Ferric Maltol was also demonstrated to be well tolerated (87% of subjects completing 12 weeks of study treatment) and with a side effect profile comparable to the placebo group. These data formed the basis of a Marketing Authorization Application (MAA) submission and subsequent EU centralized marketing

authorization. Ferric Maltol 30 mg capsules (Feraccru®) are approved for the treatment of Iron Deficiency in adults taken BID.

A randomized Phase III study (ST10-01-303) in 167 patients with IDA in Chronic Kidney Disease (CKD) over 16-week double blind phase and an open label 36-week treatment in 125 subjects demonstrated positive safety, efficacy and tolerability. Changes in TSAT, ferritin, and serum iron concentrations indicated an improvement in all iron parameters in the ferric maltol group compared to the placebo group and through the open-label 36-week treatment period to Week 52. Overall, Ferric Maltol resulted in clinically and statistically significant increase in Hb compared to placebo.

As part of the pediatric clinical development, a Phase I PK study was performed to understand the kinetics of the absorption of iron and absorption and the elimination of maltol in a pediatric subject group in order to establish a safe and effective dose in children and adolescents, aged 10-17 years. All 3 doses of Ferric maltol were well-tolerated and had a favorable safety profile over a 10-day period.

A new oral suspension formulation of ferric maltol has been developed to provide an age appropriate formulation for pediatric subjects. This study is designed to compare the PK of the new suspension, in adults, with the existing ferric maltol capsule.

Objectives

Primary objective:

To evaluate the pharmacokinetics (PK) of iron absorption after a single 30 mg dose of ferric maltol administered as capsule or oral suspension in fasted and fed conditions, via primary parameters C_{max} and AUC_{last}.

Secondary objectives:

To evaluate the pharmacokinetics (PK) after a single 30 mg dose of ferric maltol administered as a capsule or oral suspension (fasted and fed conditions); through measurements of transferrin saturation (TSAT), baseline corrected serum iron, transferrin, total and unsaturated iron binding capacity (TIBC and UIBC), and plasma of maltol and maltol glucuronide.

To assess the safety and tolerability of ferric maltol after a single dose of 30 mg administered as a capsule or oral suspension (fasted and fed conditions); based on vital signs, adverse events, concomitant medications and routine clinical laboratory safety blood tests.

Endpoints

Primary endpoints:

1. PK analysis of total serum iron concentration; C_{max}, AUC_{last} in fasted and fed conditions

Secondary endpoints:

1. PK analysis of total serum iron concentration; AUC_{inf} in fasted and fed conditions
2. PK analysis of baseline corrected serum iron concentration; C_{max}, AUC_{last}, AUC_{inf} in fasted and fed conditions
3. PK analysis of maltol and maltol glucuronide in plasma; C_{max}, AUC_{last} in fasted and fed conditions
4. PK analysis of TSAT, TIBC, UIBC, transferrin; C_{max}, AUC_{last} in fasted and fed conditions
5. Treatment-emergent Adverse Events (AEs)
6. Serious Adverse Events (SAEs)
7. Treatment-emergent Adverse Events leading to premature discontinuation of study drug/PK assessments
8. Clinical laboratory safety blood results
9. Changes in vital signs
10. Concomitant medications

Design

The study will comprise of the following stages:

- Screening: to determine subject eligibility for the study (within 14 days prior to the planned first ferric maltol dosing period Day 1 for each subject)
- Randomized, Crossover phase: A treatment period of 4 days with at least 48 hrs washout period between each dose administration.

During the crossover PK phase, subjects will be randomized in a 1:1:1:1 ratio to receive one of the following treatment sequences. 8 subjects will be randomized to each sequence:

Sequence A:

- *Period 1; single dose of 30 mg ferric maltol capsule in a fed condition*
- *Period 2; single dose of 30 mg (5 ml) ferric maltol suspension in a fed condition*
- *Period 3; single dose of 30 mg ferric maltol capsule in a fasted condition*
- *Period 4; single dose of 30 mg (5 ml) ferric maltol suspension in a fasted condition*

Sequence B:

- *Period 1; single dose of 30 mg (5 ml) ferric maltol suspension in a fasted condition*
- *Period 2; single dose of 30 mg ferric maltol capsule in a fed condition*
- *Period 3; single dose of 30 mg (5 ml) ferric maltol suspension in a fed condition*
- *Period 4; single dose of 30 mg ferric maltol capsule in a fasted condition*

Sequence C:

- *Period 1; single dose of 30 mg ferric maltol capsule in a fasted condition*
- *Period 2; single dose of 30 mg (5 ml) ferric maltol suspension in a fasted condition*
- *Period 3; single dose of 30 mg ferric maltol capsule in a fed condition*
- *Period 4; single dose of 30 mg (5 ml) ferric maltol suspension in a fed condition*

Sequence D:

- *Period 1; single dose of 30 mg (5 ml) ferric maltol suspension in a fed condition*
- *Period 2; single dose of 30 mg ferric maltol capsule in a fasted condition*

- *Period 3; single dose of 30 mg (5 ml) ferric maltol suspension in a fasted condition*
- *Period 4; single dose of 30 mg ferric maltol capsule in a fed condition*

Prior to the first treatment period, subjects will arrive at the Clinical Unit on Day -1 at least 13 hrs before dosing. After at least 10 hours overnight fasting at the Clinical Unit subjects will be randomized to one of the 4 treatment sequences. PK samples will be collected pre-dose and up to 24 hrs post-dose during each period (12 times including pre-dose) for the measurements of serum iron, TSAT, TIBC, UIBC, transferrin, plasma maltol and maltol glucuronide.

There will be at least 48 hrs washout period between dose administrations. Subjects will fast at least 10 hrs prior to each treatment period dosing.

Subjects will stay at the Clinical Unit during the 4 treatment and 3 washout periods and will be discharged on Day 8 following the last PK sampling timepoint.

- Post-treatment safety follow-up: Post study telephone follow-up will be conducted 3-7 days following Period 4 treatment. During early discontinuation a safety follow up at the Clinical Unit will be performed 3-7 days after the last study medication.

Number of Subjects

The target recruitment number is 32 and up to an additional 4 may be recruited to replace early withdrawing subjects.

Inclusion Criteria

1. Must voluntarily sign and date each Institutional Review Board (IRB)-approved informed consent form (ICF) prior to the initiation of any screening or study-specific procedures.
2. Willing and able to comply with study requirements.
3. Healthy adult subjects 18 to 55 years of age, inclusive at the time of informed consent.
4. Body Mass Index (BMI) of 18-32 kg/m^2 inclusive
5. Female subjects of childbearing potential must not be planning a pregnancy or be pregnant or lactating. All

female subjects must have a negative result for the pregnancy tests performed at screening and each treatment period.

6. Female subjects of childbearing potential (including perimenopausal females who have had a menstrual period within 1 year prior to screening) 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 hormonal contraception (oral, implant, injection, ring, or patch) and intrauterine contraceptive devices (IUDs) at least 3 months prior to Screening or a vasectomized partner.

   Note: Complete abstinence from sexual intercourse is an acceptable form of contraceptive practice.

7. Female subjects of non-childbearing potential must be either surgically sterile (hysterectomy, bilateral tubal ligation, bilateral salpingectomy and/or bilateral oophorectomy at least 26 weeks before the Screening Visit) or post-menopausal, defined as spontaneous amenorrhea for at least 2 years.
8. Male subjects with partners of childbearing potential must have had surgical sterilization (vasectomy) at least 26 weeks prior to Screening or use a male barrier method of contraception (i.e. male condom with spermicide) during any sexual intercourse, from Study Day -1 (beginning of confinement) until 3 months after the Follow-up Visit.
   Note: Complete abstinence from sexual intercourse is an acceptable form of contraceptive practice.
9. Male subjects must agree to abstain from sperm donation from initial study drug administration through 3 months after administration of the last dose of study drug.

