Official Study Title: Assessing the safety, tolerability and pharmacokinetics of benfo-oxythiamine (B-OT) in healthy volunteers – an open-label, phase I study.

NCT Number: NCT07450833

Document Date: 02 November 2022

Document Type: Statistical Analysis Plan

STATISTICAL ANALYSIS PLAN
Version 2.0 (final)

STUDY PROTOCOL: **BV-01-101**
EUDRACT: 2021-005616-60

STUDY TITLE: Assessing the safety, tolerability and pharmacokinetics of Benfo-Oxythiamine (B-OT) in healthy volunteers – An Open label, phase I Study

Sponsor: benfovir AG, Grafenhäuser Str. 26, 64296 Darmstadt, Germany

Performed by: Medistat Ltd., ks Mladost 1A bl. 520 vh. 3 ap. 54, Sofia 1729, Bulgaria

Sofia, 02 November 2022

DOCUMENT HISTORY

Date	Author	Version	Changes
May 2022	Medistat Ltd and benfovir AG	Final 1.0	Version not signed
June 2022	Medistat Ltd and benfovir AG	Final 1.1	Version signed
November 2022	Medistat Ltd and benfovir AG	Final 2.0	Following protocol amendment including MAD part analysis Some technical correction in the SAD part

STATISTICAL ANALYSIS PLAN Version 2.0
APPROVAL STATEMENT

Final SAP Date: November 2022

Upon review of the statistical analysis plan including table, listing and figure, the undersigned accepts this document as final. The analysis methods and data presentation are acceptable, and the table, listing, and figure production can begin after database lock.

Approved by Sponsor:

Name: [redacted]

Title: Biostatistics Consultant

Signature: [redacted] Date: 08-Nov-2022

Table of content

ABBREVIATIONS AND NOTATIONS 7
1. STUDY DESCRIPTION 9
2. STUDY OBJECTIVES 10
2.1 Primary objective 10
2.2 Secondary objectives 10
SAD 10
MAD 11
2. 3 Exploratory Objectives 11
2.4 Change the Primary Objective During the Conduct of the Study 11
3. STUDY DESIGN 12
3.1 General study design 12
3.1.1 SAD part 12
Fig. 1 Single administration design 12
3.1.2 MAD part 13
Fig. 2 Multiple administration design 13
3.2 Sample Size 14
3.2.1 Single dose 14
3.2.2 Multiple dose 14
3.3 Randomization and Blinding 14
3.3.1. Randomization 14
3.3.2. Blinding 14
4. STUDY POPULATIONS 15
4.1 Justification for population and design 15
4.1.1 Single dose 15
4.1.2 Multiple dose 15
4.2 Subject Disposition (SAD and MAD) 16
4.3 Definition of Sets for Analysis 17
4.3.1 Safety analysis set (SF) 17
4.3.2 Pharmacokinetic analysis set 17
4.4 Major Protocol Deviations 18
4.5 Definition of Sub-Group Population in Different Analyses 18
5. STATISTICAL ANALYSIS – GENERAL CONSIDERATIONS 19
5.1 Hypotheses 20
5.2 Assessment of statistical assumptions 20
5.3 Adjustments for covariate 20
5.4 Multiple comparisons 20
5.5 Examination of subgroups 20
5.6 Pooling of Sites 20
5.7 Interim Analyses 20
5.8 Time-Points for Analysis 20
5.9 Methods for Handling Missing, Unused and Spurious Data 20
5.9.1 Pharmacokinetic data 20
5.9.2 Non-pharmacokinetic data 21
5.9.3 Handling of drop-outs 21
5.10 Output from statistical analysis 21
6. EVALUATION OF DEMOGRAPHICS AND BASELINE CHARACTERISTICS 22
6.1 Patient Disposition 22

6.2 Demographics and baseline measurements 22
7. EVALUATION OF TREATMENT COMPLIANCE AND EXPOSURE 23
7.1 Treatment Compliance 23
7.2 Exposure to Study Drug 23
8. EVALUATION OF PHARMACOKINETIC PARAMETERS 24
8.1 SAD part 24
8.1.1 General Consideration 24
8.1.2 Computation formulas 24
8.1.3 Dose proportionality (SAD) 26
8.2 MAD part 27
8.2.1 Steady-State 27
8.2.2 General Consideration 27
8.2.3 Computation formulas (MAD) 27
8.2.4 Accumulation ratios 28
8.2.5 Dose proportionality (MAD) 28
9. EVALUATION OF EFFICACY PARAMETERS 29
10. EVALUATION OF PHARMACODYNAMIC PARAMETERS 30
10.1 SAD part 30
Table 1. PK/PD SAMPLING TIMEPOINTS: SAD Part 30
10.2 MAD part 30
Table 2. PK/PD SAMPLING TIMEPOINTS: MAD Part 31
11. EVALUATION OF SAFETY PARAMETERS 33
11.1 Adverse Events 33
11.1.1 Brief summary of adverse events 33
11.1.2 Display of Adverse Events 33
11.1.3 Analysis of Adverse Events 34
11.1.4 Listing of adverse events by patient 34
11.2 Clinical Laboratory Evaluation 35
11.2.1 Analysis of Abnormal Laboratory Value 35
11.2.2 Evaluation of Each Laboratory Examination 35
11.3 Vital Signs 35
11.4 Concomitant Therapy 35
12. GENERAL CONVENTIONS 36
13. COMPUTATIONS 37
14. REFERENCES 38
LIST OF SUMMARY TABLES AND PLOTS 39
I. SAD Part 39
I.I Tables and Figures 39
Demographic Data 39
Pharmacokinetic and Pharmacodynamic Data 39
Pharmacokinetics 39
Pharmacodynamics 39
Safety Data and Adverse events 39
I.II Individual Listings 40
II. MAD Part 41
II.1 Tables and Figures 41
Demographic Data 41
Pharmacokinetic and Pharmacodynamic Data 41
Pharmacokinetics 41

