MEDPACE

STATISTICAL ANALYSIS PLAN

Protocol Title:	Randomised, open-label, active-controlled, multicentre, comparative study to evaluate the safety and efficacy of ferric maltol (iron (III)-maltol complex) (ST10) oral suspension compared to ferrous sulfate oral liquid in children and adolescents aged 2 to 17 years with iron-deficiency anaemia, incorporating a single arm study in infants aged 1 month to less than 2 years.
Protocol Number:	ST10-01-305
Protocol Version/Date:	Version 4.1/ 6th July 2023
Investigational Product:	Ferric Maltol (ST10)
Sponsor:	Shield TX (UK) Limited, Northern Design Centre, Baltic Business Quarter, Gateshead Quays, NE8 3DF United Kingdom
SAP Version/Date:	Version 2.0 / 10-JUL-2024

SIGNATURE PAGE

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We, the undersigned, have reviewed and approved this Statistical Analysis Plan:

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VERSION HISTORY

Version	Version Date	Description
0.1	31st January 2022	Initial Drafted Version
0.2	23rd March 2022	Updates as per sponsor comments
0.3	19th January 2023	Updates to reflect protocol amendment
0.4	10th April 2023	Updates to reflect protocol amendment
0.5	21st August 2023	Updates to reflect protocol amendment
0.6	28th September 2023	Updates following sponsor comments
0.7	22nd December 2023	Updates following sponsor comments
0.8	1st February 2024	Updates following sponsor comments
0.9	8th March 2024	Updates to PK sections
0.10	28th May 2024	Consistency updates for finalisation
1.0	13th June 2024	Final Version
2.0	10th July 2024	Clarifications and corrections

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LIST OF ABBREVIATIONS

Abbreviation	Definition
ADaM	Analysis Data Model
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
BID	Twice a Day (*bis in die*)
BMI	Body Mass Index
BUN	Blood Urea Nitrogen
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
CRF	Case Report Form
CSR	Clinical Study Report
ESA	Erythropoiesis Stimulating Agent
GGT	Gamma-Glutamyl Transpeptidase
Hb	Haemoglobin
ITT	Intent-To-Treat
LOCF	Last Observation Carried Forward
MCV	Mean Cell Volume
MedDRA	Medical Dictionary For Regulatory Activities
MMRM	Mixed Model For Repeated Measures
PD	Pharmacodynamics
PK	Pharmacokinetics
PP	Per-Protocol
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SDTM	Study Data Tabulation Model
TEAE	Treatment-Emergent Adverse Event
TESAE	Treatment-Emergent Serious Adverse Event
TFL	Table, Figure, Listing
TIBC	Total Iron Binding Capacity
TSAT	Transferrin Saturation
UIBC	Unsaturated Iron Binding Capacity
WHO	World Health Organization

1 INTRODUCTION

The purpose of this Statistical Analysis Plan (SAP) is to provide a description of the statistical methods to be implemented for the analysis of data from the study with protocol number ST10-01-305. The SAP will be finalised prior to database lock. Any deviations from the SAP after database lock will be documented in the final Clinical Study Report (CSR).

2 STUDY OVERVIEW

2.1 Study Objectives

2.1.1 Primary Objective

- To compare the safety and gastrointestinal tolerability of ferric maltol oral suspension and ferrous sulfate oral liquid in children and adolescents aged 2 years to 17 years, and assess the safety and tolerability of ferric maltol oral suspension in children 1 month to less than 2 years, in the treatment of iron deficiency anaemia during the 12 weeks treatment period.
- To assess the effect on haemoglobin (Hb) in children and adolescents aged 1 month to 17 years after twice daily ferric maltol oral suspension administration for 12 weeks.

2.1.2 Secondary Objectives

- To assess the pharmacokinetics (PK) in children and adolescents aged 2 to 17 years after a single dose of ferric maltol oral suspension on Visit 2 (PK Day 1), and after twice daily administration for at least 6 days, on Visit 3 (PK Day 2) after a single morning dose through measurement of serum iron, corrected serum iron, transferrin saturation (TSAT) and plasma maltol and maltol glucuronide.
- To assess the effect on iron markers in children and adolescents aged 1 month to 17 years after twice daily ferric maltol oral suspension administration for 12 weeks.
- To assess the PK, in children aged 1 month to less than 2 years of age after a single dose of ferric maltol oral suspension (Pre-assignment PK visit) and after twice daily administration for at least 6 days, on Visit 3 (PK Day 2) after a single morning dose, through measurement of serum iron, corrected serum iron, TSAT (PK Day 2 only), plasma (PK Day 2 only) and urine concentration of maltol and maltol glucuronide.
- To assess the effect in children aged 1 month to less than 2 years of age after twice daily administration for at least 6 days on Visit 3 (PK Day 2) after a single morning dose, on serum transferrin, total and unsaturated iron binding capacity (TIBC, UIBC).
- To assess the effect, in children aged 2 to 17 years after a single dose of ferric maltol suspension Visit 2 (PK Day 1), and after twice daily administration for at least 6 days, on Visit 3 (PK Day 2) after a single morning dose, on serum transferrin, TIBC and UIBC.
- To compare the palatability from age-appropriate scoring system of ferric maltol oral suspension and ferrous sulfate oral liquid.