Exclusion Criteria

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

1. Known hypersensitivity or allergy to the active substance or excipients of Ferric maltol oral suspension or capsules;
2. Presence or history of any significant cardiovascular, gastrointestinal, hepatic, renal, pulmonary, hematologic, endocrine, immunologic, dermatologic, neurological, or psychiatric disease, as determined by the Investigator;
3. Presence or history of any other condition (including surgery) known to interfere with the absorption, distribution, metabolism, or excretion of medicines;
4. Recent (within 6 months of screening) history of drug or alcohol abuse;
5. Positive screen results for drugs of abuse or alcohol at screening or Study Day -1;
6. Consumption of alcohol within 72 hrs prior to study drug administration;
7. Positive test result for hepatitis B surface antigen (HBSaAg), hepatitis C virus antibody (HCV Ab), or human immunodeficiency virus antibody (HIV Ab) at screening;
8. Donation or loss of 550 mL or more blood volume (including plasmapheresis) or receipt of a transfusions of any blood product within 8 weeks prior to study drug administration and 14 days for plasma donation unless medically inadvisable;
9. Use of any prescription medications or over the counter medications, including herbal products from screening until study completion, other than medication used for contraception or for treatment of any emergent AE at the discretion of the Investigator;
10. Has received within 28 days prior to Screening intramuscular or intravenous (IV) injection or administration of depot iron preparation;
11. Has received oral iron supplementation within 7 days prior to Screening;
12. Has concomitant disease that would significantly compromise iron absorption or absorbed iron utilization such as swallowing disorders; gastric pH disturbances and/or extensive small bowel resection;

13. Scheduled or expected hospitalization and/or surgery during the course of the study;
14. Diagnosed to be COVID-19 positive by polymerase chain reaction testing (SARS-CoV-2-RT-PCR positive) of a respiratory specimen (preferably a nasopharyngeal swab) on Day -2;
15. Participation in any other interventional clinical study within 28 days prior to Screening;
16. Any other unspecified reason that, in the opinion of the Investigator or the Sponsor makes 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;
- Treatment with parenteral iron preparations within 28 days prior to screening and throughout the study period;
- Oral 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;
- Multivitamins within 7 days prior to screening and throughout the study period;
- Other prescription or over the counter medications, including herbal products from screening until study completion.

Permitted:

- Oral contraceptives are allowed during the study, but the subjects must have been on a stable dose for 3 months before randomisation;
- If necessary, medication used for treatment of any emergent AE at the discretion of the Investigator may be given.

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 study treatment;
- Blood transfusions for any cause during the study treatment period;

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 safety follow up at the Clinical Unit 3-7 days after last medication, unless informed consent is withdrawn (and the subject does not agree to attend this follow-up visit).

Investigational Medicinal Product

Ferric maltol oral suspension: oral suspension containing 30 mg elemental iron, in the form of 231.5 mg ferric maltol, in 5 ml suspension.

Comparator

Ferric maltol capsules: gelatin capsules with 30 mg elemental iron, in the form of 231.5 mg ferric maltol.

Packaging

Ferric maltol bottles for capsules and oral suspension will be labelled for clinical trials use.

Administration

Ferric maltol capsule and suspension fasted conditions: following an overnight fast of at least 10 hours, the Investigator or his/her staff will administer to each subject a single dose of ferric maltol according to randomization sequence in a sitting position. Capsules should be taken with 240 ml potable tap water. Suspension can be taken with 240 ml potable tap water if needed.

Water is allowed during the 10 hrs fasting but not allowed for one hour before and two hours after drug administration (except for drug administration). No food will be allowed for at least 4 hours post-dose.

Ferric maltol capsule and suspension fed conditions: following an overnight fast of at least 10 hours subjects will receive a test meal 30 minutes prior to administration of the drug product. Subjects should finish their meal in 30 minutes or less; however, the capsule or suspension will be administered by the Investigator or his staff 30 minutes after start of the meal. Capsules should be taken with 240 ml potable tap water. Suspension can be taken with 240 ml potable tap water if needed. No food will be allowed for at least 4 hours post-dose. Water is allowed during the 10 hrs fasting but not allowed for one hour before and two hours after drug administration (except for drug administration).

Statistical Methods

Sample size calculation

The sample size is based on the comparisons of each of the primary PK parameters C_{max} and AUC_{last} for total serum iron between the formulations for each of the two conditions: fed and fasted. Each comparison will be made via the ratio of the two values of the parameter between the formulations. The 90% confidence interval (CI) for this ratio will be reported.

Thus, there are 4 primary endpoints:

In fed condition

$C_{max\ (suspension)} / C_{max\ (capsule)}$

$AUC_{last\ (suspension)} / AUC_{last\ (capsule)}$

In fasted condition

$C_{max\ (suspension)} / C_{max\ (capsule)}$

$AUC_{last\ (suspension)} / AUC_{last\ (capsule)}$

Data from a previous study (ST10-01-101) were used to provide estimates of the standard deviations (SDs) of the logs of the within-subject ratios of the parameters C_{max} and AUC_{last} (between formulations). Assuming the SD is no greater than 0.38, and that the true ratio is 1, 20 subjects would provide a probability of at least 80% of each individual confidence interval lying within (80%, 125%). Further assuming that all the 4 ratios to be reported are

independent, 31 subjects would provide probability of at least 80% of all 4 confidence intervals lying within (80%, 125%). As the SD is uncertain, 32 subjects will be recruited in the study.

Statistical Methods

For each of total serum iron, baseline corrected serum iron, maltol, maltol glucuronide, TSAT, TIBC, UBIC and transferrin, concentration data will be listed for each individual subject, by formulation and condition (fed / fasted). The data will be summarized, for each of the four formulations/conditions, at each time point by using the following descriptive statistics: n (the number of subjects), arithmetic mean, standard deviation (SD), geometric mean, coefficient of variation (CV), median, minimum and maximum, and a 90% confidence interval (CI) for the mean.

Concentration-time courses of each analyte will be graphically displayed per subject. For each feeding condition, plots of the geometric mean concentration and its 90% CI, versus time, by formulation, will be provided, overlaid.

For serum iron, baseline corrected serum iron, maltol, maltol glucuronide, TSAT, TIBC, UIBC and transferrin, the PK parameters (C_{max}, T_{max}, AUC_{last}, AUC_{inf}, λ_z, $t_{½}$) will be listed and summarized, for each of the four formulations/conditions, using the following descriptive statistics: n, arithmetic mean, SD, geometric mean, CV, median, minimum and maximum.
For total serum iron and baseline corrected serum iron, the within-subject ratios between the two formulations, in each of the conditions (fed and fasted) of the parameters $C_{max,}$ AUC_{last} and AUC_{inf} will be calculated per subject. These ratios will be summarized by n, geometric mean and a 90% confidence interval for the mean.

Safety data will be listed and summarized for each formulation/condition.

5 BACKGROUND INFORMATION

5.1 OVERVIEW OF DISEASE

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 hematological and iron metabolism indices. Typically, decreased serum concentrations of hemoglobin (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 (diarrhea, 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 anemia 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 pediatric IBD (Weiss & Gasche, 2010).

Other aids to the differentiation between IDA and anemia of chronic disease, essential in order to provide the appropriate treatment, include quantification of reticulocyte hemoglobin 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 anemia of chronic disease is mostly normochromic and normocytic, IDA more frequently presents as microcytic and hypochromic anemia.

5.2 CURRENT TREATMENT OF DISEASE

There is a clear unmet medical need for an alternative oral treatment for anemic patients, particularly those who are intolerant to ferrous sulfate, to avoid the need for IV iron therapy, regardless of the cause of the iron deficiency. The proposed new pediatric oral suspension of ferric maltol is being developed in the treatment of iron deficiency (with or without anemia).

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. The ultimate goal of dietary changes or pharmacological treatment is the return of hemoglobin concentrations to the age-appropriate reference range. The duration of treatment should be sufficient to normalize not only the hemoglobin 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 anemia is oral iron supplements. Ferrous compounds (sulfate, fumarate and gluconate), which are available both in solid and liquid forms, are the most common due to the extremely low bioavailability of conventional ferric preparations. The usual adult dose is 180 mg of elemental iron/day in divided doses. Therapeutic doses can range from 100 to 200 mg of elemental iron/day, depending on severity of symptoms, ferritin levels, age of the patient, and gastrointestinal side effects.

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 anemia 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 anemia. 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 hemoglobin level, but should also take clinical symptoms and co-morbidity into account (Weiss & Gasche, 2010).

5.3 OVERVIEW OF TEST PRODUCT

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 hematopoiesis and storage on ferritin. European Commission marketing authorization was granted for Ferric Maltol in February 2016 and US FDA NDA approval was granted on 25 July 2019. The currently approved dose is 30 mg twice daily (BID), taken in the morning and evening on an empty stomach.

Unlike OFPs, which are often given with food in order to reduce side effects, Ferric Maltol should, be given on an empty stomach to maximize 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.

Phase I studies (ST10-01-101 and ST10-01-102) in adults confirm 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).

Phase I study (ST10-01-103) in children and adolescents, aged 10-17 years was performed to study 3 different doses of ferric maltol (7.8 mg, 16.6 mg and 30 mg BID) over a 10-day treatment period. All 3 doses were well-tolerated and had a favorable safety profile in this population.

A new oral suspension formulation of ferric maltol has been developed to provide an age - appropriate formulation for pediatric subjects.

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 1991 a, 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 population, 30 mg Ferric Maltol twice daily would result in correction of baseline anemia in the majority of subjects. This has been confirmed by the Phase 3 studies conducted to date (see below).