Pharmacodynamics 41
Safety Data and Adverse events 41
II.2 Individual Listings 42

ABBREVIATIONS AND NOTATIONS

AE	Adverse Event
AUC	Area Under the Plasma Concentration Curve
BLoQ	Below the Limit of Quantification
B-OT	Benfo-oxythiamine
CI	Confidence Interval
CL/F	Apparent body clearance
C_{max}	Maximum Plasma Concentration
CRF	Clinic Report Form
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CV	Coefficient of Variation
DF, df	Degrees of Freedom
ECG	Electrocardiogram
FIH	First-in-Human
IMP	Investigational Medicinal Product
INF, inf	Infinity
LSMean, LSM	Least Square Mean
λ_z	Terminal Rate Constant
LLoQ	Lower Limit of Quantification
LoQ	Limit of Quantitation
MAD	Multiple-ascending dose
OT	Oxythiamine
PD	Pharmacodynamics
PK	Pharmacokinetic(s)
PT	Preferred Term
Ra	Accumulation Ratio
SAD	Single ascending dose
SAE	Serious Adverse Event
SAS®	Statistical Analysis System
SRC	Safety Review Committee
SD	Standard Deviation
SF	Safety analysis set

SOC	System Organ Class
$t_{1/2}$	Plasma Concentration Half-Life
TLF	Tables, Listings and Figures
t_{max}	Time until Cmax is reached
TEAE	Treatment Emergent Adverse Event
Vz/F	Apparent volume of distribution

1. STUDY DESCRIPTION

The purpose of the Statistical Analysis Plan for this study is to provide a framework in which answers to the protocol objectives may be achieved in a statistically rigorous fashion, without bias or analytical deficiencies. Specifically, this Plan has the following purpose: to prospectively (a priori) outline the types of analyses and presentations of data that will form the basis for conclusions to be reached that will answer the study objectives outlined in the Protocol, and to explain in detail how the data will be handled and analysed, adhering to commonly accepted standards and practices of biostatistical analysis in the pharmaceutical industry.

The analyses described in this document will be carried out to characterize the pharmacokinetics, pharmacodynamics, and safety of administered treatments in the SAD part as well as in the MAD part of the study.

The primary aim of the analyses is to assess the safety and tolerability of single and multiple ascending doses of B-OT. Additionally, the analysis aims to evaluate the pharmacokinetics (PK) of benfo-oxythiamine (B-OT) and its active metabolite oxythiamine (OT) in plasma following single doses administered to healthy volunteers in the SAD part of the study.as well as OT in plasma following multiple doses administered in the MAD part of the study

The pharmacodynamics (PD) will be evaluated by measuring the transketolase activity in erythrocytes in the SAD part of the study and in white blood cells in the MAD part of the study.

All analyses will be performed in conformity with the Clinical Study Protocol BV-01-101, Version 3.0/13 Jul 2022.

2. STUDY OBJECTIVES

Description of primary objective and the secondary objectives of this study will be discussed in this section.

2.1 Primary objective

The primary objective of this study is to assess the safety and tolerability of SAD and MAD of B-OT.

Safety assessments will include:

- Incidence of adverse events
- Standard laboratory safety parameters
- Vital Signs
- ECG parameters
- Physical examinations

2.2 Secondary objectives

To evaluate the pharmacokinetics (PK) of benfo-oxythiamine (B-OT) and its active metabolite oxythiamine (OT) in plasma following single doses administered to healthy volunteers in the SAD part of the study

To evaluate the pharmacokinetics (PK) of benfo-oxythiamine (B-OT) active metabolite oxythiamine (OT) in plasma following multiple doses administered to healthy volunteers in the MAD part of the study.

SAD

In the SAD part of the study, the following PK parameters will be derived from plasma benfo-oxythiamine (B-OT) and oxythiamine (OT) concentration versus time data following administration according to the dosing schedule:

- Maximum measured plasma concentration (C_{max});
- Area under the plasma concentration curve from administration to last observed concentration at time t (AUC_{0-t});
- Area under the plasma concentration curve extrapolated to infinite time (AUC_{0-inf});
- Time until maximum plasma concentration is reached (t_{max});
- Plasma elimination half–life ($t_{1/2}$);
- Terminal elimination rate constant (λ_Z);
- Residual area (%);
- Apparent body clearance (CL/F);
- Apparent volume of distribution Vz/F.

