STATISTICAL ANALYSIS PLAN

Protocol Title:	A randomized, open-label, single dose, four-way crossover, Phase I study to compare the pharmacokinetics of ferric maltol capsules and oral suspension under fasted and fed conditions in adult healthy volunteers
Protocol Number:	ST10-01-104
Protocol Version/Date:	Version 2.0, 15 July 2020
Investigational Product:	Ferric Maltol (ST10)
Sponsor:	Shield TX (UK) Limited, Northern Design Center, Baltic Business Quarter, Gateshead Quays, NE8 3DF United Kingdom
SAP Version/Date:	Version 1.0, 15 October 2020

SIGNATURE PAGE

Protocol Title:	A randomized, open-label, single dose, four-way crossover, Phase I study to compare the pharmacokinetics of ferric maltol capsules and oral suspension under fasted and fed conditions in adult healthy volunteers
Protocol Number:	ST10-01-104
SAP Version/Date:	Version 1.0, 15 October 2020

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

Signature	Date
Curtis McAfee ***Principal Statistical Scientist*** ***Medpace, Inc.***	15 OCT 2020
Juan Liang ***Director, Biostatistics*** ***Medpace, Inc.***	15 OCT 2020
Julian Howell ***Medical Consultant*** ***Shield TX (UK) Limited***	19 OCT 2020

VERSION HISTORY

Version	Version Date	Description
1.0	15 Oct 2020	Initial approved version.

TABLE OF CONTENTS

1 Introduction 8
2 Study Overview 8
2.1 Study Objectives 8
2.1.1 Primary Objective 8
2.1.2 Secondary Objectives 8
2.2 Study Design 8
2.2.1 Study Overview 8
2.2.2 Treatment Assignment and Blinding 10
2.2.3 Study Drug 10
2.2.4 Sample Size Determination 10
2.3 Study Endpoints 11
2.3.1 Primary PK Endpoints 11
2.3.2 Secondary PK Endpoints 11
2.3.3 Safety Endpoints 11
3 Statistical Methodology 11
3.1 General Considerations 11
3.1.1 Other Data Handling Approaches 12
3.1.2 Analysis Day 12
3.1.3 Handling of Dropouts and Missing Data 12
3.2 Baseline 12
3.3 Analysis Populations 12
3.3.1 Randomized Population 12
3.3.2 Safety Population 12
3.3.3 Full Analysis Set (FAS) Population 13
3.4 Subject Data and Study Conduct 13
3.4.1 Subject Disposition 13
3.4.2 Protocol Deviations 13
3.4.3 Analysis Populations 13
3.4.4 Demographics 13
3.4.5 Medical History 14
3.4.6 Prior and Concomitant Medications 14
3.5 Pharmacokinetic Assessment 14
3.5.1 PK blood sampling 14
3.5.2 Handling missing PK data or concentration below the lower limit of quantification 14
3.5.3 PK Concentrations 15
3.5.4 PK Parameters 15
3.5.5 PK analysis 16

3.6 Safety Assessment 17
3.6.1 Adverse Events (AEs) 17
3.6.2 Treatment-Emergent Adverse Event 17
3.6.3 Safety Laboratory 18
3.6.4 Vital Signs 18
3.6.5 ECG 18
3.6.6 Physical Examinations 18
4 Data Safety Monitoring Board 18
5 Interim Analysis 19
6 Programming Specifications 19

LIST OF ABBREVIATIONS

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

Abbreviation	Definition
NCS	Non-Clinically Significant
NTBI	Non-Transferrin Bound Iron
OFP	Oral Ferrous Product
PHI	Protected Health Information
PIP	Pediatric Investigational Plan
PK	Pharmacokinetics
PSP	Pediatric Study Plan
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SARS-CoV-2-RT-PCR	Severe Acute Respiratory Syndrome–associated Coronavirus RealTime Reverse Transcriptase–Polymerase Chain Reaction
SD	Standard Deviation
TEAE	Treatment-emergent Adverse event
TESAE	Treatment-emergent Serious Adverse event
TIBC	Total Iron Binding Capacity
TLAG	The delay between the time of dosing and time of appearance of concentration in the sampling compartment
T_{max}	Time to Maximum Plasma Concentration
TNF-a	Tumor Necrosis Factor alpha
TSAT	Transferrin Saturation
$T_{1/2}$	Apparent terminal elimination half-life
UC	Ulcerative Colitis
UIBC	Unsaturated Iron Binding Capacity
WHO	World Health Organization
yrs	Years
λ_z	Apparent terminal elimination rate constant, determined by linear regression of the terminal points of the ln-linear plasma concentration-time curve