5.4.1 Phase 3 studies in adults

ST10-01-301/302 study

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

ST10-01-303 study

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

167 patients with IDA in Chronic Kidney Disease (CKD) over 16-week double blind phase and an open label 36-week treatment in 125 subjects demonstrated positive safety, efficacy and tolerability. Changes in TSAT, ferritin, and serum iron concentrations indicated an improvement in all iron parameters in the ferric maltol group compared to the placebo group and through the open-label 36-week treatment period to Week 52.

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

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

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

5.4.2 Phase I studies in adults

ST10-01-101 study

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

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

ST10-01-102 study

The study results showed that plasma and urinary PK parameters for maltol and maltol glucuronide were consistent with rapid metabolism of maltol to maltol glucuronide, followed by renal excretion. Total serum iron and TSAT increased after ST10 dosing, although there was no clear relationship between either of these parameters and exposure profile to maltol or maltol glucuronide. There was no evidence of intact ST10 in serum samples, as measured indirectly by NTBI, and there were no findings in this sub-study that affected the safety profile of ST10.

The low serum NTBI values are consistent with the safety profile of ST10. Unsurprisingly, given the short duration, there were no significant safety findings in this sub-study.

5.4.3 Phase I study in children and adolescents

ST10-01-103 study

An open-label, randomized, Phase I study was completed in 37 children and adolescents (aged 10-17) after BID oral doses of 7.8 mg, 16.6 mg or 30 mg ferric maltol (ST10) over a 10 days treatment period. Of the 37 subjects, there were 12 subjects in the 7.8 mg dose group, 13 subjects in the 16.6 mg dose group and 12 subjects in the 30 mg dose group. The primary objective of the study was to assess the PK and iron uptake of these 3 doses, through

measurement of serum iron, TSAT and plasma concentrations of maltol and maltol glucuronide.

A one-compartment model with first order absorption with TLAG and first order elimination kinetics describes plasma maltol glucuronide PK for ferric maltol according to the current data. The results showed that dose proportionality existed over the dose range tested in this study, although the predicted C_{max} of plasma maltol glucuronide on Day 10 slightly deviated from dose proportionality.

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

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

Safety was assessed by evaluating TEAEs, SAEs, physical examinations, vital signs, 12-lead ECGs, and laboratory parameters. In total, 20 (54.1%) subjects experienced a TEAE: 7 (58.3%) subjects in the 7.8 mg dose group, 6 (46.2%) subjects in the 16.6 mg dose group, and 7 (58.3%) subjects in the 30 mg dose group. Treatment-emergent adverse events were mostly mild and no subjects had a severe TEAE. One (7.7%) subject in the 16.6 mg dose group experienced a TEAE of tonsillitis that led to withdrawal of study drug and study discontinuation; this event was considered by the Investigator to be moderate in severity and not related to study drug. No subjects died or experienced an SAE during the study.

No clinically meaningful differences in mean changes from baseline in hematology or clinical chemistry parameters were noted between dose groups. Overall, individual shifts from normal to abnormal in hematology and clinical chemistry laboratory parameters were considered as not related to study drug and not clinically significant.

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

Refer to the Investigator Brochure for further information.

5.5 RATIONALE FOR THE STUDY

Clinical studies conducted to date, provide evidence for the effectiveness of Ferric Maltol in adult patients with ID in IBD and CKD. Study ST10-01-301/2 demonstrated that ferric maltol is effective and well-tolerated in patients who are intolerant of OFPs or are otherwise unsuitable for OFP treatment.

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

By performing this Phase I crossover study, the exposure of the adult solid dose pharmaceutical form (hard capsules) and the proposed pediatric oral suspension will be compared to confirm therapeutic interchangeability. Ferric maltol capsules and the new oral ferric maltol suspension will also be evaluated in fasted and fed conditions.

Because it is not ethical to perform non-therapeutic Phase 1 studies in children, this study is being completed using adult volunteer subjects.

5.5.1 Study Population

The study population will be healthy male and female subjects, aged between 18 and 55 yrs, inclusive at the time of informed consent.

5.5.2 Study Treatment Duration

A treatment period of 4 days with at least 48 hours washout period between each dose administration.

During the crossover PK phase, subjects will be randomized in a 1:1:1:1 ratio to receive one of the following treatment sequences. 8 subjects will be randomized to each sequence:

Sequence A:

- *Period 1; single dose of 30 mg ferric maltol capsule in a fed condition*
- *Period 2; single dose of 30 mg (5 ml) ferric maltol suspension in a fed condition*
- *Period 3; single dose of 30 mg ferric maltol capsule in a fasted condition*
- *Period 4; single dose of 30 mg (5 ml) ferric maltol suspension in a fasted condition*

Sequence B:

- *Period 1; single dose of 30 mg (5 ml) ferric maltol suspension in a fasted condition*
- *Period 2; single dose of 30 mg ferric maltol capsule in a fed condition*

- *Period 3; single dose of 30 mg (5 ml) ferric maltol suspension in a fed condition*
- *Period 4; single dose of 30 mg ferric maltol capsule in a fasted condition*

Sequence C:

- *Period 1; single dose of 30 mg ferric maltol capsule in a fasted condition*
- *Period 2; single dose of 30 mg (5 ml) ferric maltol suspension in a fasted condition*
- *Period 3; single dose of 30 mg ferric maltol capsule in a fed condition*
- *Period 4; single dose of 30 mg (5 ml) ferric maltol suspension in a fed condition*

Sequence D:

- *Period 1; single dose of 30 mg (5 ml) ferric maltol suspension in a fed condition*
- *Period 2; single dose of 30 mg ferric maltol capsule in a fasted condition*
- *Period 3; single dose of 30 mg (5 ml) ferric maltol suspension in a fasted condition*
- *Period 4; single dose of 30 mg ferric maltol capsule in a fed condition*

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). The safety and tolerability of Ferric Maltol in adults with IDA in IBD study was positive, with the overall AE rate in Ferric Maltol being comparable to the Placebo group over a 12-week period; 87% of Ferric Maltol subjects remained in the study. This data is supported by smaller published clinical studies using higher doses of Ferric Maltol and by preclinical studies testing Ferric Maltol in rodents (see Investigator's Brochure).

The safety and tolerability study with Ferric Maltol in 167 subjects with CKD and IDA have been positive with data collected over 16 weeks in a double-blind phase. The TEAE was comparable between the active (70.1%) and placebo group (75%) with the most commons system organ class of GI disorders. Only three subjects experienced study drug-related adverse events that led to discontinuation. Overall, Ferric Maltol resulted in clinically and statistically significant increase in Hb compared to placebo.

Previous Phase I PK study (ST10-01-101) was performed to describe the PK and iron uptake in 24 iron deficient subjects in three different dosing regimens (30, 60, 90 mg BID). The most commonly reported TEAEs (29.2%) were GI disorders which were consistent with the medical history of the subjects, who were recruited from specialist GI clinics. A single SAE was

reported which led to discontinuation of the study but was not considered to be related to study treatment.

The study population will recruit healthy subjects, male and female aged 18 and 55 yrs inclusive at the time of informed consent. All eligible subjects will enter a 4 Period treatment phase with 48 hrs washout between each dose administration. Subjects will either take a 30 mg ferric maltol as a capsule or 5 ml oral suspension according to the randomized sequences on each Period Day 1.

PK assessments will take place for subjects to assess the effect, the safety and tolerability of ferric maltol oral suspension and capsule. Study procedure risks are related to IV cannulation and blood sampling, with fainting, minor bleeding and bruising. The individual volume of blood collected throughout the study (screening and PK assessment days) will not exceed 335.5 mL, which is substantially below the volume of routine blood donation.

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 information gathered from this Phase I study will be very important in establishing the interchangeability between ferric maltol capsules and oral suspension.

The risk to the subject related to study procedures has been assessed as very low, therefore the risk benefit is considered acceptable.

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

6 STUDY OBJECTIVES AND ENDPOINTS

6.1 PRIMARY OBJECTIVE

To evaluate the pharmacokinetics (PK) of iron absorption after a single 30 mg dose of ferric maltol administered as capsule or oral suspension (fasted and fed conditions), via primary parameters C_{max} and AUC_{last}.

6.2 SECONDARY OBJECTIVES

To evaluate the pharmacokinetics (PK) after a single 30 mg dose of ferric maltol administered as a capsule or oral suspension (fasted and fed conditions); through measurements of transferrin saturation (TSAT), baseline corrected serum iron, transferrin, total and unsaturated iron binding capacity (TIBC and UIBC), and plasma of maltol and maltol glucuronide.

To assess the safety and tolerability after a single dose of 30 mg Ferric Maltol administered as a capsule or oral suspension (fasted and fed conditions); based on vital signs, adverse events, concomitant medications and routine clinical laboratory safety blood tests.