2.2 Study Design

2.2.1 Overview

This is a randomised, open-label, active-controlled, multicenter study.

The study will comprise of the following stages:

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

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

  The PK samples will be analysed and if evidence of metabolism and elimination of maltol is shown, these subjects will enter the treatment phase and be assigned to the ferric maltol arm. Subjects will be eligible to enter the treatment phase if the maltol level returns to baseline, or to a level confirming there is no accumulation of maltol or maltol glucuronide.
- Randomised/Assigned treatment: 12 weeks open label treatment.
  - Subjects aged 2-17 will be randomised 1:1 to receive ferric maltol oral suspension or ferrous sulfate oral liquid.
  - The first 12 subjects assigned to ferric maltol in each age sub-group (2 – 9 yrs, 10 – 17 yrs, respectively) will enter a Pharmacokinetic phase from Visit 2 (PK Day 1) till Visit 3 (PK Day 2) with 2 PK days. Following baseline pre-dose blood sample, subjects will take a single dose of 2.5 ml (2 yrs – 11 yrs) or 5 ml (12 yrs – 17 yrs) ferric maltol oral suspension under supervision and then further 2 PK blood samples will be taken up to 6 hrs post dose. Following the last scheduled PK sample on PK Day 1 (Visit 2), subjects will be reminded to take their dose twice daily (*bis in die*) (BID) until PK Day 2 (between Day 7-Day 10). On PK Day 2 (Visit 3) subjects should withhold their morning dose until attending their next PK assessments. The same procedure will be repeated for PK assessment as on PK Day 1.
  - Once the 12 subjects in each age subgroup (2 – 9 yrs, 10-17 yrs, respectively) have finished their PK visits (after PK Day 2), they will continue treatment until week 12. They will not need to have further PK samples taken.
  - Subjects randomised to ferrous sulfate oral liquid will not need to complete the PK period, they will remain on oral ferrous sulfate liquid until Week 12.
  - Ferrous sulfate 125 mg/ml (25 mg elemental iron) or equivalent dose will be used for all children/adolescents. To maximise the iron replenishment for subjects within this group as well; aged 2 – 17 yrs will be dosed 0.24ml (6mg elemental iron) per kg body weight per day, up to a maximum of 8ml given daily in two divided doses.
- Assigned treatment phase: 12 weeks open label treatment for ferric maltol children aged 1 month to less than 2 years.

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

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

Table 2.1: Schedule of Assessments for subjects aged 2 years-17 years.

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

	SCREENING	TREATMENT					FOLLOW-UP
Duration	Up to 21 days	12 WEEKS (equivalent of 84 days)					10-14 days
Day		1	7-10	28	56	84	94-98
Visit [11]	1	2	3[8]	4	5	6	7[9,10]
Palatability questionnaire		X		X			
Adverse Events		X	X	X	X	X	X
Concomitant Medications and Procedures	X	X	X	X	X	X	X
Compliance reminder		X	X	X	X	X	
Compliance assessment			X	X	X	X	

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

same on PK Day 1 and PK Day 2. Post-dose blood samples should be collected within the time windows allocated only. N.B: samples should be taken at least 1.0 hr apart.
In the event of an administered dose not being consumed or partially consumed by the patient this will be noted as a missed dose and will not be repeated.

8. Eligibility laboratory sampling/assessments must be completed before the subject is randomised and before the first dose of study treatment taken. A minimum number of 18 subjects must be recruited into each age group (2 yrs -9 yrs, 10 yrs-17 yrs) and a minimum of 25% of either sex must be recruited and at least 49 subjects per arm.
9. Subjects who have at least one dose of study medication and withdraw earlier from the study undergo Visit 7 (Day 94-98) assessments (excluding those who have withdrawn consent).
10. Visit 7 is conducted by telephone, unless the Subject has an ongoing AE that requires physical examination or investigations for assessment/management. Visit 7 will take place 10-14 days after Visit 6 (Week 12) unless subject discontinued treatment early. All withdrawn subjects should undergo Visit 7 within 10-14 days after the last dose of study drug (if the subject agrees in the case of withdrawn consent).
11. Visit Windows: Maximum of 21 days between screening and randomisation. The Subject must visit to complete:
    a. Visit 2 and Visit 3: must be 6-9 days between the scheduled PK days.
    b. Visit 4: +/- 5 days relative to date of Visit 2/first dose administered
    c. Visits 5 to 6: +/- 5 days relative to date of Visit 2/first dose administered
    d. Visit 7: 10-14 days after Visit 6 (unless subject discontinued treatment early - see Note 10.

Table 2.2: Schedule of Assessments for subjects aged 1 month to <2 years.

