STATISTICAL ANALYSIS PLAN

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

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Test Drug:	Ferric Maltol
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NCT Number:	**NCT03181451**
Study Name:	AEGIS Kids PK
Sponsor:	Shield TX (UK) Limited, Northern Design Centre, Baltic Business Quarter, Gateshead Quays, NE8 3DF United Kingdom
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Confidentiality Statement

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STATISTICAL ANALYSIS PLAN

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

Investigational Product: Ferric Maltol
Protocol Number: ST10-01-103

Sponsor:
Shield TX (UK) Limited
Northern Design Centre
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United Kingdom

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SIGNATURE PAGE

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Protocol Version / Date:	Version 3.0, Final / 08 February 2017
SAP Version / Date:	Version 2.0/ 11 May 2018

We, the undersigned, have reviewed and approve this Statistical Analysis Plan.

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VERSION HISTORY

Version	Date	Description
0.1	21 June 2017	Initial creation
0.2	28 October 2017	• Removed Per Protocol Population from Section 5; • Update Section 6.1; • Updated Section 7.2; • Updated Section 8; • Changed Safety Population to FAS/ITT for summary in Section 9.1; • Updated Section 10;
0.3	27 November 2017	• Updated signature page; • Added the time period for AE and SAE capture in Section 4.4.1; • Added descriptive statistics for vital sign in Section 4.4.3; • Added descriptive statistics for ECG in Section 4.4.4; • Removed test of significance from Section 6.2; • Added categorical data in Section 6.2; • Updated protocol deviation category in Section 7.2; • Added descriptive statistics in Section 8.3; • Added Section 8.4 for the statistics of observed maltol, maltol glucuronide, serum iron, and TSAT; • Removed the calculation of TSAT from Section 8.5.4; • Added the time curve for iron makers to Section 9.1; • Added baseline definition in Sections 9.2, 10.3, 10.4.
0.4	08 January 2018	• Replaced Randomised Population with Dosed Group. • Added PPD for TSAT in Sections 8.3.4 and 8.3.5.
0.5	22 January 2018	• Added the language “The concentration plots described above will be prepared based on the actual data, if applicable.” to Sections 8.4 and 9.1. • Updated Section 8.3: report a concentration values less than the LLOQ as <LLOQ value.

Version	Date	Description
1.0	23 January 2018	• Version 1.0.
1.1	07 March 2018	• Removed individual concentration plots for maltol, maltol glucuronide, serum iron and TSAT in Section 8.4; • Removed individual concentration plots for transferrin, TIBC, UIBC, ferritin and NTBI in Section 9.4. • Added CSR and Non-CSR reportable deviations in Section 7.2
1.2	11 May 2018	• Update the baseline definition in Sections 4.3.2, 4.4.2.1, 4.4.2.2, 4.4.4, 7.3, and 10.2.

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LIST OF ABBREVIATIONS

AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	Area Under the Plasma Concentration Curve
$AUC_{(0\text{-}6h)}$	Area Under the Plasma Concentration Curve for 0-6h
$AUC_{(0\text{-}inf)}$	Area Under the Plasma Concentration Curve for 0-infinity
BID	Twice Daily
BMI	Body Mass Index
BQL	Below the Quantifiable Limit
BUN	Blood Urea Nitrogen
CA	Competent Authority
$C_{ave(0\text{-}6h)}$	Average Steady State Plasma Concentration from 0-6h
CL/F	Apparent Systemic Clearance
C_{max}	Maximum Plasma Concentration
CSR	Clinical Study Report
C_{trough}	Minimum Plasma Concentration
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EU	European Union
FAS	Full Analysis Set
FO	First Order
FOCE	First Order Conditional Estimation
FOCEI	First Order Conditional Estimation with Interaction
GGT	Gamma-Glutamyl Transpeptidase
ITT	Intent-to-Treat
MedDRA	Medical Dictionary for Regulatory Activities
MCH	Mean Corpuscular Haemoglobin

MCHC	Mean Corpuscular Haemoglobin Concentration
MCV	Mean Cell volume
MRL	Medpace Reference Laboratory
NCA	Non-Compartmental Analysis
NTBI	Non-Transferrin Bound Iron
PIP	Paediatric Investigation Plan
PK	Pharmacokinetics
PPK	Population Pharmacokinetics
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SI	Système International d'Unités
$t_{1/2}$	Half-life
TEAE	Treatment Emergent Adverse Event
TIBC	Total Iron Binding Capacity
T_{max}	Time to Maximum Plasma Concentration
TSAT	Transferrin Saturation
UIBC	Unsaturated Iron Binding Capacity
V/F	Apparent Volume of Distribution
WHO	World Health Organisation

1 INTRODUCTION

The purpose of this document is to provide a description of the statistical methods and procedures to be implemented for the analysis of data from Shield Protocol ST10-01-103. This document is based on protocol version 3.0, dated 08 February 2017. If circumstances arise during the study such that more appropriate analytic procedures become available, the statistical analysis plan (SAP) may be revised. Any revisions to the SAP (both alternative and additional methods) will be made prior to database lock and reasons for such revisions will be described in the final Clinical Study Report (CSR).

2 OVERVIEW

2.1 Objectives

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

The secondary objectives are the following:

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

2.2 Trial Design

This is a Phase 1, open label, randomised, repeat dose, parallel group study.

Approximately 36 eligible subjects aged 10-17 years were to be randomised at a ratio of 1:1:1 to one of three doses of Ferric Maltol (7.8 mg, 16.6 mg or 30 mg BID) for nine days (Days 1 to 9); a final single dose was then be administered on the morning of Day 10. Randomisation was to be stratified by age (10-14 years, 15-17 years) and gender (male, female) to ensure a minimum of 25% of each gender and at least three children per age group are enrolled in each Ferric Maltol dose group.

The planned study consisted for three study periods:

1. Screening Period;
2. Open-Label Treatment Period; and
3. Follow-Up Period.

Table 1 contains details of the study periods, study visits and timing of the visits. A short visit name has been generated to be included in tables and listings with limited space.

Table 1 Study Visits

Study Visit	**Period**	**Study Day**	**Visit Name**	
			Long	**Short**
1	Screening	-14 to -1	Screening	Screening
2	Open-Label Treatment	1	PK Day 1	Day 1
3	Open-Label Treatment	10	PK Day 10	Day 10
4	Follow-up	3 -10	Post-Study Safety Follow-up	Follow-up

The Screening Period consisted of one visit: Study Visit 1 (Screening) scheduled to take place within 14 days prior to the planned Open-Label Treatment Period for each subject. The purpose of this visit was to determine subject eligibility for the study.

The Treatment Period was to include two visits: Study Visit 2 (Day 1; PK Day 1) and Study Visit 3 (Day 10; PK Day 10).

The Follow-up Period included the last study visit: Study Visit 4 (Post-Study Safety Follow-up). This visit was to occur 3-10 days following completion of the Open-Label Treatment Period or premature discontinuation of study drug.

The schedule of procedures can be found in Table 2.