6.3 PRIMARY ENDPOINTS

1. PK analysis of total serum iron concentration; C_{max}, AUC_{last} in fasted and fed conditions

6.4 SECONDARY ENDPOINTS

1. PK analysis of total serum iron concentration; AUC_{inf} in fasted and fed conditions

2. PK analysis of baseline corrected serum iron concentration; C_{max}, AUC_{last}, AUC_{inf} in fasted and fed conditions

3. PK analysis of maltol and maltol glucuronide in plasma; C_{max}, AUC_{last} in fasted and fed conditions

4. PK analysis of TSAT, TIBC, UIBC, transferrin; C_{max}, AUC_{last} in fasted and fed conditions

5. Treatment-emergent Adverse Events (TEAEs)

6. Serious Adverse Events (SAEs)

7. Treatment-emergent Adverse Events leading to premature discontinuation of study drug/PK assessments

8. Clinical laboratory safety blood results

9. Changes in vital signs

10. Concomitant medications

6.5 EXPLORATORY ENDPOINTS

Not Applicable

7 INVESTIGATIONAL PLAN

7.1 STUDY OVERVIEW

This is a, Phase I, randomized, open-label, single dose, four-way crossover study, to compare the pharmacokinetics of iron and maltol absorption from ferric maltol capsules and oral suspension under fasted and fed conditions in adult healthy volunteers

The study will comprise of the following stages:

- Screening: up to 14 days
- Randomized treatment:

A treatment period of 4 days with at least 48 hrs washout period between dose administration.

During the crossover PK phase, subjects will be randomized in a 1:1:1:1 ratio to receive one of the following treatment sequences. 8 subjects will be randomized to each sequence:

Sequence A:

- *Period 1; single dose of 30 mg ferric maltol capsule in a fed condition*
- *Period 2; single dose of 30 mg (5 ml) ferric maltol suspension in a fed condition*
- *Period 3; single dose of 30 mg ferric maltol capsule in a fasted condition*
- *Period 4; single dose of 30 mg (5 ml) ferric maltol suspension in a fasted condition*

Sequence B:

- *Period 1; single dose of 30 mg (5 ml) ferric maltol suspension in a fasted condition*
- *Period 2; single dose of 30 mg ferric maltol capsule in a fed condition*
- *Period 3; single dose of 30 mg (5 ml) ferric maltol suspension in a fed condition*
- *Period 4; single dose of 30 mg ferric maltol capsule in a fasted condition*

Sequence C:

- *Period 1; single dose of 30 mg ferric maltol capsule in a fasted condition*
- *Period 2; single dose of 30 mg (5 ml) ferric maltol suspension in a fasted condition*
- *Period 3; single dose of 30 mg ferric maltol capsule in a fed condition*
- *Period 4; single dose of 30 mg (5 ml) ferric maltol suspension in a fed condition*

Sequence D:

- *Period 1; single dose of 30 mg (5 ml) ferric maltol suspension in a fed condition*
- *Period 2; single dose of 30 mg ferric maltol capsule in a fasted condition*

- *Period 3; single dose of 30 mg (5 ml) ferric maltol suspension in a fasted condition*
- *Period 4; single dose of 30 mg ferric maltol capsule in a fed condition*

Prior to the first treatment period, subjects will arrive at the Clinical Unit on Day -1 at least 13 hrs before dosing. After at least 10 hours overnight fasting at the Clinical Unit subjects will be randomized to one of the 4 treatment sequences. PK samples will be collected pre-dose and up to 24 hrs post-dose during each period (11 times) for the measurements of serum iron, TSAT, TIBC, UIBC, transferrin, plasma maltol and maltol glucuronide.

On Day -1 subjects will receive standardized meals as well.

Subjects will stay at the Clinical Unit during the 4 treatment and 3 washout periods and will be discharged on Day 8 following the last PK sampling timepoint. There will be at least 48 hours washout period between dose administrations.

- Post-treatment safety follow-up: Post study telephone follow-up will be conducted 3-7 days following the Period 4 treatment day.
  During early discontinuation a safety follow up at the Clinical Unit will be performed 3-7 days after the last study medication.

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

7.2 INVESTIGATIONAL SITES

Approximately 1-2 sites

7.3 INCLUSION AND EXCLUSION CRITERIA

No deviations to the inclusion or exclusion criteria are permitted.

7.3.1 Inclusion Criteria

All of the following criteria must be met for a subject to participate in the study:

1. Must voluntarily sign and date each Institutional Review Board (IRB)-approved informed consent form (ICF) prior to the initiation of any screening or study-specific procedures.
2. Willing and able to comply with study requirements.
3. Healthy adult subjects 18 to 55 years of age, inclusive at the time of informed consent.
4. Body Mass Index (BMI) of 18-32 kg/m^2 inclusive
5. Female subjects of childbearing potential must not be planning a pregnancy or be pregnant or lactating. All female subjects must have a negative result for the pregnancy tests performed at screening and each treatment period.

6. Female subjects of childbearing potential (including perimenopausal females who have had a menstrual period within 1 year prior to screening) 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 hormonal contraception (oral, implants, injection, ring, or patch) and intrauterine contraceptive devices (IUDs), at least 3 months prior to Screening, or a vasectomized partner.

   Note: complete abstinence from sexual intercourse is an acceptable form of contraceptive practice.

7. Female subjects of non-childbearing potential must be either surgically sterile (hysterectomy, bilateral, tubal ligation, bilateral salpingectomy, and/or bilateral oophorectomy at least 26 weeks before the Screening Visit) or post-menopausal, defined as spontaneous amenorrhea for at least 2 years

   Male subjects with partners of childbearing potential must have had surgical sterilization (vasectomy) at least 26 weeks prior to Screening or use a male barrier method of contraception (i.e. male condom with spermicide) during any sexual intercourse from Study Day -1 (beginning of confinement) until 3 months after the Follow-up Visit.

   Note: Complete abstinence from sexual intercourse is an acceptable form of contraceptive practice.

8. Male subjects must agree to abstain from sperm donation from initial study drug administration through 3 months after administration of the last dose of study drug.

7.3.2 Exclusion criteria

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

1. Known hypersensitivity or allergy to the active substance or excipients of Ferric maltol oral suspension or capsules;
2. Presence or history of any significant cardiovascular, gastrointestinal, hepatic, renal, pulmonary, hematologic, endocrine, immunologic, dermatologic, neurological, or psychiatric disease, as determined by the Investigator;
3. Presence or history of any other condition (including surgery) known to interfere with the absorption, distribution, metabolism, or excretion of medicines;
4. Recent (within 6 months of screening) history of drug or alcohol abuse;
5. Positive screen results for drugs of abuse, alcohol at screening or Study Day -1 of Period 1;

6. Consumption of alcohol within 72 hrs prior to study drug administration;
7. Positive test result for hepatitis B surface antigen (HBSaAg), hepatitis C virus antibody (HCV Ab), or human immunodeficiency virus antibody (HIV Ab) at screening;
8. Donation or loss of 550 mL or more blood volume or receipt of a transfusions of any blood product within 8 weeks prior to study drug administration and 14 days for plasma donation unless medically inadvisable;
9. Use of any over the counter medications, including herbal product within 7 days prior to Screening until study completion. Except for ordinary pain (e.g. headache), some analgesics (mainly paracetamol) and contraception which have no drug interactions with the study products may be given;
10. Has received within 28 days prior to Screening intramuscular or intravenous (IV) injection or administration of depot iron preparation;
11. Has received oral iron supplementation within 7 days prior to Screening;
12. Has concomitant disease that would significantly compromise iron absorption or absorbed iron utilization such as swallowing disorders, gastric pH-disturbance and/or extensive small bowel resection;
13. Scheduled or expected hospitalization and/or surgery during the course of the study;
14. Diagnosed to be COVID-19 positive by polymerase chain reaction testing (SARS-CoV-2-RT-PCR positive) of a respiratory specimen (preferably a nasopharyngeal swab) on Day -2;
15. Participation in any other interventional clinical study within 28 days prior to Screening;
16. Any other unspecified reason that, in the opinion of the Investigator or the Sponsor makes 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;
- Treatment with parenteral iron preparations within 28 days prior to screening and throughout the study period;
- Oral 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;
- Multivitamins within 7 days prior to screening and throughout the study period;
- Other prescription or over the counter medications, including herbal products from screening until study completion.

7.4.2 Permitted

- Oral contraceptives are allowed during the study, but the subjects must have been on a stable dose for 3 months before randomisation;
- If necessary, medication used for treatment of any emergent AE at the discretion of the Investigator may be given.

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: IV iron, penicillamine, bisphosphonates, ciprofloxacin, entacapone, levodopa, levofloxacin, levothyroxine (thyroxine) moxifloxacin, mycophenolate, norfloxacin, ofloxacin, tetracyclines, calcium and magnesium salts, dimercaprol, chloramphenicol and methyldopa.