	SCREENING	PRE-ASSIGNMENT	TREATMENT					FOLLOW-UP
Duration	Up to 21 days	Up to 28 days from Screening	12 WEEKS (equivalent of 84 days)					10-14 days
Day			1	7-10	28	56	84	94-98
Visit[8]	1	Pre-assigned[6]	2	3[3]	4	5	6	7[4,9]
Informed Consent	X							
Eligibility [1,7]	X	X	X					
Demographics	X							
Medical History	X							
Physical Examination	X						X	
Vital Signs [2]	X	X	X	X	X	X	X	
Clinical Laboratory tests [4]	X						X	
Haematology, Iron markers [5]	X		X[10]				X	
PK assessment: Blood Sampling for iron markers, maltol and maltol glucuronide[6]				X[6]				

PK assessment: Urine sampling for maltol/maltol glucuronide[6]		X[6]		X[6]				
Treatment Assignment [7]			X					
Dispense Study Drug		X	X	X	X	X		
Return Study Drug for Accountability				X	X	X	X	
Adverse Events		X	X	X	X	X	X	X
Concomitant Medications and Procedures	X	X	X	X	X	X	X	X
Compliance reminder			X	X	X	X	X	
Compliance assessment				X	X	X	X	

1. *A subject may be retested once for laboratory criteria that do not meet protocol criteria so long as pre-assignment visit occurs no more than 28 days from the initial screening visit date (if eligible).*
2. *Vital Signs – body weight, length, systolic/diastolic blood pressure, pulse, and body temperature at each visit. Patient weight should be recorded at each clinic visit and drug dosing administered as per last clinic visit weight.*
3. *Visit 3 (PK Day 2) this visit will be the second PK day following the pre-assignment PK assessment.*
4. *Clinical Laboratory tests: including*
    a. *Clinical Chemistry: Vitamin B12, folate, ALT, AST, alkaline phosphatase, gamma-glutamyl transpeptidase (GGT), total bilirubin, creatinine, amylase, blood urea nitrogen (BUN), phosphorous, sodium, potassium, chloride, calcium, total cholesterol, uric acid, glucose, total protein, albumin*
5. *Haematology and Iron markers:*
    a. Haematology: Red blood cell count, haemoglobin, haematocrit, mean cell volume (MCV), white blood cell count (total and differential (% and absolute), absolute reticulocyte count and platelet count.
    b. Iron Markers: serum iron, transferrin, transferrin saturation (TSAT), total and unsaturated iron binding capacity (TIBC, UIBC) and ferritin.
6. *Pre-assignment phase: All subjects in 1 m-< 2 yrs age group will enter a 1-day PK assessment day prior to entering the treatment phase. Pre-assignment PK Day, each subject has baseline PK urine samples collected immediately prior to ferric maltol dosing (0 h). Following this, subjects will take a single dose of 0.1 ml/kg ferric maltol under supervision. Three (3) PK urine samples will be taken between 0.5 hr -3 hrs, 3 hrs -6 hrs, and 7 hrs -12 hrs post dose. N.B: samples should be taken at least 1.0 h apart. Urine collections instructions are detailed in the study's Laboratory Manual.*
   PK Day 2 (Visit 3), each subject has baseline PK blood and urine samples collected immediately prior to ferric maltol dosing (0 h). Following this, subjects will take a single dose of 0.1 ml/kg ferric maltol under supervision. Three PK Post-dose blood samples will be collected at the following windows 1.0-2.0 hrs, 3.0-4.0 hrs and 10.0-12.0 hrs; post-dose urine samples will be taken between 0.5 hr -3 hrs, 3 hrs -6 hrs and 7 hrs -12hrs post dose.
   In the event of an administered dose not being consumed or partially consumed by the patient this will be noted as a missed dose and will not be repeated.
7. *Eligibility laboratory sampling/assessments must be completed before the subject is assigned to ferric maltol. The PK samples will be analysed and if evidence of metabolism and elimination of maltol is shown, these subjects will enter the ferric maltol treatment phase Visit 2.*
8. *Subjects who have at least one dose of study medication and withdraw early from the study undergo Visit 7 (Day 94-98) assessments (excluding those who have withdrawn consent).*
9. *Visit 7 is conducted by telephone, unless the subject has an ongoing AE that requires physical examination or investigations for assessment/management. Visit 7 will take place 10-14 days after Visit 6 (Week 12) unless subject discontinued treatment early. All withdrawn subjects should undergo Visit 7 within 10-14 days after the last dose of study drug (if the subject agrees in the case of withdrawn consent).*
10. *Visit Windows: Maximum of 28 days between screening and pre-assignment phase. The Subject must visit to complete:*
    a. Visit 3: must be 7-10 days from Visit 2
    b. Visit 4: +/- 5 days relative to date of Visit 2/first dose administered

c. *Visits 5 to 6: +/- 5 days relative to date of Visit 2/first dose administered*
d. *Visit 7: 10-14 days after Visit 6 (unless subject discontinued treatment - see Note 10*

11. *Baseline Haematology and Iron markers: to be performed after urine PK assessment and prior to assignment*
    a. *Haematology: haemoglobin*
    b. *Iron Markers: serum iron, transferrin, transferrin saturation (TSAT), total and unsaturated iron binding capacity (TIBC, UIBC), ferritin*

2.2.2 Randomisation

Approximately 110 male and female children from 1 month to 17 years of age, with iron deficiency anaemia at approximately 20 sites will be recruited. The number of subjects will be reduced if the study is stopped following a successful interim analysis.

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

A maximum of 12 subjects will be recruited in the 1 month to less than 2 years age group.

2.2.3 Study Drug

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

Ferric maltol group:

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

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

Ferrous sulfate group:

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

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

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

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

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

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

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

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

2.2.4 Sample Size Determination

In total up to 110 patients will be recruited into the study. Up to 98 subjects will be randomised in the 2 -17 years cohort and up to 12 subjects will be assigned in the <2 years cohort.