Dose-proportionality for PK parameters of OT and B-OT (AUC_{0-inf}, AUC_{last}, and C_{max}) will be assessed as well.

MAD

In the MAD part of the study the following PK endpoints will be derived from plasma oxythiamine (OT) concentration versus time data following administration according to the dosing schedule:

i) on Day 1
- AUC during a dosage interval ($AUC_{0-\tau}$);
- Maximum plasma concentration (C_{max});
- Time until C_{max} is reached (t_{max}).

ii) on Day 7 (at steady-state)

- Maximum plasma concentration at steady state ($C_{max,ss}$);
- Area under the plasma concentration curve during a dosage interval at steady state ($AUC_{0-\tau}$);
- Time until $C_{max,ss}$ is reached ($t_{max,ss}$);
- Swing;
- PTF%;
- Apparent body clearance (CL_{ss}/F);
- Apparent volume of distribution V_{ss}/F;
- Observed concentration at the end of a dosing interval (C_{trough});
- Average concentration over a dosing interval (C_{av});
- Minimum observed concentration over a dosing interval (C_{min}).

iii) After Day 7 (after steady-state)

- Terminal elimination rate constant (λ_Z);
- Plasma elimination half–life ($t_{1/2}$);
- Area Under the Curve from 0 to infinity (AUC_{0-inf});
- Area Under the Curve from 0 to the time of the last quantifiable concentration (AUC_{0-last}).

In addition, accumulation ratios ($Ra(AUC_{0-\tau})$ and $Ra(C_{max})$) will be computed. Dose-proportionality for PK parameters of OT ($AUC_{0-\tau}$, AUC_{last}, and $C_{max,ss}$) will be assessed as well.

2. 3 Exploratory Objectives

Exploratory objective is to evaluate the pharmacodynamics (PD) by measuring the transketolase activity in erythrocytes in the SAD part of the study and in white blood cells in the MAD part of the study.

2.4 Change the Primary Objective During the Conduct of the Study

Not applicable.

3. STUDY DESIGN

This is a monocentric, open-label, non-randomized, uncontrolled, first-in-human study to assess the safety, tolerability, and pharmacokinetics /pharmacodynamics of B-OT in healthy subjects. This study has two parts: a single ascending dose (SAD) part and a multiple ascending dose (MAD) part.

This SAP describes the analysis of the single ascending dose (SAD) part of the study as well the multiple-ascending dose (MAD) part.

3.1 General study design

3.1.1 SAD part

In the SAD part, a single dose of B-OT is administered per oral (*p.o.*) once daily on day 1 followed by 7 days without dosing. The SAD part of the study will consist of an ambulatory screening visit, treatment period comprised of four nights (day -1 until day 4) in the clinical site where the study will be conducted during which safety parameters will be measured and numerous blood samples will be drawn for assessment of benfo-oxythiamine (B-OT) and oxythiamine PK and PD properties and a final ambulatory follow-up visit three days after subject's discharge (day 8). After the IMP administration during the treatment visit, safety, pharmacokinetic and pharmacodynamics data will be collected and reviewed 72 hours post-dose. Fig. 1 shows the design of the single dose stage.