To minimize the potential for drug interactions, concomitant medications should be taken at least 4 hrs after ferric maltol. The exact timing of any concomitant medication should be recorded in the eCRF.

7.5 INDIVIDUAL DISCONTINUATION CRITERIA

Subjects 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 3-7 days at the Clinical Unit 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)
- Use of prohibited concomitant medications
- Serious adverse events that are judged by the Investigator to be related to study treatment
- Blood transfusions for any cause during the study treatment period

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 safety follow up

at the Clinical Unit 3-7 days after last medication, unless informed consent is withdrawn (and the subject 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 center/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

Healthy male and female subjects complying with the inclusion criteria and do not meet any of the exclusion criteria will be randomly assigned to 4 treatment sequence. 8 subjects will be randomized to each sequence:

Sequence A:

- *Period 1; single dose of 30 mg ferric maltol capsule in a fed condition*
- *Period 2; single dose of 30 mg (5 ml) ferric maltol suspension in a fed condition*
- *Period 3; single dose of 30 mg ferric maltol capsule in a fasted condition*
- *Period 4; single dose of 30 mg (5 ml) ferric maltol suspension in a fasted condition*

Sequence B:

- *Period 1; single dose of 30 mg (5 ml) ferric maltol suspension in a fasted condition*
- *Period 2; single dose of 30 mg ferric maltol capsule in a fed condition*
- *Period 3; single dose of 30 mg (5 ml) ferric maltol suspension in a fed condition*
- *Period 4; single dose of 30 mg ferric maltol capsule in a fasted condition*

Sequence C:

- *Period 1; single dose of 30 mg ferric maltol capsule in a fasted condition*
- *Period 2; single dose of 30 mg (5 ml) ferric maltol suspension in a fasted condition*
- *Period 3; single dose of 30 mg ferric maltol capsule in a fed condition*
- *Period 4; single dose of 30 mg (5 ml) ferric maltol suspension in a fed condition*

Sequence D:

- *Period 1; single dose of 30 mg (5 ml) ferric maltol suspension in a fed condition*
- *Period 2; single dose of 30 mg ferric maltol capsule in a fasted condition*
- *Period 3; single dose of 30 mg (5 ml) ferric maltol suspension in a fasted condition*
- *Period 4; single dose of 30 mg ferric maltol capsule in a fed condition*

8.1 INVESTIGATIONAL MEDICINAL PRODUCT (IMP) PRESENTATION

- 5 ml (6 mg/ml elemental iron) ferric maltol oral suspension.

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

8.2 COMPARATOR

- 30 mg ferric maltol capsule

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

8.3 TREATMENT ASSIGNMENT AND BLINDING

The randomization procedure (created using a computer-generated random permutation procedure) will randomize the subject to one of the 4 treatment sequences to either Sequence A Sequence B, Sequence C or Sequence D. The site will dispense the appropriate formulation of open-label ferric maltol bottles at each scheduled PK day according to the schedule of assessments.

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

8.3.1 TREATMENT ASSIGNMENT AND ADMINISTRATION

Ferric maltol capsule and suspension fasted conditions:

Prior to the first treatment period, subjects will arrive at the Clinical Unit on Day -1 at least 13 hrs before dosing. Eligibility will be checked again before randomization and subjects will be dosed after the 0 hrs baseline blood sample according to their randomized sequence. Capsules should be taken with 240 ml potable tap water, must be swallowed whole and must not be chewed, divided or crushed. 5 ml suspension will be measured out by using 2 x 3 ml syringe, graduated up to 2.5 ml. Subject can take suspension with 240 ml potable tap water if needed.

A hand and mouth check will be performed immediately after drug administration to ensure that the study drug has been swallowed.

Water is allowed during the 10 hrs fasting but not allowed for 1 hr before and 2 hrs post-dose (except for drug administration). No food will also be allowed for at least 4 hours post-dose. Within 30 mins following the 4 hours post-dose blood samples, subjects will receive a standardized meal.

Blood samples will be taken at 11 additional times after dosing; post-dose PK sample times will be 15 mins ±2 min, 30 mins ±2 min, 45 mins ±5 min, 1 hr ±5 min, 1,5 hr ±5 min, 2 hrs ±5 min, 3 hrs ±5 min, 4 hrs ±5 min. 6 hrs ±10 min, 10 hrs ±15 min and 24 hrs ±15 min.

Standard meals will be provided to the subjects at 4, 8, 12 hrs after drug administration in the morning. Meals will be identical in each treatment period. Iron content and time of consumption of each meal will be recorded during the hospitalization in the eCRF.

Subjects will have the following mealtimes:
- Lunch will be served: approximately 4 hrs post-dose
- Snack will be served: approximately 8 hrs post-dose

- Dinner will be served: approximately 12 hrs post-dose

Subjects will stay in the Clinical Unit throughout the study period. During the washout, subjects will stay at the Clinical Unit and receive standard meals. Iron content of the meals will be measured and recorded in the eCRF.

Ferric maltol capsule and suspension fed conditions:

Prior to the first treatment period, subjects will arrive at the Clinical Unit on Day -1 at least 13 hrs before dosing. Eligibility will be checked again before randomization. Subjects will then have their baseline blood samples taken and receive a test meal 30 minutes prior to administration of ferric maltol. Subjects should finish their meal in 30 minutes or less; however, ferric maltol will be administered 30 minutes after start of the meal. Capsules should be taken with 240 ml potable tap water. Suspension can be taken with 240 ml potable tap water if needed.

A hand and mouth check will be performed immediately after drug administration to ensure that the study drug has been swallowed.

Water is allowed during the 10 hrs fasting but not allowed for 1 hr before and 2 hrs post-dose (except for drug administration). No food will also be allowed for at least 4 hours post-dose. Within 30 mins following the 4 hours post-dose blood samples, subjects will receive a standardized meal.

Blood samples will be taken at 11 additional times after dosing; the post-dose PK sample times will be 15 mins ±2 min, 30 mins ±2 min, 45 mins ±5 min, 1 hr ±5 min, 1,5 hr ±5 min, 2 hrs ±5 min, 3 hrs ±5 min, 4 hrs ±5 min, 6 hr ±10 min, 10 hrs ±15 min and 24 hrs ±15 min.

Standard meals will be provided to the subjects at 4, 8, 12 hrs after drug administration in the morning. Meals will be identical in each treatment period. Iron content and time of consumption of each meal will be recorded during the hospitalization.

Subjects will have the following meal times:
- Breakfast will be served 30 minutes prior to drug administration
- Lunch will be served: approximately 4 hrs post-dose
- Snack will be served: approximately 8 hrs post-dose
- Dinner will be served: approximately 12 hrs post-dose

A test meal should consist of, 150, 250, and 500-600 calories protein, carbohydrate and fat respectively. An example meal: 2 eggs fried in butter, 2 strips of bacon, 2 slices of toast with butter, 4 ounces (113 g) of hash brown, potato and 8 ounces (227 ml) of water. Substitutions in this test meal can be made as long as the meal provides a similar amount of calories from protein, carbohydrate, and fat and has comparable meal volume and viscosity. If the meal is different from the above mention, it should be documented in the eCRF.

Subjects will stay in the Clinical Unit throughout the study period. During the washout, subjects will stay at the Clinical Unit and receive standard meals. Iron content of the meals will be measured and recorded in the eCRF.

8.3.2 WASHOUT PERIOD

Washout period lasts for at least 48 hrs between dose administration.

8.3.3 FOLLOW UP

Post study telephone follow-up will be conducted 3-7 days following period 4 treatment day. During early discontinuation a safety follow up at the Clinical Unit will be performed 3-7 days after the last study medication.

8.4 PACKAGING

Capsule: Ferric Maltol capsules will be supplied in a white polypropylene securitainer with a tamper evident standard securitainer cap of white medium density polyethylene. Each bottle will contain 56 capsules. Site staff will dispense 1 capsule for each subject according to the randomization sequence group.

Oral suspension: Ferric maltol oral suspension will be supplied in 150 ml amber glass bottle with an amber colored graduated syringe. Site staff will administer orally 5 ml oral suspension according to the randomization sequence.

8.5 STORAGE

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

8.6 LABELLING

All bottles will be identified by a unique Bottle ID number. Bottles will be clearly labelled as ferric maltol with the the strength indicated. Labels of the IMP will contain information according to 21CFR Section 312.6.

Individual supplies packaging and labelling will be checked by the Investigator/designee before the subject takes their dose of study medication at site on each PK day.

8.7 TREATMENT COMPLIANCE

Subjects will be instructed to take the study drug as according to their individual randomization sequence.

If the subject is non-adherent, a decision will be made by the medical monitor and/or Sponsor as to whether the subject should be withdrawn from the study treatment.