The aim is to recruit up to 49 subjects in each treatment group in the 2 – 17 years cohort. At least 12 subjects in each age group respectively (i.e. 24 subjects in total) will be included in the PK analysis group in the ferric maltol oral suspension group. A sample size of 49 in the Ferric Maltol group provides at least 80% power to demonstrate that the lower bound of the 95% confidence interval for increase in Hb at 12 weeks, compared with baseline, is above zero. This assumed that the standard deviation (SD) of the change from baseline is 1.2 g/dL or lower and the true mean change is at least 0.5 g/dL.

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

If less than 91 subjects in total have been randomised when 32 ferric maltol subjects have completed treatment (or withdrawn from the study), then an interim analysis of the primary effectiveness endpoint (change in Hb concentration from baseline to Week 12) will be conducted. If significant, the study will stop recruitment. If not significant, the study will continue (all subjects will be assigned to ferric maltol) until 54 subjects have been recruited in the ferric maltol arm.

2.3 Study Endpoints

2.3.1 Primary Endpoints

- Safety and gastrointestinal tolerability:
  - Treatment-emergent Adverse Events (TEAE),
  - Treatment-emergent Serious Adverse Events (TESAEs),

  - Treatment-emergent Adverse Events leading to premature discontinuation of study drug/PK assessments from baseline to Week 12.
- Change in Hb concentration from baseline to Week 12.

2.3.2 Secondary Endpoints

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

3 STATISTICAL METHODOLOGY

3.1 General Considerations

3.1.1 Analysis Day

Analysis day will be calculated from the date of first dose of study drug in treatment phase. The day of the first dose of study drug will be Day 1, and the day immediately before Day 1 will be Day -1. There will be no Day 0.

Analysis day will be calculated as:

> Date of assessment – date of first dose of study treatment + 1 (if date of assessment ≥ date of first dose of study treatment).

3.1.2 Analysis Visits

Scheduled visits will be assigned to analysis visits as recorded on the case report form (CRF). The record occurring on the target day will be picked for analysis. If the record on a target day does not exist, then the one closest to the target date will be used. Unscheduled and early termination visits will be assigned to analysis visits according to the following visit windows:

Analysis Visit	Target Analysis Day	Low Analysis Day	High Analysis Day
Day 1	1	NA	NA
Day 7-10	7	2	17
Day 28	28	18	42
Day 56	56	43	70
Day 84	84	71	No upper limit

3.1.3 Definition of Baseline

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

3.1.4 Summary Statistics

Categorical data will generally be summarised with counts and percentages of subjects. The denominator used for the percentage calculation will be clearly defined. Continuous data will

generally be summarised with descriptive statistics including n (number of non-missing values), mean, median, standard deviation, range (minimum and maximum).

For PK parameters, descriptive statistics will also include coefficient of variation (CV %), geometric mean (GM) and GM CV (%).

3.1.5 Hypothesis Testing

Hypothesis testing will be performed for the interim analysis to test the hypothesis that the ferric maltol Hb change from baseline to Week 12 is > 0. If an interim analysis is conducted, a Pocock spending function will be used; the interim analysis will be based on a (100-3.45)% two sided confidence interval.

The efficacy primary endpoint will also involve hypothesis testing. If no interim analysis is conducted the hypothesis testing will be based on a 95% two-sided confidence interval. If the study does not stop after the interim analysis, the final analysis will be based on a (100-2.57)% two sided confidence interval.

The study safety primary endpoints will be analysed by descriptive statistics only. The secondary endpoints will be analysed by descriptive statistics only. Thus, no formal testing strategy or adjustments of the Type I error will be employed for the evaluation of secondary endpoints.

3.1.6 Handling of Dropouts and Missing Data

In general, missing data will not be imputed unless otherwise specified. Only observed data will be used in the summaries and analyses.

For adverse events (AEs) with incomplete or missing dates, imputation for start and stop dates relative to the start date of study drug is necessary to define an AE as treatment emergent. For missing AE start day, the 1st of the month will be used. If this day is before the day of study drug start and the end date of AE is on or after the date of first study drug, or if the AE end date is completely missing, the start date of study drug will be used. For missing start day and month, the start day and month will be January 1st. If January 1st is before start day and month of study drug, the start date of study drug will be used.

Partial dates for concomitant medications will be imputed to determine prior and concomitant status. Partial dates will be imputed as above for AEs. If the start date is completely missing, the start date will equal the date of first study drug. If the stop date is known and prior to the first date of study drug, the start date will equal the stop date of concomitant medication. If the stop date is completely missing, the concomitant medication will be considered as ongoing.

3.2 Analysis Populations

3.2.1 Randomised Population/Intention to treat (ITT) Population

The ITT Population is defined as all subjects who were randomised/assigned to treatment arms.

3.2.1 Modified Intention to treat (mITT) Population

The mITT Population is defined as all subjects in the ITT population who have received at least 1 treatment dose.

3.2.2 Per-Protocol (PP) Population

The PP Population will consist of those randomised/assigned subjects who do not have major protocol deviations during the study. Data will be reviewed during a data review meeting prior to database lock to identify subjects to be included/excluded from the per-protocol population. The subjects to be included/excluded will be noted in a note to file (NTF).

3.2.3 Safety Population

The Safety Population is defined as all randomised/assigned subjects who receive at least one dose of study drug. All safety data will be analyzed using the Safety Population.