Table 2 Schedule of Procedures

Period	**Screening**	**Open-Label Treatment**		**Follow-up**
Study Visit	**1**	**2**	**3**	**4**
Short Name	**Screening**	**Day 1**	**Day 10**	**Follow-up[4]**
Day		**1**	**10**	
Informed Consent	X			
Demographics[7]	X			
Medical History	X			
Concomitant Medications and Procedures	X	X	X	X
Physical Examination	X			X
Vital Signs[1]	X	X	X	X
12-lead ECG[2]	X		X	
Urine Pregnancy Test[3]	X	X	X	X
Haematology, Clinical Chemistry and screening Iron markers blood sampling[3]	X		X[6]	
Eligibility confirmation and Randomisation	X	X[3]		
Dispense Study Drug		X		
Supervised morning dosing with Ferric Maltol		X	X	
Sparse PK Blood Sampling for Iron markers, maltol/maltol glucuronide and NTBI[5, 6]		X	X	
Issue and Review of Subject Study Dosing Diary		X	X	
Subject to Return Study Drug for Accountability			X	
Adverse Events		X	X	X

[1] *Vital Signs – supine systolic/diastolic blood pressure, pulse rate and body temperature at each visit.*

[2] *12-lead ECG at Screening and Day 10 (between 1h and 4h post-dose) – machine reported routine ECG parameters (heart rate, PR interval, RR interval, QTS duration, QT interval) and overall clinical ECG interpretation.*

[3] *Eligibility central laboratory sampling/assessments must be completed at Screening (Study Visit 1), before the subject is randomised and before the first dose of Ferric Maltol study drug is taken. Screening parameters to be tested:*
Haematology: red blood cell count, haemoglobin, haematocrit, mean cell volume (MCV), mean corpuscular haemoglobin (MCH), mean corpuscular haemoglobin concentration (MCHC), white blood cell count (total and differential (% and absolute), absolute reticulocyte count and platelet count.
Clinical Chemistry: ALT, AST, alkaline phosphatase, gamma-glutamyl transpeptidase (GGT), total bilirubin, creatinine, amylase, blood urea nitrogen (BUN), phosphorous, sodium, potassium, chloride, calcium, total cholesterol, uric acid, glucose, total protein, albumin.
Iron Markers: serum iron, transferrin, transferrin saturation (TSAT), total and unsaturated iron binding capacity (TIBC, UIBC) and ferritin.
Urine pregnancy test for female subjects of childbearing potential.
On Day 10, haematology and clinical chemistry blood samples will be collected at one of the PK sampling times between 1h to 4h post dose). Female subjects of childbearing potential will undergo urine pregnancy tests pre-dose on Day 1 and Day 1- and at the Post-study visit.

[4] *Subjects who discontinue from the study prematurely should have final assessments conducted per Study Visit 4,*

unless consent is withdrawn.

5 On PK study Days1 and 10, all subjects will have baseline PK blood samples collected immediately prior to Ferric Maltol dosing (0h). Subjects will then have further PK blood samples collected at two additional times between 0.5h and 6h after dosing on Days 1 and 10; the post-dose PK sample time collection windows will be 0.5-1h, 1.0-2.0h, 2.0-3.0h, 3.0-4.0h and 4.0-6.0h. Subjects will be assigned to the required post-dose PK blood sampling schedule in sequential order at the time of randomisation, based on current subject enrolment across all study sites. For each individual subject, the post-dose PK blood sampling schedule will be the same on Day 1 and Day 10.

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

[7] Demographics include age, gender, ethnicity and race and are recorded at the Screening Visit; Height (m) and body weight (kg) will be measured at the Screening Visit only.

3 STUDY ENDPOINTS

3.1 Primary Endpoints

The primary endpoints for the study are pharmacokinetic parameters.

1. Population PK analysis of maltol and maltol glucuronide in plasma from PK samples collected on Day 1 (after first morning dose) and Day 10 (after last morning dose). Parameters to be derived and reported for each Ferric Maltol dose are:
    - C_{max}, $C_{ave(0\text{-}6h)}$, $AUC_{(0\text{-}6h)}$, and $AUC_{(0\text{-}Inf)}$ on Day 1 and Day 10 and ratios of Day 10/Day 1 for these parameters;
    - $T_{max;}$
    - Half-life ($t_{1/2}$);
    - Apparent systemic clearance (CL/F); and
    - Apparent volume of distribution (V/F).

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

2. Descriptive and population PK analysis of serum iron and TSAT from PK samples collected on Day 1 and Day 10. Parameters to be derived and reported for each Ferric Maltol dose are:
    - Change from pre-dose (C_{trough}) to maximum post-dose (C_{max}) value for serum iron and TSAT; $C_{ave(0\text{-}6h)}$;
    - Pre-dose adjusted Incremental $AUC_{(0\text{-}6h)}$ on Day 1 and Day 10 from a population PK analysis approach, and percent change from Day 1 to Day 10; and
    - Apparent systemic clearance (CL/F), apparent volume of distribution (V/F).

    Serum iron and TSAT by time of collection on Day 1 and Day 10 will also be presented.

3.2 Secondary Endpoints

The secondary endpoints for the study are:

1. Transferrin, TIBC, UIBC and ferritin concentrations from PK samples collected on Day 1 and Day 10;
2. Non-transferrin bound iron (NTBI) concentrations from PK samples collected on Day 1 and Day 10; and
3. Haemoglobin concentration and absolute reticulocyte count from haematology samples collected at Screening and Day 10.

3.3 Safety Endpoints

The safety endpoints for the study are:

1. Adverse Events (AEs) - Treatment Emergent Adverse Events (TEAEs), Treatment Emergent Serious Adverse Events (SAEs) and TEAEs leading to premature discontinuation of study drug/PK assessments;
2. Clinical laboratory safety blood results at Screening and Day 10;
3. Changes in vital signs and 12-lead ECG; and
4. Concomitant medications.

4 STUDY ASSESSMENTS

4.1 Screening Visit and Baseline

Written informed consent was to be obtained from each subject/legal guardian on the Screening Visit before any study assessment or test was conducted.

Demographic information, including date of birth, race, ethnicity and gender, was to be recorded at the Screening Visit.

All current medical conditions, all medical history relevant to iron deficiency diagnosis regardless of onset and all clinically significant medical history from the past five years including all malignancies, sterilisations, hospitalisations and surgeries were to be collected at the Screening Visit. For female subjects of childbearing potential, the method of contraception was also collected at this visit.

Body weight and height were to be measured at the Screening Visit only. Body Mass Index (BMI) will be derived using height and weight as measured at the Screening Visit as:

$$BMI = \frac{Weight\ (kg)}{[Height\ (m)]^2}$$

4.2 Primary Pharmacokinetic Measurements and Variables

4.2.1 PK blood sampling

On study days 1 and 10, all subjects were to have baseline (pre-dose) PK blood samples collected immediately prior to Ferric Maltol dosing (0h). Subjects were then to have further PK blood samples collected at two additional times between 0.5h and 6h after dosing on Days 1 and 10; within each Ferric Maltol dose group (7.8 mg, 16.6 mg or 30 mg BID), the post-dose PK sample time collection windows were 0.5-1h, 1.0-2.0h, 2.0-3.0h, 3.0-4.0h and 4.0-6.0h. The 12 subjects within each Ferric Maltol dose group were assigned to the required post-dose PK blood sampling schedule in sequential order at the time of randomisation, based on current subject enrolment across all study sites. Table 3 details the sparse PK blood sample schedule.