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

The information gathered from this Phase I study will be very important in establishing the interchangeability between ferric maltol capsules and oral suspension. Once this Phase I study has been completed, the results will be submitted to the FDA prior to commencing the Phase III Pediatric study. No further provisions are made for access to the study treatment under this protocol.

9 ENROLMENT AND RANDOMIZATION 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 randomization 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 randomization, 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 randomization occurs no more than 14 days from the initial Screening visit date (if eligible based on retest results).

9.2 COVID-19 TESTING AND IMPLICATIONS ON THE TRIAL

All efforts will be made by the unit to avoid screening any subjects who might have a known exposure to SARS-CoV-2 or any symptoms suggestive of any infection with it by following the guidelines provided by the Centers for Disease Control and Prevention (CDC) for evaluating patients for COVID-19.

All subjects who remain qualified after their screening visit will get a respiratory specimen (preferably a nasopharyngeal swab) on Day -2 which will be tested for SARS-CoV02 RT. Subjects diagnosed to be COVID-19 positive by the polymerase chain reaction testing will not be admitted to the unit and excluded from the trial.

The inpatient portion of the admitted and randomized trial subjects will be conducted in compliance with the most current guidelines for COVID-19 prevention at that time.

If there is an occurrence or suspicion (based upon signs and symptoms) of new COVID-19 infection in a subject after randomization, the subject may be withdrawn from the trial treatment and procedures.

All COVID-19 positive test results will be recorded as an adverse event in the eCRF. The subjects with known positive results or suspected COVID-19 will be advised to follow up with their primary care physician or call the local health board for taking the appropriate next steps for diagnosis and treatment of COVID-19.

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

9.3 RANDOMIZATION

Subjects will be assigned a unique 3-digit subject identification number at the Screening visit.

A final eligibility evaluation must be conducted by the Investigator/designee prior to randomization, once the results of all Screening and Day -1 assessments are available. No subject may begin treatment prior to being randomized. The randomization procedure (created using a computer-generated random permutation procedure) will randomize the subject to one of the 4 treatment sequences.

9.4 REPLACEMENT POLICY

Discontinuations after randomization for any reasons may be replaced at the discretion of the Sponsor, in order to reach the agreed number of evaluable subjects for pharmacokinetic endpoints. Up to a maximum of 4 subjects may be recruited to replace early discontinuation.

9.5 BLINDING PROCEDURES

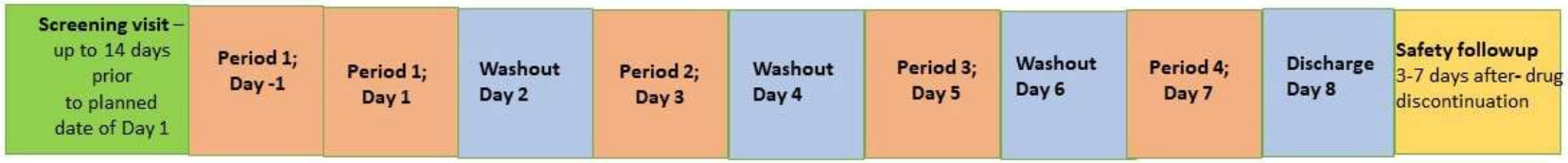
Not applicable as this is an open label study.

9.6 EMERGENCY UNBLINDING

Not applicable as this is an open label study.

10 STUDY PROCEDURES

10.1 DESIGN SCHEMATICS



Subjects will be hospitalized from Period 1 Day-1 and discharged Period 4, following the 24 hrs post-dose sampling.

Safety blood sampling will take place at Period 4 following the 24 hrs post-dose sampling and 3-7 days post-dose subjects will have a telephone safety follow-up. Subjects who discontinued early and did not withdrawn their consent, will need to attend a safety follow-up 3-7 days after drug discontinuation.

10.2 SCHEDULE OF ASSESSMENTS

PERIODS	SCREENING		PERIOD 1		Washout	PERIOD 2	Washout	PERIOD 3	Washout	PERIOD 4	Discharge [15]	FOLLOW-UP[13]
Study Day	Screening [1]	-2	-1	1	2	3	4	5	6	7	8	10-14 Follow-up
Informed Consent	X											
Demographics	X											
Medical History	X											
Concomitant Medications and Procedures [14]	X		X	X	X	X	X	X	X	X	X	X
Physical Examination	X										X	(X)
Vital Signs [2]	X		X	X		X		X		X		(X)
ECG [16]	X											
Pregnancy Test [3]	X		X								X	(X)
Blood sampling for Hepatitis B, C and HIV [4]	X											
Urine test for drug screen [5]	X		X									
Alcohol breathalyzer [6]	X		X									
Haematology, Clinical Chemistry and Iron markers blood sampling [8]	X										X	(X)
SARS-CoV-2 RT-PCR[17]		X										
Eligibility Confirmation and Randomization [7]	X		X									

PERIODS	SCREENING		PERIOD 1		Washout	PERIOD 2	Washout	PERIOD 3	Washout	PERIOD 4	Discharge [15]	FOLLOW-UP[13]
Study Day	Screening [1]	-2	-1	1	2	3	4	5	6	7	8	10-14 Follow-up
Dispense Study Drug [10]				X		X		X		X		
Hospitalisation			X									
Standardised supervised meal [11]				X		X		X		X		
Standardised meal			X	X	X	X	X	X	X	X		
Supervised morning dosing with ferric maltol [12]				X		X		X		X		
PK Blood Sampling for Iron markers, maltol/maltol glucuronide [9]				X	X	X	X	X	X	X	X	
Adverse Events			X	X	X	X	X	X	X	X	X	X
Subject discharge of hospitalisation [15]											X	
Telephone contact												X

1. *A subject may be retested once for screening laboratory criteria that do not meet protocol in/exclusion criteria, so long as randomization occurs no more than 14 days from the initial screening date (if eligible based on retest results).*
2. *Vital Signs –systolic/diastolic blood pressure, pulse rate and body temperature at each treatment day, to be taken after subject has been sitting for at least 5 minutes*
3. *Pregnancy test for female subjects of childbearing potential. Serum pregnancy test at Screening and Urine pregnancy test at Day -1 and Day 8 for female subjects of childbearing potential.*
4. *All subjects will have blood test at screening to show if they have been infected with Hepatitis C or HIV, or if they have ever been infected with Hepatitis B and still have Hepatitis B in the subject`s system. HIV testing will be a 2-step process. If the first test is positive, the blood will be tested again. Until the second test results are negative, subjects will not be able to participate in the study.*
5. *Urine for drug test: 5 Panel Multi-Line Test to detect amphetamines, cocaine, THC, opiates and PCP.*
6. *Breath test will be performed at Screening and at Period 1 Day -1 to measure the Breath Alcohol Content (BAC) of each subject.*
7. *Eligibility central laboratory sampling/assessments must be completed at Screening and on Period 1 Day -1 before the subject is randomized.*
8. *Hematology, Clinical Chemistry and screening Iron markers blood sampling*
9. *On all four PK study days, all subjects will have baseline PK blood samples collected immediately prior to Ferric Maltol dosing (0 hr). Subjects will then have further PK blood samples collected at 11 additional times after dosing; the post-dose PK sample times will be 15 mins ±2 min, 30 mins ±2 min, 45 mins ±5 min, 1 hr ±5 min, 1,5 hr ±5 min, 2 hrs ±5 min, 3 hrs ±5 min, 4 hrs ±5 min, 6 hr ±10 min, 10 hrs ±15 min and 24 hrs ±15 min. For each individual subject, the post-dose PK blood sampling schedule will be the same on all four PK days. PK blood samples on the PK days will be: serum iron, total and unsaturated iron binding capacity (TIBC, UIBC), transferrin, transferrin saturation (TSAT), maltol and maltol glucuronide.*
10. *Drug dispensing: subjects will be randomized to either Sequence A, B, C or D*

Sequence A:

- *Period 1; single dose of 30 mg ferric maltol capsule in a fed condition*
- *Period 2; single dose of 30 mg (5 ml) ferric maltol suspension in a fed condition*
- *Period 3; single dose of 30 mg ferric maltol capsule in a fasted condition*
- *Period 4; single dose of 30 mg (5 ml) ferric maltol suspension in a fasted condition*

Sequence B:

- *Period 1; single dose of 30 mg (5 ml) ferric maltol suspension in a fasted condition*
- *Period 2; single dose of 30 mg ferric maltol capsule in a fed condition*
- *Period 3; single dose of 30 mg (5 ml) ferric maltol suspension in a fed condition*
- *Period 4; single dose of 30 mg ferric maltol capsule in a fasted condition*

Sequence C:

- *Period 1; single dose of 30 mg ferric maltol capsule in a fasted condition*
- *Period 2; single dose of 30 mg (5 ml) ferric maltol suspension in a fasted condition*
- *Period 3; single dose of 30 mg ferric maltol capsule in a fed condition*
- *Period 4; single dose of 30 mg (5 ml) ferric maltol suspension in a fed condition*

Sequence D:

- *Period 1; single dose of 30 mg (5 ml) ferric maltol suspension in a fed condition*
- *Period 2; single dose of 30 mg ferric maltol capsule in a fasted condition*
- *Period 3; single dose of 30 mg (5 ml) ferric maltol suspension in a fasted condition*
- *Period 4; single dose of 30 mg ferric maltol capsule in a fed condition*

11. *A test meal should consist of, 150, 250, and 500-600 calories protein, carbohydrate and fat respectively. An example meal: 2 eggs fried in butter, 2 strips of bacon, 2 slices of toast with butter, 4 ounces (113 g) of hash brown, potato and 8 ounces (227 ml) of water. Substitutions in this test meal can be made as long as the meal provides a similar amount of*

calories from protein, carbohydrate, and fat and has comparable meal volume and viscosity. If the meal is different from the above mention, it should be documented in the eCRF.
Subjects will have their test meal supervised by site staff.