1 INTRODUCTION

This statistical analysis plan (SAP) provides a detailed, technical elaboration of the statistical analyses of pharmacokinetic (PK) and safety data as described in the study protocol 2.0 dated 15 July 2020. Specifications for tables, listings, and figures are contained in a separate document. Any deviation from this analysis plan will be substantiated by sound statistical/PK/PD rationale and will be documented in the final clinical study report.

2 STUDY OVERVIEW

2.1 Study Objectives

2.1.1 Primary Objective

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

2.1.2 Secondary Objectives

The secondary objectives are:

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

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

2.2 Study Design

2.2.1 Study Overview

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

A total of 32 eligible subjects will be randomized at a ratio of 1:1:1:1 to receive one of the following treatment sequences comprised of four treatment periods. Treatment periods will last 4 days with at least 48 hours washout period between each dose administration. Eight subjects will be randomized to each treatment sequence:

Sequence A:

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

Sequence B:

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

Sequence C:

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

Sequence D:

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

The planned study consists of three study phases:

1. Screening Phase;
2. Treatment Phase;
3. Follow-Up Phase.

Table 1 contains details of the study periods, study visits and timing of the visits.

Table 1 Study Visits

Phase	**Period**	**Study Visit**	**Study Day**
Screening	Screening	1	-14 to -1
Treatment	Treatment Period 1	2	1
	Treatment Period 2	3	3
	Treatment Period 3	4	5
	Treatment Period 4	5	7
Follow-Up	Follow-Up	6	10-14

The Screening Phase will consist of one visit: Study Visit 1 (Screening) scheduled to take place within 14 days prior to the planned Treatment Phase for each subject. The purpose of this visit is to determine subject eligibility for the study.

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

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

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

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

The schedule of procedures can be found in Table 10.2 from Protocol.

2.2.2 Treatment Assignment and Blinding

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

The randomization procedure (created using a computer-generated random permutation procedure) will randomize the subject to one of the 4 treatment sequences to either Sequence A Sequence B, Sequence C or Sequence D. The site will dispense the appropriate formulation of open-label ferric maltol bottles at each scheduled PK day according to the schedule of assessments. The randomization scheme will be programmed by Medpace independent statistician using SAS®. Detailed randomization methods and procedures are described in a stand-alone document.

2.2.3 Study Drug

Investigational Medicinal Product

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

Comparator

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

2.2.4 Sample Size Determination

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

Thus, there are 4 primary endpoints:

In fed condition

> C_{max} (suspension) / C_{max} (capsule)
>
> AUC_{last} (suspension) / AUC_{last} (capsule)

In fasted condition

> C_{max} (suspension) / C_{max} (capsule)
>
> AUC_{last} (suspension) / AUC_{last} (capsule)

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

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

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

2.3 Study Endpoints

2.3.1 Primary PK Endpoints

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

2.3.2 Secondary PK Endpoints

1. PK analysis of total serum iron concentration; AUC_{inf} in fasted and fed conditions
2. PK analysis of baseline corrected serum iron concentration; C_{max}, AUC_{last}, AUC_{inf} in fasted and fed conditions
3. PK analysis of maltol and maltol glucuronide in plasma; C_{max}, AUC_{last} in fasted and fed conditions
4. PK analysis of TSAT, TIBC, UIBC, transferrin; C_{max}, AUC_{last} in fasted and fed conditions

2.3.3 Safety Endpoints

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

3 STATISTICAL METHODOLOGY

3.1 General Considerations

All available data will be presented in subject data listings, which will be sorted by treatment sequence 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 summarize data for all attended visits.

Formulation / condition groups will be displayed in all output using the following labels:

- Ferric Maltol Capsule/Fed
- Ferric Maltol Suspension/Fed
- Ferric Maltol Capsule/Fasted

- Ferric Maltol Suspension/Fasted

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

- Ferric Maltol Sequence A
- Ferric Maltol Sequence B
- Ferric Maltol Sequence C
- Ferric Maltol Sequence D

3.1.1 Other Data Handling Approaches

In general, descriptive statistics (n, mean, standard deviation (SD), median, maximum and minimum) will be used to summarize 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.).