3.2.4 Pharmacokinetic (PK) Population (Full Analysis Set)

The PK Population is defined as all randomised/assigned subjects who have had at least one dose of study drug and who have at least one evaluable post-dose PK sample (applicable only for ferric maltol group). All PK data will be analyzed using the PK population.

3.3 Subject Data and Study Conduct

3.3.1 Subject Disposition

Counts and percentages of subjects who were screened (signed informed consent), discontinued early during screening (screen failures), and randomised/assigned will be summarised in total based on all screened subjects. Reasons for early discontinuation will also be summarised.

Counts and percentages of subjects who were randomised/assigned, discontinued early from the study, and completed the study will be summarised by treatment and in total based on all randomised subjects. Reasons for early discontinuation will also be summarised.

3.3.2 Protocol Deviations

Counts and percentages of subjects with CSR reportable protocol deviations by deviation category will be summarised by treatment and in total based on all randomised/assigned subjects.

3.3.3 Analysis Populations

Counts and percentages of subjects in each analysis population will be summarised by treatment and in total based on all randomised/assigned subjects.

3.3.4 Demographic and Baseline Characteristics

The following demographic and baseline characteristics will be summarised:

- Age (years) and age categories (1 month to <2 years, 2 years to 9 years, 10 years to 17 years),
- Sex,
- Childbearing potential, if Female or Undifferentiated,
- Race,
- Ethnicity,
- Height/Length (cm),
- Weight

- Body mass index (BMI) (kg/m^2).

Demographic and baseline characteristics will be summarised with descriptive statistics or counts and percentages of subjects as appropriate by treatment and in total for all randomised/assigned subjects split by age categories of 1 month to 2 years and 2 years to 17 years.

3.3.5 Medical History

Medical history will be coded to system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA) version 24.0. Counts and percentages of subjects with medical history by system organ class and preferred term will be summarised by treatment and in total based on all randomised/assigned subjects. This will also be displayed for those patients in the 1 month to 2 years, 2 years to 9 years and 10 years to 17 years age group.

3.3.6 Concomitant Medications

Concomitant medications will be coded to anatomical therapeutic chemical (ATC) class and preferred term using the WHODrug Dictionary version B3 Global, March 2021. For summary purposes, medications will be considered prior medications if they were taken within 3 months prior to the first dose of study drug and concomitant medications if they were taken at any time after the first dose of study drug (i.e. started prior to the first dose of study drug and were ongoing or started after the first dose of study drug).

If a medication has incomplete start or stop dates, dates will be imputed to determine whether a medication should be considered prior or concomitant. If a medication start date is incomplete, the first day of the month will be imputed for missing day and January will be imputed for missing month. If a medication stop date is incomplete, the last day of the month will be imputed for missing day and December will be imputed for missing month. Incomplete start and stop dates will be listed as collected without imputation.

Counts and percentages of subjects taking prior and concomitant medications by ATC class and preferred term will be summarised by treatment and in total based on the Safety Population. This will also be displayed for those patients in the 1 month to 2 years, 2 years to 9 years and 10 years to 17 years age group.

3.3.7 Concomitant Procedures

Concomitant procedures will be coded to class and standardised procedure name using MedDRA version 24.0. For summary purposes, procedures will be considered prior procedures if they took place within 3 months prior to the first dose of study drug and concomitant procedures if they took place at any time after the first dose of study drug (i.e. started prior to the first dose of study drug and were ongoing or started after the first dose of study drug).

If a procedure has incomplete start or stop dates, dates will be imputed to determine whether a procedure should be considered prior or concomitant. If a procedure start date is incomplete, the first day of the month will be imputed for missing day and January will be imputed for missing month. If a procedure stop date is incomplete, the last day of the month will be imputed for missing day and December will be imputed for missing month. Incomplete start and stop dates will be listed as collected without imputation.

Counts and percentages of subjects who had prior and concomitant procedures by class and standardised procedure name will be summarised by treatment and in total based on the Safety Population.

3.3.8 Study Drug Exposure and Compliance

Days of exposure to study drug will be calculated as date of last dose of study drug – date of first dose of study drug + 1. For subjects who received a dose during the pre-screening period the date of first dose will be the date of first dose in the treatment phase. Note that the exposure calculation is intended to describe the length of time a subject was exposed to study drug and therefore does not take study drug interruptions into account. Days of exposure to study drug will be summarised by treatment based on the Safety Population with descriptive statistics and with counts and percentages of subjects with exposure in the following categories:

- <=6 days,
- 7 - 27 days,
- 28 - 55 days,
- 56 - 83 days,
- >= 84 days.

Days of exposure to study drug will be summarised separately for those who received a dose in the pre-assignment phase and those who didn't.

Percent compliance to the study drug regimen will be calculated as 100 x doses taken/ doses expected as recorded in dosing diary. Percent compliance to the study drug regimen will be summarised by treatment based on the Safety Population with descriptive statistics and with counts and percentages of subjects with compliance in the following categories:

- <80%,
- 80-120%,
- >120%.

3.4 Efficacy Assessment

Efficacy data will be summarised by randomised/assigned treatment based on the mITT Population for the primary and on the ITT Population for the secondary endpoints. Sensitivity analysis will be performed on the ITT Population for the primary endpoint.