12. *Ferric maltol capsule and suspension fasted conditions: Prior to the first treatment period, subjects will arrive at the Clinical Unit on Day -1 at least 13 hrs before dosing. Eligibility will be checked again before randomization and subjects will be dosed after the 0 hrs baseline blood sample according to their randomized sequence. Capsules should be taken with 240 ml potable tap water, must be swallowed whole and must not be chewed, divided or crushed. Suspension can be taken with 240 ml potable tap water if needed. A hand and mouth check will be performed immediately after drug administration to ensure that the study drug has been swallowed. Water is allowed during the 10 hrs fasting but not allowed for 1 hr before and 2 hrs post-dose (except for drug administration). No food will also be allowed for at least 4 hours post-dose. Within 30 mins following the 4 hours post-dose blood samples, subjects will receive a standardized meal.*
    Blood samples will be taken at 11 additional times after dosing; post-dose PK sample times will be 15 mins ±2 min, 30 mins ±2 min, 45 mins ±5 min, 1 hr ±5 min, 1,5 hr ±5 min, 2 hrs ±5 min, 3 hrs ±5 min, 4 hrs ±5 min. 6 hrs ±10 min, 10 hrs ±15 min and 24 hrs ±15 min.
    Standard meals will be provided to the subjects at 4, 8, 12 hrs after drug administration in the morning. Meals will be identical in each treatment period. Iron content and time of consumption of each meal will be recorded during the hospitalization in the eCRF.
    Subjects will have the following mealtimes:
    - *Lunch will be served: approximately 4 hrs post dose*
    - *Snack will be served: approximately 8 hrs post dose*
    - *Dinner will be served: approximately 12 hrs post dose*

    Ferric maltol capsule and suspension fed conditions: Prior to the first treatment period, subjects will arrive at the Clinical Unit on Day -1 at least 13 hrs before dosing. Eligibility will be checked again before randomization. Subjects will then have their baseline blood samples taken and receive a meal 30 minutes prior to administration of ferric maltol. Subjects should finish their meal in 30 minutes or less; however, ferric maltol will be administered 30 minutes after start of the meal. Capsules should be taken with 240 ml potable tap water. Suspension can be taken with 240 ml potable tap water if needed. A hand and mouth check will be performed immediately after drug administration to ensure that the study drug has been swallowed. Water is allowed during the 10 hrs fasting but not allowed for 1 hr before and 2 hrs post-dose (except for drug administration). No food will also be allowed for at least 4 hours post-dose. Within 30 mins following the 4 hours post-dose blood samples, subjects will receive a standardized meal.
    Blood samples will be taken at 11 additional times after dosing; the post-dose PK sample times will be 15 mins ±2 min, 30 mins ±2 min, 45 mins ±5 min, 1 hr ±5 min, 1,5 hr ±5 min, 2 hrs ±5 min, 3 hrs ±5 min, 4 hrs ±5 min, 6 hr ±10 min, 10 hrs ±15 min and 24 hrs ±15 min.

    Standard meals will be provided to the subjects at 4 and 8 hrs after drug administration in the morning. Meals will be identical in each treatment period. Iron content and time of consumption of each meal will be recorded during the hospitalization.
    A hand and mouth check will be performed immediately after drug administration to ensure that the study drug has been swallowed.

    Subjects will have the following mealtimes:
    - *Breakfast will be served 30 minutes prior to drug administration*
    - *Lunch will be served: approximately 4 hrs post-dose*
    - *Snack will be served: approximately 8 hrs post-dose*
    - *Dinner will be served: approximately 12 hrs post-dose*

    Subjects will receive standardised meal during the study period and iron content will be measured and recorded in the eCRF.

13. *Post study telephone follow-up will be conducted 3-7 days following Period 4 treatment day. Subjects who discontinue from the study prematurely should have final assessments conducted per /Post-study Safety Follow Up at the Clinical Unit, unless consent is withdrawn.*

14. *To minimize the potential for drug interactions, concomitant medications should be taken at least 4 hrs after ferric maltol. The exact timing of any concomitant medication should be recorded in the eCRF.*

15. *Subject will be discharged from the Clinical Unit following the 24 hrs blood sampling in Period 4 (Day 8), providing the Investigator has no ongoing safety concerns*
16. *ECG – machine reported ECG parameters and overall clinical ECG interpretation will be recorded in the eCRF. ECG to be obtained after the subject has been supine for at least a 10-minute rest.*
17. *SARS-CoV-2 RT-PCR will be performed on Day -2. Subjects with only negative results will be able to admit to the Clinical Unit on Day -1.*

10.3 DEMOGRAPHICS AND MEDICAL HISTORY

The following will be documented at Screening and updated (if required) prior to randomization: Date of Birth, race and ethnicity, gender, all current medical conditions, all clinically significant medical history from the past 5 years including all malignancies, sterilizations, hospitalizations 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 randomization: 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).

To minimize the potential for drug interactions, concomitant medications should be taken at least 4 hrs after ferric maltol. The exact timing of any concomitant medication and its iron content should be recorded in the eCRF.

10.6 VITAL SIGNS

Body temperature (°C), blood pressure and pulse rate will be assessed at Screening for all subjects on all four PK days at pre-dose. Blood pressure and pulse rate should be measured after the subject has been sitting for at least 5 minutes at Screening visit and at each PK days pre-dose.

10.7 LABORATORY ASSESSMENTS

10.7.1 Hematology and Clinical Chemistry

Routine clinical laboratory safety bloods for hematology (3.0 mL) and clinical chemistry/iron markers (7.5 mL) evaluations will be collected at Screening to assess eligibility. Hematology (3 mL) and clinical chemistry (5.0 mL) will be repeated at Period 4; 24 hrs post-dose sampling or at the Follow-up visit for early discontinued subjects. Additional testing may be required if any abnormal value is reported and this must be followed until it is resolved.

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 Hematology test parameters

Red blood cell count, hemoglobin, hematocrit, 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, blood urea nitrogen (BUN), sodium, potassium, chloride, calcium, total cholesterol, uric acid, glucose, total protein, albumin, bicarbonate, LDH, CK, triglycerides

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

10.7.2 Pharmacokinetics

Blood samples for maltol and maltol glucuronide on PK days

4 ml venous blood samples will be collected in lithium-heparin tubes by indwelling cannula or venipuncture at the required times on the PK assessment days relative to the time of ferric maltol morning dosing: pre-dose then 11 further times between 0.15 to 24 hours post-dose (10.2).

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 transfer to the central laboratory on dry ice for subsequent assay of maltol and maltol glucuronide plasma concentrations using appropriately validated bioanalytical methods. Full details of the required sample collection, processing and handling logistics will be specified in the study specific Laboratory Manual. Samples will be destroyed at the end of the study, once all analyses are complete.

Blood samples for iron markers on PK days

2.5 mL venous blood samples will be collected in serum separator tubes (SST) by indwelling cannula or venipuncture at the following times on the PK assessment days, relative to the time of ferric maltol dosing: pre-dose then 11 further times between 0.15-24 hours post-dose (same times as blood samples for maltol/maltol glucuronide for each individual, section 10.2).

Following collection and mixing, blood samples will be centrifuged, and the resultant serum samples separated and split into 1 primary (ambient) and 1 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).

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 Hepatitis B, C and HIV test

All subjects will have blood test (5 ml) at screening to show if they have been infected with Hepatitis C or HIV, or if they have ever been infected with Hepatitis B and still have Hepatitis B in the subject`s system. HIV testing will be a 2-step process. If the first test is positive, the blood will be tested again. Until the second test results are negative, subjects will not be able to participate in the study.