3.1.2 Analysis Day

Analysis day will be calculated from the date of first dose of study drug. 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.

3.1.3 Handling of Dropouts and Missing Data

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

3.2 Baseline

Baseline is defined as reading or measurements at Day 1 prior to study drug administration of each period. If the reading at Day 1 predose is missing, the last reading before first dosing will be set as baseline.

3.3 Analysis Populations

3.3.1 Randomized Population

All subjects who are randomized.

3.3.2 Safety Population

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

3.3.3 Full Analysis Set (FAS) Population

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

3.4 Subject Data and Study Conduct

3.4.1 Subject Disposition

Subject disposition will be presented for the Randomized Population. The number and percentage of subjects in each of the following categories will be summarized by treatment sequence and overall, as appropriate:

- Randomized;
- Dosed;
- Completed each treatment period;
- Completed the study;
- Prematurely discontinued the study and reasons for study discontinuation; and
- Prematurely discontinued the study due to COVID-19 pandemic.

3.4.2 Protocol Deviations

Protocol deviations will be summarized with frequency distributions (counts and percentages) by treatment sequence group and category for the FAS and Randomized Population. The denominators for calculating percentages will be based on the number of subjects in the FAS and Randomized Population for each treatment sequence group and overall.

Protocol deviations will be listed by treatment sequence for the Randomized Population.

3.4.3 Analysis Populations

Counts and percentages of subjects in each analysis population will be summarized by treatment sequence, formulation / condition and in total based on the Randomized Population.

3.4.4 Demographics

The following demographic and baseline characteristics will be listed and summarized by treatment sequence and formulation / condition with descriptive statistics or counts and percentages of subjects for the Randomized Population and repeated for all other analysis populations if they are different from the Randomized Population:

- Age (years)
- Sex
- Childbearing potential
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not reported, Unknown)
- Race (Asian, American Indian or Alaska Native, Black or African American, Native Hawaiian or Other Pacific Islander, White, Other)
- Height (cm)
- Weight (kg)
- Body Mass Index (BMI) (kg/m2)

3.4.5 Medical History

Medical history reported terms will be coded to system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA) version 21.1. Medical history by system organ class and preferred term will be summarized by treatment sequence and in total for the Safety Population as well as listed

3.4.6 Prior and Concomitant Medications

Prior and concomitant medications will be coded with the World Health Organization Drug Dictionary Global B3 September 2018 version.

Prior medications will be defined as those medications (both prescribed and OTC) taken prior to the first dose of study drug in each treatment sequence. Medications taken at and after the time of first dose during the study will be defined as concomitant medications. Each treatment period will be defined as the period from the date and time of study drug dosing up to but not including the date and time of study drug dosing for the next treatment period (or end of study for the last treatment period). Concomitant medications taken at any time during a treatment period will be attributed to the corresponding treatment.

Concomitant medications will be summarized by formulation / condition for the Safety Population. All prior and concomitant medications will be listed.

3.5 Pharmacokinetic Assessment

3.5.1 PK blood sampling

PK samples were to be collected on Day 1 to Day 8, pre-dose and post-dose according to the PK Sample Schedule Group that the subject was assigned to.

On all four PK study days, all subjects will have baseline PK blood samples collected immediately prior to Ferric Maltol dosing (0 hr). Subjects will then have further PK blood samples collected at 11 additional times after dosing; the post-dose PK sample times will be 15 mins ±2 min, 30 mins ±2 min, 45 mins ±5 min, 1 hr ±5 min, 1.5 hr ±5 min, 2 hrs ± 5 min, 3 hrs ± 5 min, 4 hrs ± 5 min, 6 hr ±10 min, 10 hrs ±15 min and 24 hrs ±15 min.

For each individual subject, the post-dose PK blood sampling schedule will be the same on all four PK days. PK blood samples on the PK days will be: serum iron, total and unsaturated iron binding capacity (TIBC, UIBC), transferrin, transferrin saturation (TSAT), maltol and maltol glucuronide.

3.5.2 Handling missing PK data or concentration below the lower limit of quantification

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 dosing history information for a subject is missing, the sampling for that subject relative to the missing dose will not be included in the analysis.