Table 3 Sparse PK Blood Sampling Schedule

	PK Sample Schedule			
	Group 1 (N = 3/12)	**Group 2 (N = 3/12)**	**Group 3 (N = 3/12)**	**Group 4 (N = 3/12)**
Pre-dose (0h)	X	X	X	X
0.5 – 1h	X	X		
1.0 – 2.0h	X		X	
2.0 – 3.0h		X		X
3.0 – 4.0h			X	
4.0 – 6.0h				X

For each individual subject, the post-dose PK blood sampling schedule was to be the same on Day 1 and Day 10. Post-dose samples for each subject were to be collected within the allocated time-windows (e.g. between 0.5-1h or 1-2h); the exact time of the sample collection was to be recorded in the eCRF. For those subjects in PK Sample Schedule Group 1 (see Table 3), the PK blood samples for the 0.5-1h timepoint window were to be taken at 30 minutes prior to the PK blood samples for the 1-2h timepoint window on Day 1 and Day 10, to provide an adequate spread of actual sampling times for the population PK analysis.

4.2.2 PK Parameters

PK samples were to be collected on Day 1 and Day 10, pre-dose and post-dose according to the PK Sample Schedule Group that the subject was assigned to.

Maltol (ng/dL) and Maltol Glucuronide (µg/mL) results will be available from the data export from the bioanalytical laboratory, ABS Laboratories Ltd.

Serum iron (µmol/L) and TSAT (%) will be available from the standard export from Medpace Reference Laboratory (MRL). The data transport files from MRL will contain serum iron and

TSAT in the standard reporting units of the reporting laboratory and in Système International d'Unités (SI) units.

C_{max}, $C_{ave(0\text{-}6h)}$, $AUC_{(0\text{-}6h)}$, $AUC_{(0\text{-}inf)}$, T_{max}, half-life ($t_{1/2}$), apparent systemic clearance (CL/F), apparent volume of distribution (V/F) and C_{trough} will be derived for maltol, maltol glucuronide, serum iron and TSAT at Day 1 and Day 10.

4.3 Secondary Endpoint Measurements and Variables

4.3.1 Iron Markers and Non-Transferrin Bound Iron (NTBI)

Iron markers include transferrin, total and unsaturated iron binding capacity (TIBC and UIBC) and ferritin. Iron markers and NTBI were to be collected on Day 1 and Day 10, pre-dose and post-dose according to the PK Sample Schedule Group that the subject was assigned to.

The following list of iron markers and NTBI will be available from the standard export from MRL:

- Transferrin (units) g/l
- TIBC (units) µmol/L
- UIBC (units) µmol/L
- Ferritin (µg/L) µg/L
- NTBI (units) <0.2 eLPI unit =negative, ≥0.2 eLPI unit=positive

The data transport files from MRL will contain iron markers in the standard reporting units of the reporting laboratory and in SI units. All iron markers will be converted to and reported using units indicated in parenthesis above.

Baseline for iron markers and NTBI is defined as the pre-dose value observed at the Day 1 Visit. Change from baseline to each post-baseline visit/timepoint will be derived for each parameter as visit/timepoint value minus baseline.

NTBI results will be available from the data export from Afferix Ltd.

4.3.2 Haemoglobin Concentration and Absolute Reticulocyte Count

Haemoglobin concentration and absolute reticulocyte counts were to be collected at the Screening Visit and on Day 10.

Haemoglobin concentration (g/dL) and absolute reticulocyte counts (10^6 Cells/µL) will be available from the standard export from MRL. The data transport files from MRL will contain haemoglobin concentration and absolute reticulocyte counts in the standard reporting units of the

reporting laboratory and in SI units; values will be converted to and reported using units indicated in parenthesis above.

Baseline for haemoglobin concentration and absolute reticulocyte count is defined as the value observed at the Screening Visit. If the Screening retest is performed, the values of Screening retest will be used as baseline. Change from baseline to Day 10 will be derived for each parameter as visit value minus baseline.

4.4 Safety Measurements and Variables

4.4.1 Adverse Events

An adverse event (AE) is any untoward medical occurrence in a subject administered a pharmaceutical product and does not necessarily have a causal relationship with this treatment.

Any serious adverse event (SAE) that occurred from informed consent being obtained at the Screening Visit until two week after the last dose was to be recorded in the eCRF. Any AE that occurred from the time of dosing until the end of the study was to be recorded in the eCRF. The following details were to be recorded for each adverse event:

- Adverse event reported term;
- Start date and time and stop date;
- Outcome (fatal, ongoing/not resolved, recovered, recovered with sequelae, unknown);
- Severity (mild, moderate, severe);
- Relationship to study drug (related, not related);
- Action taken with study drug (dose increased, dose not changed, dose reduced, drug interrupted, drug withdrawn, not applicable, other, unknown);
- Other action taken, not related to study drug (none, concomitant medication required, non-drug therapy required);
- Cause study discontinuation (yes, no);
- Serious (yes, no); and
- If serious:
    - Death (yes, no);
    - Life-threatening (yes, no);
    - Inpatient hospitalisation (yes, no);
    - Prolongation of hospitalisation (yes, no);
    - Congenital anomaly or birth defect (yes, no);
    - Persistent or significant disability/incapacity (yes, no); and
    - Judged as medically significant (yes, no).

Adverse events will be coded using MedDRA version 19.0.

Adverse events defined as treatment emergent adverse events (TEAE) if they occur after the first dose intake of study drug. Treatment emergent adverse events will be identified by comparing the recorded start date and time of the event with the date and time of the first dose intake of study drug. Identification of the treatment emergent status of adverse events with a partial start date will be determined using the available incomplete date information. For example, if the adverse event has a missing day field but the non-missing month and year fields place the start of the event after the start of study drug, then the event will be assigned to the treatment emergent class. For adverse events where the available partial date information is inconclusive (for example, missing day but available month and year are equal to the month and year of start of study drug) then the event will be classified as treatment emergent. In particular, adverse events with a completely missing start date will be assumed to be treatment emergent (unless the stop date places the event prior to starting study drug).

4.4.2 Safety Clinical Laboratory Measurements

Routine clinical laboratory safety bloods for haematology and clinical chemistry evaluations were to be obtained at the Screening Visit and at Day 10.

4.4.2.1 Haematology

The following haematology parameters will be available from the standard export from MRL:

- Red blood cell count (10^12/L);
- Haematocrit (%);
- Mean cell volume (MCV) (fL) ;
- Mean corpuscular haemoglobin (MCH) (pg);
- Mean corpuscular haemoglobin concentration (MCHC) (g/L);
- White blood cell count (total and differential (% and absolute)) (10^9/L); and
- Platelet count (10^9/L).