10.7.4 Urine Drug test

A 5 panel Multi-Line Test will also be conducted at Screening to detect amphetamines, cocaine, THC, opiates and PCP.

10.7.5 Pregnancy Test

Females of childbearing potential only. A serum pregnancy test should be conducted at the Screening visit to assess eligibility using the test kits provided by the central laboratory. A urine pregnancy test will be conducted at Period 1, Day -1 and Period 4 Day 8 following the 24 hrs post dose blood sampling.

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

10.7.6 Breath Alcohol Content Test

Each subject will have a breath alcohol content test at screening and Period 1, Day -1.

10.7.7 COVID-19 Testing

COVID-19 polymerase chain reaction testing (SARS-CoV-2 RT-PCR) of a respiratory specimen (preferably a nasopharyngeal swab) will be performed on Day -2.

10.7.8 ECG

Machine reported standard ECG with overall clinical ECG interpretation will be recorded at Screening in the eCRF.

10.7.9 Overall blood volume

The individual volume of blood collected throughout the study (Screening, PK assessment and Safety Follow up) will be approximately 335.5 ml.

Number of blood samples

Total number of samples per period: 12 PK timepoints, 1 pre-dose and 11 post-dose.

Volume per blood sample

Screening: 15.5 ml
Total blood volume per PK day including 24 hrs post-dose (Period 1, Period 2, Period 3): 78 ml
Total blood volume per PK day including 24 hrs post-dose (Period 4, including safety follow up blood samples): 86 ml
Total blood volume per subject: 335.5 ml

11 SAFETY

11.1 DEFINITIONS

11.1.1 ADVERSE EVENT (AE)

An AE is any untoward medical occurrence in a subject administered a pharmaceutical product and does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable 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 the AE (e.g. appendicitis, abdominal pain).
- Pre-existing disease or medical condition documented at baseline that does not worsen.

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

11.1.2 SERIOUS ADVERSE EVENT (SAE)

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

- is fatal,
- is life-threatening,
- requires inpatient hospitalization or prolongation of existing hospitalization,
- results in persistent or significant disability/incapacity,
- results in a congenital anomaly/birth defect or
- is otherwise judged as medically significant (may jeopardize 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 hospitalization: Subject has to stay in hospital at least overnight. The following reasons for hospitalizations are not considered AEs, and therefore not SAEs:

- Hospitalizations 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., hospitalization 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., hospitalization for chemotherapy for cancer, elective hip replacement for arthritis, vein stripping for preventive and/or cosmetic purpose.

Prolongation of hospitalization: Complications that occur during hospitalization are AEs. However, if a complication prolongs hospitalization or would have required hospitalization 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 hospitalization. When in

doubt as to whether “prolongation of hospitalization” 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 hospitalization but might/may jeopardize 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 hospitalization, 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 catheterization), 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 SAE 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. For AEs related to COVID-19 testing, see section 9.2.

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 stabilization 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 +44 800 781 6187

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

If the site obtains relevant follow-up information, this information needs to be forwarded to the Sponsor within 24 hrs 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. Adverse events, toxicities and medical surgery/history will be categorized by primary system organ class (SOC) and preferred term using the MedDRA dictionary. Toxicities will also be graded as mild, moderate or severe.

11.3.1 Intensity

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

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

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

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

A mild, moderate or severe AE may or may not be serious. These terms are used to describe the intensity of a specific event (as in mild, moderate, or severe myocardial infarction). 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 hospitalization.

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 and routine clinical laboratory abnormalities.

12 STATISTICAL CONSIDERATIONS

12.1 SAMPLE SIZE AND POWER CALCULATIONS

The sample size is based on the comparisons of each of the primary PK parameters C_{max} and AUC_{last} for total serum iron between the formulations, within each of the two conditions: fed and fasted. Each comparison will be made via the ratio of the two values of the parameter between the formulations. The 90% confidence interval (CI) for this ratio will be reported.

For each of the two comparisons (suspension vs capsule (fed condition); suspension vs capsule (fasted condition)) the CIs for two parameter ratios (C_{max} and AUC_{last}) for serum iron will be calculated, making a total of 4 CIs. If these ratios were all independent, and the probability of being within (80%, 125%) was 80% for each, then the probability that all 4 would fall within the required limits would be $(80\%)^4$ = 41%. With individual probabilities of 90%, the combined probability would be 66%. However, if the ratios were positively correlated, the combined probabilities would be higher.

Data from a previous study (ST10-01-101) were used to provide estimates of the standard deviations (SDs) of the logs of the within-subject ratios of the parameters C_{max} and AUC_{last}, for both total serum iron and TSAT. Assuming the SD is no greater than 0.38, if the true ratio is 1, 31 subjects would provide a probability of at least 80% of all 4 CIs lying within (80%, 125%).

The aim of the study is to demonstrate that the 4 CIs for serum iron are all within (80%, 125%). As the SD, and the degree of correlation, are uncertain, 32 subjects will be recruited to the study.

12.2 STATISTICAL METHODS

For each of serum iron, maltol, maltol glucuronide, TSAT, TIBC, UBIC and transferrin, concentration data will be listed for each individual subject, by formulation / condition. The concentration data will be summarized, for each formulation / condition, at each time point by using the following descriptive statistics: n (the number of subjects), arithmetic mean, standard deviation (SD), geometric mean, coefficient of variation (CV), median, minimum and maximum, and a 90% confidence interval (CI) for the mean.

Concentration-time courses of each component will be graphically displayed per subject. Plots of the geometric mean and its 90% CI, by formulation, will be provided, overlaid, for each condition separately.

For serum iron, baseline corrected serum iron, maltol, maltol glucuronide, TSAT, TIBC, UIBC and transferrin, PK parameters (C_{max}, T_{max}, AUC_{last}, AUC_{inf}, λ_z, $t_{½}$) will be calculated by non-compartmental analysis and listed by subject and by period. The parameters will be summarized, for each formulation / condition, by using the following descriptive statistics: n, arithmetic mean, SD, geometric mean, CV, median, minimum and maximum.

For each analyte, the within-subject ratios between capsule and suspension of C_{max}, AUC_{last} and AUC_{inf} will be also be calculated and listed per subject, for each of the fed and fasted conditions separately. These ratios will be summarized by n, geometric mean and a 90% confidence interval for the mean.

Other endpoints and safety data will be listed and summarized for each formulation.

Full details will be specified in the Analysis Plan prior to database lock.

All secondary endpoints will be summarized by formulation / condition:

1. Treatment-emergent Adverse Events (TEAEs)
2. Serious Adverse Events (SAEs)
3. Treatment-emergent Adverse Events leading to premature discontinuation of study drug/PK assessments
4. Routine clinical laboratory safety blood results
5. Changes in vital signs
6. Concomitant medications

12.2.1 Sensitivity Analyses

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

12.2.2 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 Randomized Population

All subjects who are randomized.

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 analyzed for safety.

12.3.3 Full Analysis Set

All subjects who have had at least one dose of study drug and who have at least one evaluable post-dose PK sample will be included in the FAS population. This population will be utilized for the PK Analysis.

13 ETHICAL CONSIDERATIONS

The Sponsor and Investigator must comply with this protocol, all applicable national and local regulations including International Conference on Harmonization (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 Form and any other required study documents prior to starting the study. The Sponsor must approve any changes to the Information Sheet and Consent 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 form must be obtained prior to use. The Information Sheet will provide the subject 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 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 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 forms.

Each consent form must also contain an authorization 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 has been provided.

A copy of the information sheet and consent form signed and dated by the subject must be given to the subject. The signed consent form(s) will be retained with the study records at site. A description of the consent 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 must provide authorization as required by local law, eg. PHI. Subjects will not be identified by name (or initials) in the eCRF or any study reports. Data will be used for research purposes only. Every effort will be made to keep the subject's personal medical data confidential. All data will be used for research purposes only.

13.5 SUBJECT INSURANCE

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

13.6 CONFLICT OF INTEREST

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

13.7 REGISTRATION OF STUDY AND DISCLOSURE OF RESULTS

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

14 STUDY MANAGEMENT

14.1 SOURCE DATA

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

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

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

14.2 QUALITY ASSURANCE

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

14.3 MONITORING

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

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

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

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

14.4 STUDY FUNDING

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

14.5 CONTRACT RESEARCH ORGANIZATION (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 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 (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 documentation, disposition of the IMP, hard-copy eCRFs, medical records and other source data for at least 25 years after completion or discontinuation of the trial or for at least 2 years after the granting of the last marketing authorization in the EC (when there are no pending or contemplated marketing applications in the EC) or for at least 2 years after formal discontinuation of clinical development of the investigational product. Prior to proceeding with destruction of records, the Investigator must notify the Sponsor in writing and receive written authorization 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 licensing partners or specialist groups.

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