Missing concentrations related to serum iron, TSAT, transferrin, TIBC, and UIBC will not be 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, 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. The following general rules will be applied for the concentration summary (including tabulation and plotting) for each period:

- Mean concentrations at any individual time point will only be calculated if at least half of the subjects have valid values (i.e. quantifiable and not missing) at this time point for each formulation / condition.
- In cases where a mean value is not calculated, due to the above criterion not being met, the mean value will be set to missing for mean plotting purposes and to BLQ for summary table.
- BLQ will be set to zero for maltol and maltol glucuronide and to LLOQ for other analytes for the calculation of these mean values if applicable.

3.5.3 PK Concentrations

The observed values for maltol, maltol glucuronide, serum iron, baseline corrected serum iron, TSAT, TIBC, UBIC, and transferrin will be summarized by formulation / condition and by visit/timepoint for FAS Population using the following descriptive statistics: n (the number of subjects), arithmetic mean, standard deviation (SD), geometric mean, coefficient of variation (CV), median, minimum and maximum, and a 90% confidence interval (CI) for the mean.

The observed data for maltol, maltol glucuronide, serum iron (uncorrected and baseline corrected), TSAT, TIBC, UBIC, and transferrin will also be listed by formulation / condition group for each individual subject for FAS Population.

For maltol, maltol glucuronide, serum iron (uncorrected and baseline corrected), TSAT, TIBC, UIBC, and transferrin the mean observed plasma concentrations will be plotted on a linear and semi-logarithmic scale against nominal time range by formulation / condition. Geometric mean observed plasma concentrations and 90% CI will be plotted on a linear scale against nominal time range by formulation/condition. Individual observed concentrations be plotted on a linear and semi-logarithmic scale against actual timepoint for each formulation/condition.

3.5.4 PK Parameters

For serum iron, baseline corrected serum iron, maltol, maltol glucuronide, TSAT, TIBC, UIBC and transferrin, the following parameters will be calculated by non-compartmental analysis.

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 (serum iron, maltol, and maltol glucuronide only)
$t_{½}$	Terminal elimination half-life, calculated as ln(2)/ λ_z (serum iron, maltol, and maltol glucuronide only)
AUC_{last}	Area under the plasma concentration versus time curve from time zero to last.
AUC_{inf}	Area under the plasma concentration versus time curve from time zero extrapolated to infinity time (serum iron, maltol, and maltol glucuronide only)

The actual collection times will be used for the calculation of PK parameters. 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, if applicable.

The apparent terminal elimination rate constant (λ_z), will not be presented for subjects who do not exhibit a terminal elimination phase in their concentration-time profiles. In order to estimate λ_z, linear regression of concentration in logarithm scale versus time will be performed using at least 3 data points. Uniform weighting will be selected to perform the regression analysis to estimate λ_z.

Generally, the λ_z will not be assigned if one of the following happens:

1. T_{max} is one of the 3 last data points,

2. The adjusted regression coefficient (R-squared) is less than 0.80,

3. The AUC_{extrap} exceeds 20%,

4. The estimated elimination rate indicates a positive slope, or

5. The terminal elimination phase is not linear (as appears in a semi-logarithmic scale) based on visual inspection.

If the λ_z is not assigned, the values of associated PK parameters (e.g. λ_z, AUC_{inf}, or $t_{½}$) will not be calculated.

Parameters will be listed by treatment sequence group for each individual subject and summarized by formulation/condition 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.

3.5.5 PK analysis

To compare the pharmacokinetics of ferric maltol capsules and oral suspension under fasted and fed conditions, a subject must have a calculable PK parameter for both formulations under fasted or fed condition.

An ANOVA model will be performed on the ln-transformed PK parameters (C_{max}, AUC_{last} and AUC_{inf}) of the two formulations including terms for sequence (treatment sequence), treatment (formulation/condition), and period as fixed effects, and subjects nested within a sequence as a

random effect. The estimates will be back-transformed into original scale. The point estimates for ratios and the corresponding 90% CIs will be provided.

The PK parameters analyses will be based on the FAS Population.

The sample SAS code for this analysis is included here for α = 0.10:

```
proc mixed;
class subject treatment sequence period;

model logPKvar = treatment sequence period /ddfm=Satterthwaite; random
subject(sequence);

lsmeans treatment/pdiff cl alpha=0.1;

run;
```

3.6 Safety Assessment

Safety analyses will be performed based on the Safety Population. Safety will be evaluated through assessments of AEs, treatment emergent adverse events (TEAEs), ECG, vital signs, physical examinations and clinical laboratory tests.