The data transport files from MRL will contain haematology parameters in the standard reporting units of the reporting laboratory and in SI units; values will be converted to and reported using units indicated in parenthesis above.

Baseline for all haematology parameters is defined as the value observed at the Screening Visit. If the Screening retest is performed, the values of Screening retest will be used as baseline. Change from baseline to Day 10 will be derived for each parameter as visit value minus baseline.

4.4.2.2 Clinical Chemistry

The following clinical chemistry parameters will be available from the standard export from MRL:

- ALT (U/L);
- AST (U/L);
- Alkaline phosphatase (U/L);
- Gamma-glutamyl transpeptidase (GGT) (U/L);
- Total bilirubin (µmol/L);
- Creatinine (µmol/L);
- Amylase (U/L);
- Blood urea nitrogen (BUN) (mg/dL);
- Phosphorous (mg/dL);
- Sodium (mmol/L);
- Potassium (mmol/L);
- Chloride (mmol/L);
- Calcium (mmol/L);
- Total cholesterol (mmol/L);
- Uric acid (µmol/L);
- Glucose (mmol/L);
- Total protein (g/L); and
- Albumin (g/L).

The data transport files from MRL will contain clinical chemistry parameters in the standard reporting units of the reporting laboratory and in SI units; values will be converted to and reported using units indicated in parenthesis above.

Baseline for all clinical chemistry parameters is defined as the value observed at the Screening Visit. If the Screening retest is performed, the values of Screening retest will be used as baseline. Change from baseline to Day 10 will be derived for each parameter as visit value minus baseline.

4.4.2.3 Urine Pregnancy Test

For females of childbearing potential, a urine pregnancy test will be conducted at the Screening Visit, prior to first dose of study drug on Day 1, prior to study drug dosing on Day 10 and at the Follow-Up Visit.

For all Safety Clinical Laboratory measurements, values outside the reference range will be categorized as above (RH: Reference High) or below (RL: Reference Low) the reference range based on the Central Laboratory's normal reference range. Notable Low (NL), Notable High (NH), Critical Low (CL) and Critical High (CH) values will also be flagged.

4.4.3 Vital Signs

Body temperature (ºC), diastolic and systolic blood pressure (mmHg) and pulse rate (beats/min) were to be assessed at the Screening Visit, pre-dose on Days 1 and 10 and at the Follow-up Visit.

For all vital signs parameters, baseline is defined as the pre-dose value on Day 1. If a pre-dose value at Day 1 is not available, the value from the Screening Visit will be used as the baseline value. Change from baseline to each post-baseline visit (Day 10 and Follow-up) will be derived as visit value minus baseline. Observed values and change from baseline will be summarized by dose group and visit/timepoint descriptively. Data will also be listed by dose group and visit/timepoint.

4.4.4 12-Lead ECG

A 12-lead ECG was to be recorded at the Screening Visit and at Day 10 (between 1h and 4h post-dose). Machine reported standard ECG parameters were to be recorded in the eCRF and include:

- Heart Rate (beats/min);
- PR Interval (msec);
- RR Interval (msec);
- QRS Duration (msec);
- QT Interval (msec); and
- Overall clinical interpretation (Normal, Abnormal, Indeterminate, Not Evaluable, Unknown).

The following additional parameters will be derived from the standard ECG parameters:

- QTcB Interval (msec), defined as:

$$QTcB = \frac{QT\ Interval}{\sqrt{RR\ Interval}}$$

- QTcF Interval (msec), defined as:

$$QTcF = \frac{QT\ Interval}{\sqrt[3]{RR\ Interval}}$$

For all ECG parameters, baseline is defined as the value observed at the Screening Visit. If the Screening retest is performed, the values of Screening retest will be used as baseline. Change from baseline (to Day 10) will be derived as visit value minus baseline. Observed values and change from baseline will be summarized descriptively by dose group and visit/timepoint. Data will also be listed by dose group and visit/timepoint.

4.4.5 Physical Examination

A brief physical examination was to be conducted at the Screening and Follow-up Visits. The examination was to include an assessment of general appearance, skin, head, eyes, ears, nose and throat, cardiovascular, respiratory, abdominal, gastrointestinal and musculoskeletal systems.

4.4.6 Prior and Concomitant Medications and Procedures

Medications taken blood transfusion at the time of the Screening Visit and those stopped within three months of the Screening Visit were to be documented on the Prior & Concomitant Medications eCRF. Medications initiated, stopped or with dose and/or frequency changes throughout the study were also to be documented on the Prior & Concomitant Medications eCRF. The medication name, dose (and unit), start and stop dates of medication, indication, frequency and route were to be recorded. All medications will be coded using the WHO Drug, Dictionary, September 2016.

Any medical procedure performed within three months prior to the Screening Visit or performed throughout the study were to be documented on the Concomitant Procedures eCRF. Medical procedures include any therapeutic intervention such as surgery/biopsy, physical therapy of diagnostic assessment. Details of the procedure with start and stop dates were to be recorded.
All medical procedures will be coded using MedDRA version 19.0.

Medications and procedures will be identified as either prior or concomitant according to the start and/or stop dates recorded on the eCRF. Medications/procedures with a stop date prior to the Screening Visit will be considered as prior medications/procedures. Medications/procedures that start before the Screening Visit and are continued into the study are considered as concomitant medications/procedures as are medications/procedures that have a reported start date on or after the date of the Screening Visit. The prior/concomitant status for medications/procedures with a partial start and/or stop date will be determined using the available incomplete date information using a similar method as that described previously for adverse events with partial start dates.

4.4.7 Study Drug Exposure and Compliance

Study drug was to be dispensed at the Day 1 Visit and returned at the Day 10 Visit or Early Termination Visit. The first dose intake of Ferric Maltol was to be taken on site during the Day 1 Visit and the last intake was to be taken on site on the morning of the Day 10 Visit after the pre-dose PK blood samples had been taken. All unused medication was to be returned at the Day 10 or Early Termination Visit. A record of the number of capsules dispensed and returned for each subjects was to be documented in the eCRF.

Compliance will be evaluated by comparing the expected number of capsules of study drug administered with the actual number of capsules of study drug administered during the open-label treatment period.

Assuming that the subject takes the first dose on the morning of Day 1 and the last dose on the morning of Day 10, the expected number of capsules taken is assumed to be 19 capsules (i.e. 2 capsules per day on Days 1 to 9 plus 1 capsule on the morning of Day 10). If the subject does not complete the open-label treatment period as planned then the expected number of capsules will be calculated taking into account the timing of the first and last doses.

The actual number of capsules taken will derived as the difference in the number of capsules dispensed and returned as recorded in the eCRF.

Compliance will therefore be derived as:

$$Compliance = \frac{Actual\ number\ of\ capsules\ taken}{Expected\ number\ of\ capsules\ taken} \times 100\%$$

5 ANALYSIS POPULATIONS

The analysis populations, defined below, will be used to perform the data analyses. In the Dosed Group subjects will be presented according to the dose group they were allocated to. In the Safety, Full Analysis Set/Intent-to Treat Populations, any subjects who received a different dose than they were allocated will be presented according to the dose they actually received.