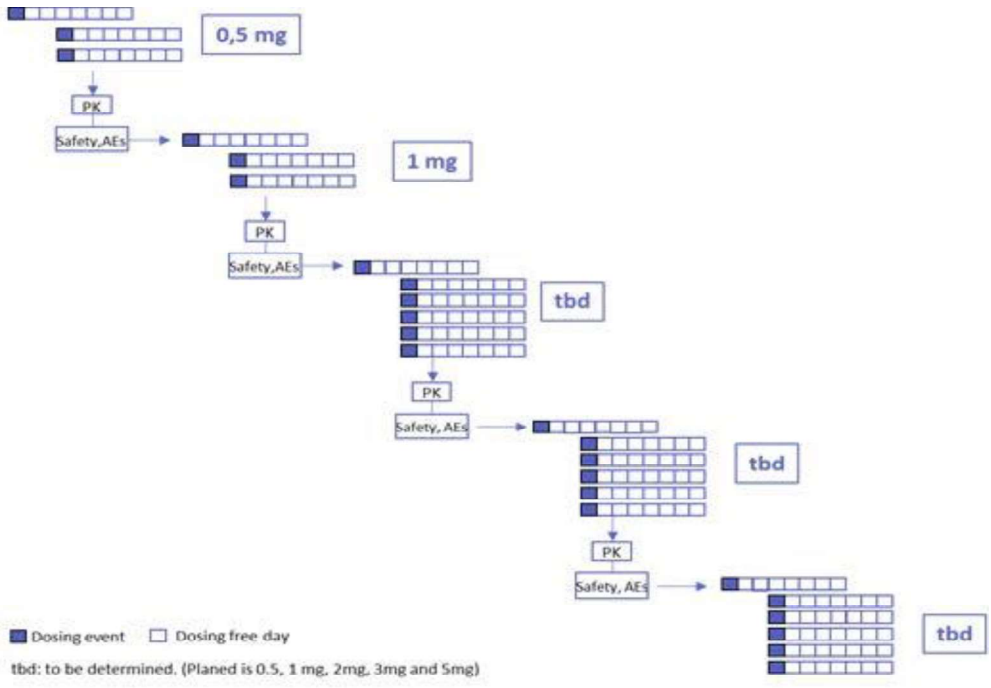

Fig. 1 Single administration design

The filled boxes represent a dosing event, a white box a represents a dosing free day. Single dose treatment will be administered on day 1.
The total duration of the study for each subject will be up to 5 weeks.

3.1.2 MAD part

In the MAD part of the study, B-OT will be administered orally (*p.o.*) once daily for 7 days (D1-D7), followed by 7 days without dosing. The first dose will be 1 mg, as the PK and safety data have shown a very low concentration of OT at 0.5 mg dose and no safety issues were observed at any dosage in the SAD part.
Each cohort will start with a sentinel subject (subject No1). Subjects No2 - No6 of the same cohort will start treatment after a minimum of 72 hours if no adverse event is observed in the sentinel subject. The Fig. 2 represents the study design of the MAD part:

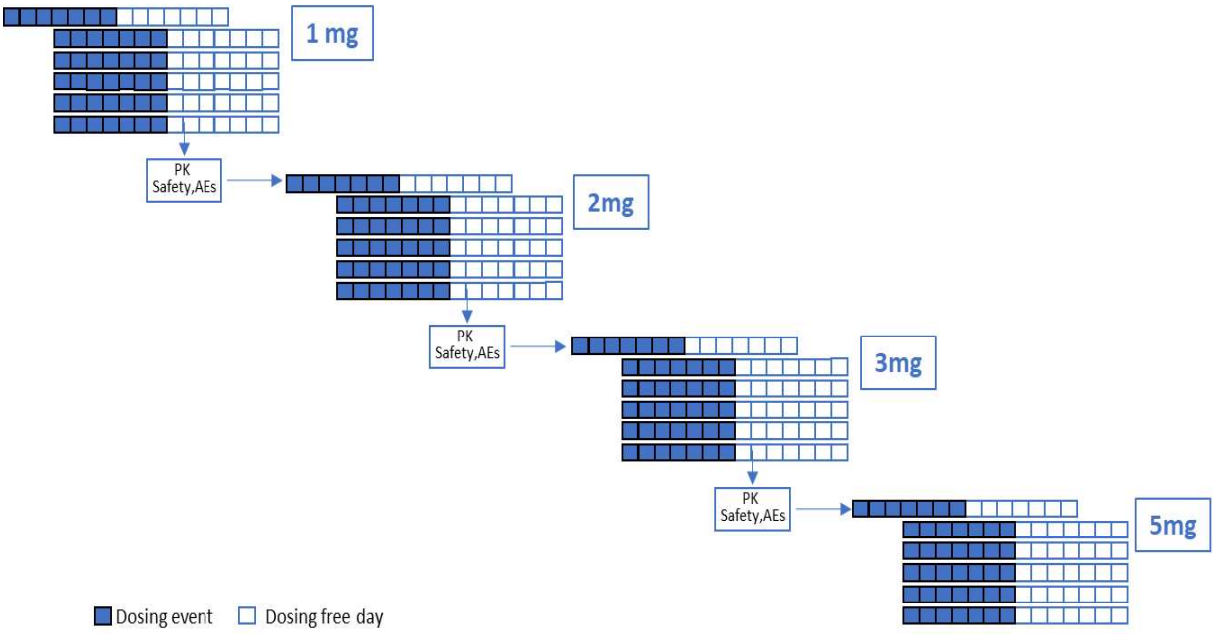

Fig. 2 Multiple administration design

The filled boxes represent a dosing event, a white box a represents a dosing free day.
The total duration of the MAD part of the study for each subject will be up to 6 weeks.

3.2 Sample Size

No formal statistical hypothesis has been set for this exploratory study. The sample size of this study is based on the design of similar studies, and it is expected to be adequate in the evaluations underlying the objectives of the study.

3.2.1 Single dose

The sample sizes for the SAD cohorts are typical for a Phase 1 first in human (FIH) study. The total number of subjects accrued in the study will depend on the number of dose levels, but is currently set to a maximum of 24 subjects (2 cohorts with 3 subjects and 3 cohorts with 6 subjects each).

3.2.2 Multiple dose

A total of 24 subjects will be enrolled in the MAD part of the study and assigned to multiple ascending dose groups in consecutive order.

3.3 Randomization and Blinding

3.3.1. Randomization

This is not a randomized study.

3.3.2. Blinding

This is an open-label study.