3.4.1 Primary Endpoint Analysis

<u>Primary Analysis</u>

The change in Hb concentration from baseline to Week 12 will also be summarised based on the mITT Population for each treatment group using descriptive statistics summarised by mean, standard deviation, median, and range (minimum and maximum).

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

If no interim analysis is conducted then 95% CIs will be displayed. If an interim analysis is conducted and the study does not stop after the interim analysis, the final analysis will be based on a (100-2.57)% two sided confidence interval.

The MMRM analysis will be implemented using SAS® Proc Mixed. Example SAS code can be found in Appendix C.

Sensitivity Analysis

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

Change in Hb concentration from baseline to Week 12 will also be assessed for the ITT and PP population.

3.4.2 Secondary Endpoints Analysis

The secondary endpoints will be reported for each treatment group using descriptive statistics summarised by mean, median, and range (minimum and maximum), and 95% confidence interval for the mean where applicable, split by age group.

Any measurement obtained after a patient received a blood transfusion, or received an intravenous iron or erythropoiesis stimulating agent (ESA) will be excluded from the analysis.

The secondary endpoints are as follows: PK analysis of Serum Iron, Corrected serum iron, TSAT, Transferrin, TIBC, UIBC, Maltol and Maltol Glucuronide.

Descriptive summary statistics will be summarised for children and adolescents aged 1 month to 17 years in the ferric maltol group for the PK analysis of Serum Iron, Corrected serum iron, TSAT, Transferrin, TIBC, UIBC, Maltol and Maltol Glucuronide.

Changes in iron markers from baseline to Weeks 4 and 12

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

Achieving Hb concentration within normal range at Week 12

The number and percentage of subjects achieving normal range, based on the central laboratory's normal reference range, at Week 12 will be summarised by treatment group.

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

Qualitative assessments from subject questionnaires that evaluate acceptability, palatability and ease of use will be summarised separately for children aged 5 and under and those aged 6 and over.

3.5 Pharmacokinetic Assessment

3.5.1 Sample Collections for Pharmacokinetic Analysis

PK analysis of serum iron, baseline corrected serum iron, TSAT, transferrin, TIBC, UIBC, maltol and maltol glucuronide in children and adolescents aged 1 month to 17 years in the ferric maltol group.

PK blood sampling in the 2 – 17 yrs age groups:

On PK study Day 1 (Visit 2) and PK study Day 2 (Visit 3) for the first 12 subjects in each age group (2 yrs – 9 yrs, 10 yrs-17 yrs, respectively) who have been randomised to ferric maltol groups have baseline PK blood samples collected immediately prior to ferric maltol dosing (0 hr). Subjects will then have further PK blood samples collected at two (2) additional times between 0.5 hr and 6 hrs after dosing on Visit 2 and 3; the post-dose PK sample time collection windows will be 0.5-1h, 1.0-2.0 hrs, 2.0-3.0 hrs, 3.0-4.0 hrs and 4.0-6.0 hrs. For each individual subject, the post-dose PK blood sampling schedule will be the same on PK Day 1 and PK Day 2. Post-dose blood samples should be collected within the time windows allocated only.

N.B: samples should be taken at least 1.0 hr apart. For each individual subject, the post-dose PK blood sampling schedule will be the same on PK Day 1 and PK Day 2.

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

Post-dose blood samples should be collected within the time windows allocated only. Samples should be taken at least 1.0 hr apart.

PK blood sampling in the 1 m – < 2 yrs age groups:

Pre-assignment phase: All subjects in 1 m-< 2 yrs age group will enter a 1-day PK assessment day prior to entering the treatment phase. Pre-assignment PK Day, each subject has baseline PK urine samples collected immediately prior to ferric maltol dosing (0 h). Following this, subjects will take a single dose of 0.1 ml/kg ferric maltol under supervision. Three (3) PK urine samples will be taken between 0.5 hr -3 hrs, 3 hrs -6 hrs, and 7 hrs -12 hrs post dose. N.B: samples should be taken at least 1.0 h apart.

PK Day 2 (Visit 3), each subject has baseline PK blood and urine samples collected immediately prior to ferric maltol dosing (0 h). Following this, subjects will take a single dose of

0.1 ml/kg ferric maltol under supervision. Three PK Post-dose blood samples will be collected at the following windows 1.0-2.0 hrs, 3.0-4.0 hrs and 10.0-12.0 hrs; postdose urine samples will be taken between 0.5 hr -3 hrs, 3 hrs -6 hrs and 7 hrs -12hrs post dose.

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

3.5.2 Handling Missing or Below the Lower Limit of Quantification Data

In the event of an administered dose not being consumed or partially consumed by the patient this will be flagged.

If the actual sampling time is missing, but a valid concentration value has been measured, the concentration value will be flagged, and the scheduled time point may be used for the calculation of PK parameters. If the nominal timepoint is a range (e.g., 4-6 hours), the midpoint will be used for the missing timepoint.

If the dosing history information for a subject is missing, the sampling for that subject relative to the missing dosing period will be flagged and not be included in summary statistics. For other cases (i.e., missing pre-dose beyond the first dose of the treatment group), missing data will not be imputed.

In individual concentration and PK parameter calculations employing the naive-pooled approach, BLQ values are treated as follows:

- If BLQ values occur at pre-dose will be assigned as zero
- All other instances of BLQ values, beyond the first predose, will be set as missing.