5.1.1 Screened Population

The Screened Population will include all subjects screened for inclusion into the study.

5.1.2 Dosed Group

The Dosed Group will include all subjects who take at least one dose of study drug.

5.1.3 Safety Population

The Safety Population will include all subjects who take at least one dose of study drug and have one subsequent contact with the Investigator. This population will be used to summarize all safety data.

5.1.4 Full Analysis Set (FAS)/Intent-to-Treat (ITT) Population

The Full Analysis Set (FAS)/Intent-to-Treat (ITT) Population will include all subjects who take at least one dose of study drug and have at least one evaluable post-dose PK sample. This population will be used in the PPK analysis.

6 GENERAL CONSIDERATIONS FOR DATA ANALYSIS

Statistical analyses will be performed using SAS® (Version 9.3 or later). All available data will be presented in subject data listings, which will be sorted by dose group, subject identifier and where appropriate, visit number and visit/assessment date.

Listings will contain data for all attended visits whether scheduled or unscheduled and visits will be listed in the order in which they were attended. Tables will only summarise data for the scheduled visits.

Dose groups will be displayed in all output using the following labels:

- Ferric Maltol 7.8 mg bid
- Ferric Maltol 16.6 mg bid
- Ferric Maltol 30 mg bid

6.1 Date Format

Only the actual age will be used in this study. The YYYY-01-01 will be used for the Date of Birth. Partial days will be allowed for the duration of disease.

6.2 Other Data Handling Approaches

Descriptive statistics (n, mean, standard deviation (SD), median, maximum and minimum) will be used to summarise the continuous data. Discrete measures will be summarized using counts and percentages (derived from the number of non-missing observations); the number of non-missing (n) observations will also be presented.

Unless otherwise stated, descriptive statistics showing the mean or median will be displayed to one more decimal place than the original data; the standard deviation will be displayed to two decimal places more than the original data and minimum and maximum values will be displayed to the same number of decimal places as the original data.

All fractional numeric values will be printed with a zero to the left of the decimal point (e.g., 0.12, 0.3 etc.). Percentage values will be printed with one digit to the right of the decimal point (e.g., 52.3%, 8.9% etc.).

Categorical data will be summarized descriptively using frequency counts and corresponding percentages.

7 ANALYSIS OF DISPOSITION AND SUBJECT CHARACTERISTICS

7.1 Disposition and Analysis Populations

Subject disposition will be presented for all subjects in the Screened Population. The number and percentage of subjects who meet each of the following categories will be summarised by dose group and overall, as appropriate:

- Screened;
- Screen success;
- Screen failure and reasons for screen failure;
- Dosed;
- Complete the open-label treatment period; and
- Prematurely discontinue during the open-label treatment period and reasons for study discontinuation.

Subjects who screen fail will be listed detailing date of screen failure and primary reason for screen failure.

The number of subjects in the Screened Population, Dosed Group, Safety Population, and FAS/ITT Population will be tabulated by dose group and overall. A listing of analysis population inclusion will also be provided.

Inclusion/Exclusion criteria deviations will be listed and summarized for the Dosed Group and those excluded from the Screened Population.

All available visit dates will be listed for the Screened Population.

A listing of informed consent will be provided for the Screened Population. This listing will contain the date of informed consent (for the subject and/or parent/guardian) and the protocol version to which informed consent was provided; details of reconsent, as appropriate, will also be included.

Treatment details will be listed for the FAS/ITT Population and will contain, for each subject, details of the stratification variables (gender and age group), date of randomization, randomization number, the dose group the subject was randomised/assigned to ('Planned') and the dose the subject actually received ('Actual'), the date of first dose of study drug and the PK Sampling Group the subject was allocated to.

7.2 Protocol Deviations and Violations

CSR reportable protocol deviation include the following categories:

- Inclusion: Subject enrolled did not meet all inclusion criteria (CRA to specify inclusion criteria not met in eMVR);
- Exclusion: Subject enrolled met exclusion criteria (CRA to specify exclusion criteria met in eMVR);
- Withdrawal Criteria: Patient met one or more withdrawal criteria and continued in the study:

    - Subject withdrew informed consent;
    - Subject unwilling or unable to comply with protocol requirements;
    - Subject became pregnant or was not using a reliable method of birth control, if female and of childbearing potential;
    - Subject experienced SAEs judged by the investigator to be related to study drug (Ferric Maltol); or
    - Subject used prohibited concomitant medication(s).
- Investigational Product:
    - Subject received incorrect dose of study medication (specify dose and timepoint);
    - Subject was dispensed incorrect dose;
    - Study drug compliance <80% per Patient Dosing Card on V3 Day 10 or IP accountability;
    - Study drug compliance >120% per Patient Dosing Card on V3 Day 10 or IP accountability; or
    - Incorrect data provided for stratification at randomisation (specify data).
- Restricted Concomitant Procedure/Medication Change:
    - Subject initiated drug therapy not permitted per protocol (specify medication and timepoint);
    - Immunosuppressant (specify) not take at a stable dose 12 week prior to randomisation
- Study Procedures:
    - Hematology, chemistry, and iron markers not obtained at appropriate visit(s) (specify visit and marker);
    - PK sample not collected (specify visit, PK schedule group and timepoint(s)); or
    - PK sample collected, but not within assigned timepoints ((specify visit, PK schedule group, timepoint(s) assigned and timepoint(s) collected)
    - Day 10 visit was not performed on day 10 past Day 1 visit exactly.
- Breaches in GCP:
    - Subjects (or legal representative) did not sign Informed Consent and Assent prior to study procedures;
    - Patient (or legal representative) did not sign amendment to Informed Consent and Assent which included new study procedures prior to those procedures being performed.

CSR non-reportable protocol deviations include the following categories:

- SAE reporting: Investigator site did not complete the required SAE information including relevant CRF pages or SAE reporting Form and/or notify/submit report to Medpace within 24 hours;
- Informed consent:

- An error in the Informed Consent and Assent administration occurred (specify);
- The Subjects (or legal representative) did not properly sign or did not date the ICF (specify versions);
- The ICF signed by the subject or legally authorized representative is not in the subject's primary language;
- Incorrect Informed Consent and Assent version signed by the subject (specify ICF/assent version);
- Updated Informed Consent and Assent not signed at the first opportunity following approval (specify updated Informed Consent and Assent version);
- A study procedure or medication administration occurred prior to signing the Informed Consent and Assent;
- A subject received IP or has further visits or data collected AFTER withdrawing consent for participation in the study; or
- Subject was not given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study.
- Subjects (or legal representative) did not sign Informed Consent and Assent prior to second screening

- Study procedures:
  - Physical exam not completed at visit (specify visit);
  - Physical exam not completed at visit (specify visit);
  - Subject was not at rest for 5 minutes prior to Vital signs (BP and HR) being obtained (specify visit);
  - Urine pregnancy test not completed (specify visit); or
  - Vital signs not completed at visit (specify vital sign and visit).
- Investigational product (other than wrong treatment):
  - Study IP stored outside specified ranges in the protocol;
  - IP storage temperature excursion not reported (specify range and dates);
  - Subject dosed with study medication before all inclusion/exclusion were confirmed (specify criteria not confirmed prior to first dose); or
  - IP dose administration instructions not followed (please specify).
  - Day 9 evening dose missed
- Visit windows: Subject was outside of the visit window (specify # of days) for Screening, Day 1 Treatment and Post-Study Follow-Up visits (specify visit).