4. STUDY POPULATIONS

4.1 Justification for population and design

This study is based on established designs for FIH studies and will comprise of single ascending dose (SAD) and multiple ascending dose (MAD) cohorts in sequential order. It will be conducted in healthy volunteers to evaluate the safety, tolerability and PK, of oral benfo-oxythiamine (B-OT) administration.
The sentinel dosing maximizes the chance that, in the event of a significant unanticipated safety risk, dosing will be discontinued after exposure of a single healthy volunteers to a given dose level of benfo-oxythiamine (B-OT).
The sequential nature of the cohorts requires that the necessary data is reviewed by the SRC before the next cohort/sub-part/part can begin.
The study is to be conducted in healthy male subjects. 24 subjects represented in the SAD PK Analysis Set and another 24 subjects represented in the MAD PK Analysis Set will be required to complete the study. A healthy subject population with carefully considered inclusion/exclusion criteria will avoid the potential for interaction of benfo-oxythiamine (B-OT) with any underlying disease state or concomitant medication that might be necessary to administer to patients, while ensuring that subjects are fit and well enough for participation in the study.

4.1.1 Single dose

A total of 24 healthy subjects from both sexes are planned to be included in the study distributed as follows:
Cohort 1 (0.5 mg B-OT): 3 subjects
Cohort 2 (1 mg B-OT): 3 subjects
Cohort 3 (TBD mg B-OT): 6 subjects
Cohort 4 (TBD mg B-OT): 6 subjects
Cohort 5 (TBD mg B-OT): 6 subjects.

Each cohort starts with a sentinel subject (eligible subject 1). Subjects eligible 2 - 3 or 2 - 6 of the same cohort start treatment after a minimum of 48 hours if safety data indicate that dosing of subsequent subjects of this cohort is justified. Dose escalation to the next dose level occurs if three (first and second cohort) or six subjects (3 next cohorts) have completed the single dose treatment and if PK at Day 2 as well as safety data allow an escalation to the next dose level.

4.1.2 Multiple dose

A total of 24 subjects will be enrolled in the MAD part of the study and assigned to multiple ascending dose groups in consecutive order, in each group 6 volunteers will be included:
Group 1 (1 mg B-OT): 6 subjects
Group 2 (2 mg B-OT): 6 subjects
Group 3 (3 mg B-OT): 6 subjects
Group 4 (5 mg B-OT): 6 subjects.

Each cohort will start with a sentinel subject (subject 1). Subject 2 - 6 of the same cohort will start treatment after a minimum of 72 hours if safety data indicate that dosing of subsequent subjects of this cohort is justified. Dose escalation to the next dose level will occur if six subjects have

completed the multiple dose treatment and if PK at Day 5 as well as safety data allow an escalation to the next dose level.

4.2 Subject Disposition (SAD and MAD)

The summary of subject disposition will include the number of subjects in each treatment group who are treated and who completed the study. Reasons for discontinuing treatment and/or study will be tabulated. Volunteers withdrawn from the study because of safety reasons or for reasons unrelated to the study medication will not be replaced. The reasons for withdrawal will be recorded. The number of subjects enrolled, treated, and completing treatment will be tabulated and represented graphically.

Subject disposition will be listed by subject.
The following subject data will be summarized:

- Number and percentage of subjects screened,
- Number and percentage of subjects enrolled,
- Number and percentage of subjects completed and,
- Number and percentage of subjects included in safety population,
- Number and percentage of subjects included in PK and PD populations
- Number and percentage of subjects included in statistical analyses.

A subject who completed the study is defined as a subject for whom the last PK blood sample was assessed.

4.3 Definition of Sets for Analysis

Data of all subjects participating in the study will be included in the analyses if the data can meaningfully contribute to the objectives of the study. Subjects who do not complete the sampling schedule of 1 or more study periods may be included in the PK population for only the PK parameters that are judged not to be affected by the missing sample(s).
The decision of which subjects will be included in the PK Analysis Set is to be taken before the start of the sample analysis by the bioanalytical facility.
Statistical analysis and data tabulation will be performed for both SAD and MAD parts using the following subject sets.

4.3.1 Safety analysis set (SF)

The safety population will be defined as all subjects who received at least one dose of B-OT and for whom any safety post-dose data are available.
Unless otherwise stated, the safety analysis set will be used for the presentation of all safety analyses. Exposure to IMP will also be presented using the safety analysis set.
The SF set will be used for summaries of safety and other variables (such as, disposition, concomitant medications, etc.), as well as demographics and subject characteristics.

4.3.2 Pharmacokinetic analysis set

Subjects will be allocated to the PK Analysis Set on a per treatment basis. The PK Analysis Set for a treatment will include all subjects who receive one dose of B-OT, do not violate the protocol in a way that may invalidate or bias the results (major protocol deviation) and have sufficient plasma concentration-time profiles complying with the following criteria at Day 1 (SAD/MAD) and at Day 7 (MAD only):

- Do not have an occurrence of vomiting or diarrhoea which renders the plasma concentration profile unreliable (e.g., if vomiting occurs at or before 2 times median T_{max});
- Do not use a concomitant medication which renders the plasma concentration profile unreliable; Day 1: Do not have a pre-dose plasma concentration that is greater than 5% of the C_{max} value. For SAD part, a subject with pre-dose concentration above 5% of the Cmax will be excluded from the PK population; in the MAD part, subject's MAD Day 1 profile will be excluded.
- Have at least one evaluable plasma concentration that is preceded by a lower evaluable concentration and followed by a lower evaluable concentration for the calculation of C_{max}, T_{max} and AUCs.