The following general rules will be applied for the concentration summary for each period:

- In cases where a mean value is not calculated, due to more than half (>50%) of the values at schedule time point are BLQ or missing, the mean value will be set to BLQ for the summary table.

3.5.3 Pharmacokinetic Concentration

The following PK concentrations for the two age groups, 2 – 17 yrs and 1 m – < 2 yrs, will be determined and the observed values will be summarised by age group, formulation / condition, and by visit/timepoint for PK Population using the following statistics: n (the number of subjects), geometric mean, geometric standard deviation (SD), coefficient of variation (CV), median, minimum and maximum. The observed data will also be listed by age group, formulation / condition group for each individual subject for PK Population.

If the PK data for any age group is too limited and does not support summary statistics, only listings will be provided.

For age group 2-17 yrs, the mean observed plasma concentrations will be plotted on a linear and semi-logarithmic scale against nominal time range, formulation / condition. Geometric mean observed plasma concentrations will also be plotted on a linear scale against nominal time range by formulation/condition.

If the PK data for any age group is too limited and does not support summary statistics (i.e., mean and geomean), only individual concentrations will be plotted.

Individual observed concentrations will be plotted on a linear and semi-logarithmic scale against actual timepoint for each formulation/condition. Due to the sparse collection of data, all individuals within an age group will be plotted on the same plot.

2 – 17 yrs age groups:

- Plasma maltol and maltol glucuronide, serum iron, baseline corrected serum iron, transferrin, transferrin saturation (TSAT), total and unsaturated iron binding capacity (TIBC, UIBC).

1 m – < 2 yrs age groups:

- Serum iron, baseline corrected serum iron, total and unsaturated iron binding capacity (TIBC,UIBC), transferrin, transferrin saturation (TSAT), plasma maltol and maltol glucuronide, urine concentration of maltol and maltol glucuronide.

3.5.4 Pharmacokinetic Parameters

The following PK parameters will be determined for the 2 – 17 yrs age groups using a naïve pooled approach on PK Day 1 and Day 2:

- PK analysis of serum iron, corrected serum iron, maltol and maltol glucuronide in the ferric maltol group.

Parameters	**Description**	**Precision**
C_{max}	Maximum plasma concentration; determined directly from the concentration time profile; if the maximum plasma concentration occurs at more than one time point, C_{max} is defined as the first maximum value	sig/3
T_{max}	Time to C_{max}; If the maximum value occurs at more than one time point, T_{max} is defined as the first time point with this value.	dec/2
AUC_{last}	Area under the plasma concentration vs time curve (AUC) from predose (time 0) to the last quantifiable plasma concentration (C_{last})	sig/3
AUC_{inf}	AUC from time 0 to infinity; calculated as (AUC_{last} + $C_{last}/\lambda z$)	sig/3
$t_{½}$	Apparent first-order terminal elimination half-life; calculated as $\ln(2)/\lambda z$	dec/2

Note: "Precision" is defined as the default type (significant figures "sig" or decimal places "dec") and value that will be displayed in outputs unless specifically defined elsewhere.

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

3.6 Safety Assessment

Safety data will be summarised by actual treatment received (and in total for selected analyses) based on the Safety Population.

Safety and gastrointestinal tolerability will be compared between ferric maltol oral suspension and ferrous sulfate oral liquid via the incidence of TEAEs, TESAEs and TEAEs leading to premature discontinuation of study drug, estimated as the number of subjects with at least one event divided by the number of subjects in the Safety Population.

Adverse Events (AEs) will be categorised by primary system organ class and MedDRA preferred term as coded using the MedDRA dictionary version 24.0. The number, intensity, relation to study medication and action taken will be described by incidence tables. Serious Adverse Events (SAEs) will be listed and tabulated separately.

3.6.1 Adverse Events (AEs)

AEs will be captured from the date of informed consent through study completion (Follow-up visit). All AEs will be coded to system organ class and preferred term using MedDRA version 24.0. TEAEs are defined as AEs that start after the first dose of study drug.

An overview of AEs will be provided including counts and percentages of subjects (and event counts) with the following:

- Any AEs,
- Any TEAEs (overall and by maximum severity),
- Any study drug related TEAEs (overall and by maximum severity),
- Any SAEs,
- Any TESAEs,
- Any study drug related TESAEs,
- Any TEAEs leading to discontinuation of study drug,
- Any study drug-related TEAEs leading to discontinuation of study drug,
- Any AEs leading to death.

Counts and percentages of subjects (and event counts) will also be presented by system organ class and preferred term for each of the categories in the overview.

Listings will be presented specifically for SAEs and TEAEs leading to discontinuation of study drug.

3.6.2 Clinical Laboratory Tests

Clinical Chemistry and Haematology will be collected at the Screening Visit and Visit 6 (Day 84). In addition, Haematology will be collected at Visit 4 (Day 28) for those subjects in the 2-17 years of age group. Additionally, Hematology and iron markers will be collected at Visit 2 for the 1 month to < 2 years age group.

At Visit 7, Clinical Chemistry and Haematology will be collected if the subject has an ongoing AE that requires onsite assessment/management, or if the subject early discontinued.

Chemistry parameters include vitamin B12, folate, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), 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.

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

Descriptive statistics for each safety laboratory parameter will be presented for baseline values and for values and the change from baseline at each post-baseline visit.