Protocol deviations will be summarized with frequency distributions (counts and percentages) by dose group and category for the FAS/ITT population. The denominators for calculating percentages will be based on the number of subjects in the FAS/ITT population for each dose group and overall.

Protocol deviations will be provided within a data listing by subject for each dose group.

7.3 Demographics and Baseline Characteristics

Demographic characteristics (year of birth, age, ethnicity, race and gender) and baseline characteristics (height, weight and BMI) as recorded at the Screening Visit will be summarised by dose group and overall using descriptive statistics for the Safety and ITT/FAS Populations. A demographics and baseline characteristics listings will also be produced for the Screened Population. If the Screening retest is performed, the values of Screening retest will be used as baseline.

A listing of reproductive status will be provided for the female subjects only and will contain details of whether the female is of child bearing potential and the method(s) of contraception.

7.4 Medical History

Medical history (event/diagnosis, start and stop dates and status at end of study) will be presented for the Screened Population. Medical history will be summarised by dose group and overall by System Organ Class and Preferred Term for the Safety Population.

8 PHARMACOKINETIC ANALYSIS

8.1 Analysis Populations

The FAS/ITT Population will be used for the primary endpoint analysis.

8.2 Missing Dosing Information

If dosing information is missing, a patient's pre-dose time will be used to impute dosing time to calculate relative time for post-dosing timepoints.

8.3 Missing concentrations

Missing concentrations related to serum iron, TSAT, transferrin, TIBC, UIBC, and NTBI will not be not imputed or used in the analysis. If the dosing history information for a patient is missing, the sampling for that patient relative to the missing dose will not be included in the analysis.

For maltol and maltol glucuronide assessment, all drug concentration below the quantifiable limit (BQL) are treated as zero. When more than half (>50%) of the values at a single timepoint are BQL, mean and median values are reported as BQL. Standard deviation and %CV are not reported; maximum and minimum values are reported as observed (including BQL). If, as the result of the calculation (eg. dose normalization, descriptive statistics) a concentration value is less than the LLOQ the value should be reported as <LLOQ value.

8.4 Observed Maltol, Maltol Glucuronide, Serum Iron, and TSAT

The observed values for maltol, maltol glucuronide, serum iron, and TSAT will be summarized by dose group and by visit/timepoint for FAS/ITT Population using the flowing descriptive statistics: n (the number of subjects), arithmetic mean, minimum and maximum.

The change from baseline values of serum iron and TSAT will be summarized by dose group for each post-baseline visit/timepoint for FAS/ITT Population using the flowing descriptive statistics: n (the number of subjects), arithmetic mean, median, minimum and maximum.

The observed data for maltol, maltol glucuronide, serum iron, and TSAT will also be listed by dose group for each individual subject for FAS/ITT Population.

For maltol and maltol glucuronide, the mean observed plasma concentrations will be plotted on a linear and semi-logarithmic scale against nominal time range by dose group and visit. Geometric mean observed plasma concentrations will be plotted on a linear scale against nominal time range by dose group and visit. Combined observed plasma concentrations will be plotted on a linear and semi-logarithmic scale against actual timepoint for each dose group and visit.

For serum iron, the mean observed serum concentrations will be plotted on a linear and semi-logarithmic scale against nominal time range by dose group and visit. Combined observed serum concentrations will be plotted on a linear and semi-logarithmic scale against actual timepoint for each dose group and visit. The change of baseline will be plotted similarly.
Mean observed TSAT will be plotted on a linear scale against nominal time range by dose group and visit. Combined observed TSAT will be plotted on a linear scale against actual timepoint for each dose group and visit. The change of baseline will be plotted similarly.

The concentration plots described above will be prepared based on the actual data, if applicable.

8.5 Population Pharmacokinetic Modelling

The FAS/ITT Population will be used for the PPK analysis.

8.5.1 Basic Model Construction

The maltol and maltol glucuronide concentrations will be analysed simultaneously by means of fitting the compartment models to observed concentration data using a population PK (PPK) approach.

Likewise, the serum iron and TSAT concentrations will be analysed. If the PPK modelling for TSAT is not feasible, population PD (PPD) approach may be performed.

Population PK models will be built using a nonlinear mixed effects modelling technique with NONMEM® software. It is planned that the first order conditional estimation with interaction (FOCEI) method will be used for model development. If this is not feasible (i.e. the model will fail to converge), the first order conditional estimation (FOCE) and the first order (FO) method will be used instead.

Different models will be attempted to fit the PK concentration-time data. The models will include, but are not limited to, one-compartment linear model, one-compartment linear model with first order absorption, two-compartment linear mammillary model, two-compartment linear mammillary model with first order absorption, three-compartment linear model, and three-compartment linear model with first order absorption, linear compartment model with zero order absorption or saturable absorption. Furthermore, a nonlinear compartment model may also be tested, if possible.
For each individual model, model stability will be assessed with the following:

- Model parameter estimates not close to a boundary;
- Shrinkage for interindividual variability terms (ETA) and residual unknown variability (EPS) < 30%;
- Condition number (ratio of the largest to the smallest eigenvalues) <1000; and
- Correlation less than 0.90 between any two parameter estimates.

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

8.5.2 Final Model Construction

Based on the results of the above assessments, the final base model will be judged and finalized.

8.5.3 Covariate Model Construction

If applicable, the following covariates will be evaluated for their potential significant impact on the PK. Age, race and ethnicity, gender, all current medical conditions, all medical history relevant to iron deficiency diagnosis regardless of onset, all clinically significant medical history from the past five years including all malignancies, sterilisations, hospitalisations and surgeries, the method of contraception for female subjects of childbearing potential and body weight.

8.5.4 Concentration Prediction and Parameter Derivation

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

Standard non-compartmental methods (NCA) will be used for the PK parameter calculations based on the predicted concentrations. The Linear Up Log Down method (equivalent to the Linear Up/Log Down option in WinNonlin® Professional) will be used in the computation of AUC.