In case of an important protocol deviation or AEs, affected PK data will be excluded from the descriptive statistical analysis. Where all PK data for a subject are impacted, the subject will be excluded from the PK analysis set. The exclusion of any subjects or time points from the calculation of the PK parameters will be documented by the statistician including the reason(s) for exclusion.

4.3.3 Pharmacodynamic analysis set

The PD analysis set will consist of all subjects in the safety analysis set who received at least one dose of B-OT and who have at least one post-dose values present, with no important protocol deviations thought to impact on the analysis of the PD data.

4.4 Major Protocol Deviations

Major protocol deviations, if any, will be reported overall and by treatment groups. The volunteers with major deviations may be excluded from the pharmacokinetic analysis if and only if these deviations could affect the pharmacokinetic parameters.

Major protocol deviations will be identified before the study closure. A list of all protocol deviations will be given.

Major protocol deviations, including taking any concomitant medication that may confound study results or having any non-compliance issues raised by the investigator or sponsor will be summarized by treatment groups, if appropriate. Protocol deviations will be summarized and grouped into different categories, such as:

- Protocol entry criteria.
- Forbidden concomitant medications.
- Missing evaluations for relevant endpoints.
- Other protocol deviations occurring during study conduct.

4.5 Definition of Sub-Group Population in Different Analyses

No sub-group analysis is planned for this study. However, where data suggest, exploratory sub-group analysis may be performed.

5. STATISTICAL ANALYSIS – GENERAL CONSIDERATIONS

This section summarizes the statistical principles and methods planned to analyze the data for this clinical study. The statistical methodology below describes the statistical analysis as it is foreseen when the study is being planned. If circumstances should arise during the study rendering these analyses inappropriate, or if in the meantime improved methods of analysis should come to light, different analyses may be made. Any deviations from the statistical methodology, reasons for such deviations and all alternative or additional statistical analyses that may be performed, will be described in the CSR. Such changes to analyses may be written into an abbreviated SAP, if appropriate.

The calculation of pharmacokinetic parameters will be done with current version of WinNonlin® software [1].

All statistical analyses as well TLFs will be conducted with SAS® current version 9.4 [2] using procedures appropriate for each analysis.

All results will be analysed and presented by treatment group and by time where applicable and separate for SAD and MAD parts.

This study is exploratory and not addresses any pre-defined hypotheses. The assessment of safety and tolerability will be performed on the safety analysis set..

Demographic and baseline data will be summarized by treatment (dose level of B-OT) and overall. Pharmacokinetic data will be summarized by dose level of B-OT. Safety and tolerability data will be summarized.

Frequency (number of subjects and percentages) will be presented for each qualitative variable. Descriptive statistics (n, mean, SD, min, median, max) will be calculated for each quantitative variable (unless otherwise stated). Descriptive statistics will only be presented if $n \geq 3$. If no subjects have data at a given time point, then only n=0 will be presented. If $n < 3$, only the n, minimum and maximum will be presented. The other descriptive statistics will be left blank.

The following rules will apply to any repeated safety assessments occurring within each cohort:

• If the repeated measurement of a specific parameter occurs prior to IMP administration (Day 1), then the last obtained value prior to dosing will be used in the descriptive statistics and in the calculation of changes from baseline.

• If the repeated measurement of a specific parameter occurs after IMP administration (Day 1), then the first (non-missing) value after dosing will be used in descriptive statistics and in the calculation of changes from baseline.

The planned sequence for measurement of multiple assessments at the same time point is described in Section 12.2.1 Blood samples collection.

For safety assessments performed at Screening and the follow-up, the following rules will apply for any repeated assessments:

• If the repeated assessment occurs at Screening the last available value will be used in the summary statistics.

• If the repeated assessment occurs at the Follow-up Visit the first non-missing assessment will be used in the summary statistics.

Any decisions to deviate from the planned analyses described in the protocol and SAP will be documented in the clinical study report. The clinical study report will also provide a detailed explanation for any deviations from the planned analyses.

5.1 Hypotheses

Not applicable. This is an exploratory study.

5.2 Assessment of statistical assumptions

Not applicable.

5.3 Adjustments for covariate

Not applicable.

5.4 Multiple comparisons

Not applicable.

5.5 Examination of subgroups

There will be no sub-group analysis.

5.6 Pooling of Sites

Not applicable. This is a single-site study.

5.7 Interim Analyses

There is no formal interim analysis planned in this study.