Values outside the normal range will be categorised as below the lower limit of normal or above the upper limit of normal based on the central laboratory's normal reference range. Values

outside of the normal range will be summarised. Shifts from baseline to worst post-baseline category will be tabulated by laboratory parameter and shift category (low to low, normal to low, high to low, low to normal, normal to normal, high to normal, low to high, normal to high or high to high) for chemistry and haematology parameters.

3.6.3 Vital Signs

Vital signs parameters include weight, height/length, systolic blood pressure, diastolic blood pressure, heart rate and body temperature (°C). Blood pressure and heart rate will be measured after the subject has been sitting for at least 5 minutes. Vital signs will be measured at Screening, Visit 2, Visit 3, Visit 4, Visit 5 and Visit 6. Additionally, vital signs will also be measured at the pre-assignment visit for the 1 month to < 2 years age group. At Visit 7, vital signs are measured if the subject has an ongoing AE that requires onsite assessment/management, or if the subject early discontinued.

Values and change from baseline will be summarised at each scheduled visit by parameter.

3.6.4 Physical Examinations

Physical examination parameters include an assessment of general appearance, skin, head, eyes, ears, nose and throat, cardiovascular, respiratory, abdominal, gastrointestinal and musculoskeletal systems. A physical examination will be performed at Screening and Visit 6. At Visit 7, those in the 2 years – 17 years age group will have a physical examination if the subject has an ongoing AE that requires onsite assessment/management, or if the subject early discontinued.

Values will be summarised at each scheduled visit.

All physical examinations data will be listed.

4 ANALYSIS TIMING

4.1 Interim Analysis

If less than 91 subjects in total have been randomised when 32 ferric maltol subjects have completed, then an interim analysis of the primary effectiveness endpoint (change in Hb concentration from baseline to Week 12) will be conducted. If significant, the study will stop recruitment. If not significant, the study will continue (all subjects will be assigned to ferric maltol) until 54 subjects have been recruited in the ferric maltol arm.

If an interim analysis is conducted, a Pocock spending function will be used. The interim analysis will be based on a (100-3.45)% two sided confidence interval. If the study does not stop after the interim analysis, the final analysis will be based on a (100-2.57)% two sided confidence interval.

4.2 Pre-Final Analysis

After the database is locked and exclusions from analysis populations have been finalised, the pre-final analysis will be generated. If the study does not stop after the interim analysis, the analysis will be based on a (100-2.57)% two sided confidence interval. Topline tables, figures and listings (TFLs) will be provided approximately 1 week after database lock and pre-final TFLs will be provided approximately 3 weeks after database lock.

4.3 Final Analysis

After all comments on the pre-final analysis have been resolved and the study database is declared final, the final analysis will be generated. Final TFLs will be provided approximately 1 week after the study database is declared final. If there were no changes to the pre-final analysis or the study database, the pre-final TFLs may be considered final. In addition to TFLs, SDTM (study data tabulation model) data and ADaM data along with associated files will be provided. Associated files may include: annotated CRFs, SDTM specifications, SDTM programs, ADaM specifications, ADaM programs, TFL programs, and CDISC (Clinical Data Interchange Standards Consortium) Define packages for both SDTM and ADaM data.

5 CHANGES FROM PROTOCOL-SPECIFIED STATISTICAL ANALYSES

The primary analysis for change in Hb is based on mITT, and additional sensitivity analyses will be based on the ITT and PP population.

The addition of changes in iron markers from baseline to Week 4 as a secondary endpoint deviates from the secondary endpoints listed in section 6.4 of the protocol.

6 PROGRAMMING SPECIFICATIONS

Analyses will be performed using SAS® version 9.4 or higher. All available data will be presented in subject data listings which will be sorted by subject and visit date as applicable. Detailed Programming Specifications will be provided in a separate document.

APPENDIX A: REFERENCES

APPENDIX B: LABORATORY TESTS

Clinical Chemistry

Albumin	Alanine Aminotransferase
Alkaline Phosphatase	Amylase
Aspartate Aminotransferase	Blood Urea Nitrogen
Calcium	Chloride
Creatinine	Folate
Gamma-glutamyl Transferase	Glucose
Phosphorous	Potassium
Sodium	Total Bilirubin
Total Cholesterol	Total Protein
Uric Acid	Vitamin B12

Hematology

Absolute reticulocyte count	Haemoglobin
Haematocrit	Mean Cell Volume

Platelet count Red blood cell count

White blood cell count (total and differential (% and absolute))

Iron Markers

Ferritin Serum Iron

Total Iron Binding Capacity Transferrin

Transferrin Saturation Unsaturated Iron Binding Capacity

APPENDIX C: SAMPLE CODE

****

Note:

USUBJID = Unique subject identifier

TREATMENT = Treatment

VISIT = Visit

BASE = Baseline value

CHG = Change from Baseline

****

```
proc mixed;
  class USUBJID TREATMENT VISIT;
  model CHG=TREATMENT BASE VISIT TREATMENT*VISIT / solution cl;
  repeated VISIT / type=UN sub=USUBJID;
  lsmeans VISIT*TREATMENT/cl diffs;
run;
```

Note: In case the model will not converge with the unstructured covariance structure, the heterogeneous compound symmetry (CSH) or the heterogeneous Toeplitz structure (TOEPH) will be used instead.