Maltol and maltol glucuronide:

The following parameters for Day 1 will be derived for each Ferric Maltol dose based on the predicted maltol and maltol glucuronide concentrations, if applicable:

Table 4 Parameters for Maltol and Maltol Glucuronide on Day 1

Parameters	Description
C_{max}	Maximum plasma concentration directly from data
T_{max}	Time to reach maximum concentration directly from data
λ_z	Apparent first-order terminal elimination rate constant
$t_{½}$	Terminal elimination half-life, calculated as $\ln(2)/ \lambda_z$
$AUC_{0\text{-}6h}$	Area under the plasma concentration versus time curve from time zero to 6hr.
$AUC_{0\text{-}inf}$	Area under the plasma concentration versus time curve from time zero extrapolated to infinity time
CL/F	Apparent clearance calculated as $Dose/AUC_{0\text{-}inf}$
V_z/F	Apparent volume of distribution (as $Dose/ [\lambda_z * AUC_{0\text{-}\infty}]$)

The following parameters for Day 10 will be derived for each subject based on the predicted maltol and maltol glucuronide concentrations, if applicable:

Table 5 Parameters for Maltol and Maltol Glucuronide on Day 10

Parameters	**Description**
Tau	The dosing interval for steady-state data tau=12
C_{max}	Maximum concentration between dose time and dose time + Tau. If not unique, then the first maximum is used.
C_{trough}	Minimum concentration between dose time and dose time + Tau
T_{max}	Time to reach C_{max} during a dosing interval
$AUC_{0\text{-}6h}$	Area under the plasma concentration versus time curve from time zero to 6hr.
$AUC_{0\text{-}tau}$	Area under the plasma concentration versus time curve from time zero to Tau
$C_{ave(0\text{-}6h)}$	Average Steady State Plasma Concentration from 0-6h, calculated as $AUC_{0\text{-}6h}$ divided by 6
CL_{ss}/F	Apparent clearance calculated as Dose/$AUC_{0\text{-}tau}$
R_{Cmax}	Accumulation ratio based on maximum concentrations after first dose and last dose, calculated as $C_{maxDay10}/C_{maxDay1}$
$R_{AUC0\text{-}6h}$	Accumulation ratio based on $AUC_{0\text{-}6}$ after first dose and last dose, calculated as $AUC_{0\text{-}6(Day10)}/AUC_{0\text{-}6(Day1)}$

Pharmacokinetic parameters of maltol and maltol glucuronide will be listed by dose group for each individual subject and summarized by dose group using the following descriptive statistics: n (the number of subjects), arithmetic mean, SD (standard deviation), geometric mean, geometric CV (coefficient of variation), median, minimum and maximum.

Plasma concentration-time courses of maltol/maltol glucuronide on Day 1 and Day 10, including C_{trough}, will be tabulated and graphically displayed per subject and summary statistics will be provided for each dose group for a specific timepoint/day. Plots of mean and geometric mean and plots with combined individual time courses will be provided by dose group.

Actual and/or dose-normalized pharmacokinetic parameters of C_{max} and AUCs will be graphically displayed for maltol and maltol-glucuronide as function of the dose, to explore dose-proportionality.

Serum iron and TSAT:

The following parameters for serum iron and TSAT on Day 1 will be derived for each subject based on the uncorrected and baseline-corrected predicted serum iron concentrations and TSAT, if applicable:

Table 6 Parameters for Serum Iron and TSAT on Day 1

Parameters	Description
C_{max}	Maximum plasma concentration directly from data
C_{trough}	Pre-dose plasma concentration
Change from C_{trough} to C_{max}	C_{max} - C_{trough}
T_{max}	Time to reach C_{max}
λ_z	Apparent first-order terminal elimination rate constant
AUC_{0-6h}	Area under the plasma concentration versus time curve from time zero to 6 h using the pre-dose adjusted concentration data
AUC_{0-inf}	Area under the plasma concentration versus time curve from time zero extrapolated to infinity time using the pre-dose adjusted concentration data
CL/F	Apparent clearance calculated as Dose/AUC_{0-inf}
V_z/F	Apparent volume of distribution (as Dose/ [λ_z *$AUC_{0-\infty}$])

The following parameter for serum iron and TSAT on Day 10 will be derived for each subject based on the uncorrected and baseline-corrected predicted serum iron concentrations and TSAT, if applicable:

Table 7 Parameters for Serum Iron and TSAT on Day 10

Parameters	**Description**
Tau	The dosing interval for steady-state data tau=12
C_{max}	Maximum concentration between dose time and dose time + Tau. If not unique, then the first maximum is used.
C_{trough}	Minimum concentration between dose time and dose time + Tau
Change from C_{trough} to C_{max}	C_{max} - C_{trough}
AUC_{0-6h}	Area under the plasma concentration versus time curve from time zero to 6 h using pre-dose adjusted concentration data
AUC_{0-tau}	Area under the plasma concentration versus time curve from time zero to Tau
$C_{ave(0-6h)}$	Average Steady State Plasma Concentration from 0-6h, calculated as AUC_{0-6h} divided by 6
CL/F	Apparent clearance calculated as Dose/AUC_{0-tau}
R_{Cmax}	Accumulation ratio based on maximum concentrations after first dose and last dose, calculated as $C_{maxDay10}/C_{maxDay1}$
$R_{AUC0-6h}$	Accumulation ratio based on AUC_{0-6} after first dose and last dose, calculated as $AUC_{0-6(Day10)}/AUC_{0-6(Day1)}$

Pharmacokinetic parameters of serum iron and TSAT will be listed by dose group for each individual subject and summarized by dose group using the following descriptive statistics: n (the number of subjects), arithmetic mean, SD (standard deviation), geometric mean, geometric CV (coefficient of variation), median, minimum and maximum.

Concentration-time courses of serum iron and TSAT on Day 1 and 10, including C_{trough} on Day 1 and 10 will be tabulated and graphically displayed per subject and summary statistics will be provided for each dose group and visit/timepoint. Plots of mean and geometric mean and plots with combined individual time courses will be provided by dose group.

Actual and/or dose-normalized pharmacokinetic parameters of C_{max} and AUCs will be graphically displayed for serum iron and TSAT as function of the dose, to explore dose-proportionality.

If the PPK model is not feasible for TSAT and PPD model is used for TSAT, the following parameters for TSAT on Days 1 and 10 will be derived for each subject based on the predicted TSAT, if applicable:

Table 8 Parameters for TSAT on Days 1 and 10

Parameters	**Description**
Baseline	Baseline response value before dosing
R_{max}	Maximum response value
R_{min}	Minimum response value
T_{max}	Time to reach R_{max}
T_{min}	Time to reach R_{min}
$AUC_{0\text{-}6h}$	Area under the effect versus time curve from time zero to 6 h
$AUC_{0\text{-}24h}$	Area under the effect versus time curve from time zero to 24 h
AUC_Above_B	Area under the response curve that is above the baseline
AUC_Below_B	Area that is below the baseline and above the response curve
AUC_Net_B	= AUC_Above_B - AUC_Below_B
Time_Above_B	Total time that response >= Baseline
Time_ Below_B	Total time that response < Baseline

9 SECONDARY ENDPOINT ANALYSIS

9.1 Transferrin, TIBC, UIBC, ferritin and Non-Transferrin Bound Iron (NTBI)

Transferrin, TIBC, UIBC and ferritin will be summarised by dose group and overall by visit/timepoint (Day 1 and Day 10/Pre-dose, 0.5-1h, 1-2h. 2-3h, 3-4h, 4-6h) for the FAS/ITT Population. An additional summary table will present the change from baseline values at each post-baseline visit/timepoint and will include the baseline, visit/timepoint value and change from baseline values for subjects with both baseline and the specified post-baseline values.
Baseline is defined as the last value observed before the first dose.