3.6.1 Adverse Events (AEs)

An adverse event is defined as any untoward medical occurrence in a subject regardless of its causal relationship to study treatment. An adverse event can be any unfavorable and unintended sign (including any CS abnormal laboratory test result), symptom, or disease temporally associated with the use of the study drug, whether or not it is considered to be study drug-related.

Adverse events will be coded using the latest version of Medical Dictionary for Regulatory Activities (MedDRA) Version 21.1.

The Investigator will grade the intensity of the adverse event as mild, moderate, or severe.

The relationship of an adverse event to study drug will be assessed as: related and not related.

3.6.2 Treatment-Emergent Adverse Event

A treatment-emergent adverse event (TEAE) is defined as an AE that emerges, having been absent prior to the study, or an AE that worsens in severity after the first dose of study drug in this study. Each treatment period will be defined as the period from the date and time of study drug dosing up to but not including the date and time of study drug dosing for the next treatment period (or end of study for the last treatment period). TEAEs that started during a treatment period will be attributed to the corresponding treatment. TEAEs will be summarized by MedDRA system organ class (SOC) and preferred term (PT) for each formulation / condition and overall. The number and percentage of subjects experiencing TEAEs, and the number of TEAEs will be tabulated. Subjects reporting more than one adverse event for a given MedDRA preferred term will be counted only once for that term using the most severe incident. Subjects reporting more than one type of event within a system organ class (SOC) will be counted only once for that SOC. The following summaries of adverse events will be presented for each part:

- Overall summary of TEAEs by formulation / condition with a breakdown by AE maximum severity;
- TEAEs by SOC and PT by formulation / condition;

- TEAEs by SOC, PT, and relationship to study drug by formulation / condition;
- TEAEs by SOC, PT, and maximum severity by formulation / condition; and
- TEAEs by SOC, PT, maximum severity, and the relationship to study drug by formulation / condition.

Separate listings will be prepared for SAEs, AEs leading to death and AEs leading to study discontinuation.

3.6.3 Safety Laboratory

Blood samples for safety laboratory will be collected at Screening and Day 8/ET.

Safety laboratory values and changes from baseline will be summarized at each scheduled visit by treatment sequence. A table summarizing abnormal values of safety laboratory tests will also be presented. All safety laboratory data, including normal ranges and abnormal laboratory flags, will be provided in data listings.

Pregnancy test results, drug and alcohol testing results, hepatitis and HIV test results, and COVID-19 test results will be listed.

3.6.4 Vital Signs

Vital signs including blood pressure, pulse rate, temperature, and respiratory rate will be measured at Screening, Day -1, Day 1, Day 3, Day 5, Day 7, and Safety Follow-Up/ET. Height, weight, and body mass index (BMI) will be measured at Screening only.

Vital signs values and changes from baseline will be summarized at each scheduled visit by treatment sequence.

All vital signs data will be listed.

3.6.5 ECG

Electrocardiograms will be performed at Screening.

Continuous ECG parameters (heart rate, PR interval, RR interval, QRS duration, QT interval, and QTcF interval) values and overall interpretation will be summarized at Screening by treatment sequence.

All ECG data will be listed.

3.6.6 Physical Examinations

Physical examinations will be performed at Screening, Day 8, and Safety Follow-Up/ET.

Physical examination results by body system will be summarized at each scheduled visit by treatment sequence.

Findings from the physical examinations will be listed.

4 DATA SAFETY MONITORING BOARD

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

5 INTERIM ANALYSIS

No interim analysis is planned for this study.

6 PROGRAMMING SPECIFICATIONS

The creation of analysis datasets and all statistical analyses will be performed using SAS® Version 9.4. Medpace standard operating procedures GL-DS-02-S3 and GL-DS-03-S2 will be followed for the generation and validation of all programs and outputs.

Phoenix WinNonlin version 7.0 or higher will be used in the determination of the PK terminal phase and the calculation of PK parameters. Medpace standard operating procedures GL-DS-26-S1 and GL-DS-27-S1 will be followed for conducting NCA analysis and statistical analysis.

Detailed Programming Specifications will be provided in a separate document.