5.8 Time-Points for Analysis

Statistical analysis will be performed at the end of the MAD part of the study and when the database has been locked. However, PK data of the SAD part have been analyzed prior to the start of the MAD part to allow for selecting dose levels for the MAD part.

5.9 Methods for Handling Missing, Unused and Spurious Data

All available data will be included in the analyses and will be summarized as far as possible. Unless otherwise specified there will be no substitution of missing data, i.e. missing data will not be replaced, missing data will be handled as 'missing' in the statistical evaluation.

5.9.1 Pharmacokinetic data

Concentrations below the Lower Limit of Quantification (LLoQ) will be indicated as Below the Limit of Quantification (BLoQ) on individual results tabulations. For all descriptive statistics, pre-dose BLoQ concentrations will be set to zero (for single dose concentrations). All other BLoQ concentrations will be set to LLoQ/2.

For computation of PK parameters and relevant statistical evaluations:

i) Zero (0) imputation will be implemented before the first quantifiable concentration;

ii) LLoQ/2 imputation will be used between quantifiable concentrations, and

iii) Values will be ignored (i.e. considered as missing) after the last quantifiable concentration.

iv) Values reported as missing (no sample or no valid analytical result) will be set as such and will not be included in PK and statistical evaluation. If single data points for plasma B-OT or OT concentrations are missing, the AUC parameters will be derived by linear interpolation with regard to the two neighboring non-missing concentrations.

v) If the actual sampling time is missing, but a valid concentration value has been measured, the scheduled protocol time will be used for the calculation of derived PK. Pre-dose sampling time will be considered as if it had been taken simultaneously with the drug administration (at zero-hour time point).

5.9.2 Non-pharmacokinetic data

All available data will be included in the analyses and will be summarized as far as possible. Unless otherwise specified there will be no substitution of missing data, i.e. missing data will not be replaced, missing data will be handled as 'missing' in the statistical evaluation.

5.9.3 Handling of drop-outs

Volunteers withdrawn from the study because of safety reasons or for reasons unrelated to the study medication will not be replaced.

5.10 Output from statistical analysis

Complete SAS output will be given for all produced analyses as an Appendix to Statistical Report.

6. EVALUATION OF DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Separate tables will be produced for SAD and for MAD parts of the study.

6.1 Patient Disposition

The number of patients will be presented for each treatment group. It will be displayed in Fig. *"Patient Disposition"*.
In addition, table will display the number and percent of patients included in the study as well as discontinuing patients for each treatment group and overall. This table will also contain the number and percentage of patients corresponding to the reason for discontinuation.

6.2 Demographics and baseline measurements

Baseline is defined as the last value prior to dosing. Absolute change from baseline will be calculated for all continuous safety parameters. Baseline demographic data will be tabulated and presented by dose.
Demographic data: age, height, weight and body mass index (BMI) will be summarized by descriptive statistics (n, mean, standard deviation, median, minimum and maximum), and gender and race, will be summarized by the number and percentage of subjects in each category in Table "*Demographics*".

7. EVALUATION OF TREATMENT COMPLIANCE AND EXPOSURE

7.1 Treatment Compliance

Administration of investigational products will only be performed by authorized clinical research staff and will be followed by a hand and oral cavity check in order to confirm the swallowing of the product and fluid intake, if applicable.
Upon dispensing medication, the clinical research staff will record the related information on the applicable source documents, to allow investigational product accountability and evaluation of subject compliance.

7.2 Exposure to Study Drug

The information regarding exposure to study drug will be listed accordingly in Listing "*Exposure to study drugs*".

8. EVALUATION OF PHARMACOKINETIC PARAMETERS

8.1 SAD part

8.1.1 General Consideration

The PK parameters will be derived individually for each volunteer from drug concentrations in blood samples. Values below or above the limit of quantification, if any, will be indicated as such and will be taken into account for the calculation of pharmacokinetic parameters after confirming or correcting the relevant value. Blood samples will be taken according to the schedule given in Table 1 (see Section 10.1 below).
Actual blood sampling time points will be used for individual calculations and presentations. Nominal times will be used for calculations and presentations of summarised data.
Descriptive statistics will be calculated for all PK parameters (C_{max}, t_{max}, $AUC_{0\text{-}last}$, $AUC_{0\text{-}\infty}$, λ_z, λ_z, CL/F, V_z/F) concentration-time data using Phoenix WinNonlin 8.3. A non-compartmental model will be assumed for all parameters. Linear regression analysis on the log–transformed concentrations for the determination of λ_z will be performed using at least 3-4 data points in the terminal phase, excluding C_{max}. The terminal phase elimination rate constant λ_z will not be calculated if the terminal phase is not evident. Also, the square of the adjusted Pearson correlation coefficient for the goodness of the fit (coefficient of determination) of the regression line through the data points (R^2_{adj}) must be 0.80 or higher, for the value of λ_z to be considered reliable. In cases where the λ_z rate is not assigned, the values of $AUC_{0\text{–}inf}$ and $t_{1/2}$ will not be estimated and will be reported as “Not calculated”. The value of AUC0-inf will be considered unreliable but will be reported if the terminal area beyond the last quantified sample is greater than 20% of the total AUC0-inf.
Graphical images will be given as individual and overlaying (pooled) plots by treatment. Linear and semi-logarithmic views will be produced.
All plasma concentrations and derived PK parameters for each treatment will be listed and summarized descriptively (mean values (arithmetic and geometric), standard deviations, minimum and maximum values, medians, and valid Ns for the calculated variables). Coefficient of variation (CV%) of the arithmetic and geometric mean values will also be presented. 95% CI for arithmetic mean will be given where possible.