NTBI will be listed by dose and timepoint for each individual subject; the number of samples considered negative (<0.2ePLI) and positive (=>0.2ePLI) will be summarised by dose group. Individual positive NTBI results (=>0.2ePLI units) will also be listed separately along with the corresponding serum iron, and TSAT results from those timepoints; plus the plasma C_{max}, $AUC_{0\text{-}6h}$ for maltol and maltol glucuronide on the corresponding study day (Day 1 or Day 10).

A listing of the iron markers and NTBI at each visit/timepoint will be provided for the FAS/ITT Population.

Mean observed values of transferrin. TIBC, UIBC, and ferritin will be plotted on a linear scale against nominal time range by dose group and visit. Combined observed values will be plotted on a linear scale against actual timepoint for each dose group and visit. The change of baseline will be plotted similarly.

Mean observed NTBI will be plotted on a linear scale against nominal time range by dose group and visit. Combined observed NTBI will be plotted on a linear scale against actual timepoint for each dose group and visit.

The concentration plots described above will be prepared based on the actual data, if applicable.

9.2 Haemoglobin Concentration and Absolute Reticulocyte Count

Haemoglobin concentration and absolute reticulocyte count will be summarised by dose group and overall by visit (Screening and Day 10) for the FAS/ITT Population. An additional summary table will present the change from baseline values at Day 10 and will include the baseline, Day 10 and change from baseline values for subjects with both baseline and Day 10 values. Baseline is defined as the last value observed before the first dose.

A listing of haemoglobin concentration and absolute reticulocyte count will be provided for the FAS/ITT Population.

10 SAFETY ANALYSIS

10.1 Adverse Events

All adverse events reported during the study will be listed for the Safety Population; the listing will contain an indicator for whether the event was considered as treatment emergent. An additional listing will be provided for all serious adverse events.

A summary overview of all adverse events by dose group and overall will be provided, which will present the number and percentage of subjects from the Safety Population satisfying each of the following categories:

- Any adverse event (AE);
- Any treatment emergent adverse event (TEAE);
- Maximum severity of TEAEs – mild, moderate, severe;
- Relationship of TEAE to study drug – not related, related;
- Action taken with study drug in relation to TEAE – dose not changed, dose reduced/increased, drug interrupted, drug withdrawn;
- Any TEAE leading to study discontinuation;
- Any serious adverse event (SAE);
- Maximum severity of SAE – mild, moderate, severe;
- Relationship of SAE to study drug – not related, related;
- Action taken with study drug in relation to SAE – dose not changed, dose reduced/increased, drug interrupted, drug withdrawn;
- Any SAE leading to study discontinuation;
- Any SAEs leading to death.

For the treatment emergent adverse events, the number, severity, relationship to study drug and action taken will be described by incidence tables. Subjects with multiple episodes of the same TEAE (i.e. same Preferred Term) will be counted once in these tables. Similarly, subjects with multiple severities for the same TEAE will be categorized by the maximum severity experienced; subjects with instances of the same TEAE recorded as both related an unrelated to study drug will be categorized as related and subjects with multiple actions taken within the same TEAE will be categorized according to the worst case. Actions taken include drug withdrawn, drug interrupted, dose reduced/increase and dose not changed (listed from worst case to best case).

Similar incidence tables will be presented for the serious adverse events. Separate incidence tables will also be presented for those TEAEs leading to withdrawal of study drug and to study discontinuation.

10.2 Safety Laboratory Parameters

The safety laboratory parameters (Haematology and Clinical Chemistry) will be summarised by dose group and overall by visit (Screening and Day 10) for the Safety Population. An additional summary table will present the change from baseline values at Day 10 and will include the baseline, Day 10 and change from baseline values for subjects with both baseline and Day 10 values. Shift tables (from Screening to Day 10) will also be presented the safety laboratory data. If the Screening retest is performed, the values of Screening retest will be used as baseline.

All safety laboratory data, including normal ranges and abnormal laboratory flags, will be provided in data listings for the Screened Population.

Pregnancy test results will be also be listed for the Screened Population.

10.3 Vital Signs

Vital signs data will be summarised by dose group and overall by visit (Screening, Days 1 and 10 and Follow-up) for the Safety Population. Change from baseline at each post-baseline visit (Day 10 and Follow-up) will be presented in a separate summary table and will include baseline, post-baseline values and change from baseline values for subjects with both baseline and specific post-baseline values. Baseline is defined as the last value observed before the first dose.

All vital signs data will be listed for the Screened Population and FAS/ITT Population.

10.4 12-Lead ECG Parameters

Continuous ECG parameters (Heart Rate, PR Interval, RR Interval, QRS Duration, QT Interval, QTcB Interval and QTcF Interval) will be summarised by dose group and overall by visit (Screening and Day 10) for the Safety Population. Change from baseline at Day 10 will be presented in a separate summary table and will include baseline, post-baseline values and change from baseline values for subjects with both baseline and Day 10 values. Baseline is defined as the last value observed before the first dose.

Overall interpretation will also be summarised by dose group and overall by visit. Shift tables (from baseline to Day 10) will also be generated for the overall interpretation results.

All ECG data will be listed for the Screened Population and FAS/ITT Population.

10.5 Physical Examination

Findings from the physical examinations will be listed for the Screened Population.

Shift tables (from Screening to Day 10) will generated for the overall interpretation of the physical examination.

10.6 Prior and Concomitant Medications and Procedures

Prior and concomitant medications will be considered separately and will be summarised by dose group and overall by Anatomical Therapeutic Chemical (ATC) Classification System and Preferred Term for the Safety Population. All medications will be listed for the Screened Population with an indicator for whether the medication is regarded as prior or concomitant.

Similar summary tables and listings will be provided for the prior and concomitant procedures for FAS/ITT Population.

10.7 Study Medication Exposure and Compliance

The duration of exposure (days) to study drug and compliance will be summarised by dose group and overall for the Safety Population and FAS/ITT Population.

Details of drug accountability (dispensing and return) will be listed for the Safety Population. An additional listing will be provided for the Safety Population detailing exposure and compliance for each subject.

11 DATA SAFETY MONITORING BOARD

There are no provisions for a Data Safety Monitoring Board for this study.

12 INTERIM ANALYSIS

No interim analysis is planned for this study.

13 SAMPLE SIZE AND POWER CONSIDERATIONS

No formal sample size calculation has been carried out for this study. The sample size is based on observations from previous studies (see protocol for more details) and has been agreed with the EU CAs in the PIP. The inclusion of 36 subjects aged 10-17 years (12 per treatment group) is considered to be adequate to characterize the iron update and PK parameters for the range of Ferric Maltol doses in an iron deficient adolescent population (with or without anaemia).

14 CHANGES FROM PROTOCOL-SPECIFIED STATISTICAL ANALYSES

There are no planned changes to the current version of the protocol (Version 3.0, dated 08 February 2017).