8.1.2 Computation formulas

Pharmacokinetic parameters will be calculated assuming a non-compartmental model as follows:

- $AUC_{0\text{-}t}$ (h.ng/mL) – The area under the plasma concentration versus time curve, from time 0 to the last measurable concentration, as calculated by the linear–up/log–down trapezoidal method. When concentrations are increasing (as in the absorption phase), the linear trapezoidal method will be used. When concentrations are decreasing (as in the elimination phase), the logarithmic trapezoidal method will be used. If $C_i > C_{i-1}$ then:

$$AUC_i = AUC_{i-1} + \frac{C_i + C_{i-1}}{2} * (t_i - t_{i-1})$$

otherwise:

$$AUC_i = AUC_{i-1} + \frac{C_i - C_{i-1}}{\ln C_i - \ln C_{i-1}} * (t_i - t_{i-1})$$

where C_i is the value of observed plasma concentration at moment t_i. If the logarithmic trapezoidal rule fails in an interval due to lack of strict *monotonicity*, then the linear trapezoidal rule will apply for that interval.

- AUC_{0-inf} (h.ng/mL) The area under the plasma concentration versus time curve from time 0 to infinity, calculated as $AUC_{0-inf} = AUC_{0-t} + C_t/\lambda_z$, where C_t is the last measurable concentration, λ_z is the terminal elimination rate constant.

- Residual area (%) $\frac{(AUC_{0-inf} - AUC_{0-t})}{AUC_{0-inf}} \times 100\%$.

- C_{max} (ng/mL) - Maximum measured plasma concentration over the time span specified.

- t_{max} (h) – Time of the maximum measured plasma concentration. If the maximum value occurs at more than one time point, t_{max} is defined as the first time point with this value.

- λ_z (1/h) – Apparent first–order terminal elimination rate constant calculated from a semi–log plot of the plasma concentration versus time curve. The parameter will be calculated by linear least–squares regression analysis using at least three points during the terminal log–linear phase, and "best fit" rule.

- $t_{1/2}$ (h) – Apparent first–order terminal elimination half–life will be calculated as $t_{1/2} = \ln 2 / \lambda_z$. $t_{1/2} = \ln 2 / \lambda_z$.

- CL/F (L/h) – Apparent total body clearance following extravascular administration will be estimated as $CL/F = \frac{Dose}{AUC_{0-inf}}$.

- V_z/F - Apparent volume of distribution will be estimated as $V_z/F = \frac{CL/F}{\lambda_z}$.

8.1.3 Dose proportionality (SAD)

Dose-proportionality for PK parameters of OT and B-OT ($AUC_{0-\infty}$, AUC_{0-last}, and C_{max}) will be assessed by the power model [6]. The slope and the associated 90% CI will be reported. For the first 2 low doses where only 3 subjects are enrolled, no dose proportionality will be assessed. The key modelling assumption is that the logarithm of the PK variable is linearly related to logarithm of dose:

$$\log(PK\ parameter) = \alpha + \beta.\log(Dose)\ .$$

Let X_l is the lowest dose, and X_h is the highest dose, respectively. The predicted geometric mean of the highest dose is $e^{\alpha} X_h^{\beta}$ and that of the lowest dose is $e^{\alpha} X_l^{\beta}$.. Dose proportionality may be defined as the ratio $e^{\alpha} X_h^{\beta} / e^{\alpha} X_l^{\beta} = X_h / X_l$ which can be rewritten as: $\left(X_h / X_l\right)^{\beta-1} = r^{\beta-1}$, where r is the ratio of the highest dose to the lowest dose in the study.

Lower and upper limits may be defined as: $\vartheta_l < r^{\beta-1} < \vartheta_h$. This inequality solved for β gives the criterion for proportionality: $1 + \frac{\ln(\vartheta_l)}{\ln(r)} < \beta < 1 + \frac{\ln(\vartheta_h)}{\ln(r)}$.

Dose proportionality would be declared when the (1-2α)*100% CI for β lies entirely within the critical region $\left(1 + \frac{\ln(\vartheta_l)}{\ln(r)}; 1 + \frac{\ln(\vartheta_h)}{\ln(r)}\right)$.

Consequently, the dose proportionality of a certain exposure measure of the active ingredient for a given drug product can be concluded at the a significance level if the 100(1-2a)% confidence interval for β is completely contained within critical region.
SAS/REG[1] procedure will be used to estimate the regression coefficient and its 90% CI.

If the power model has failed to converge and the ANOVA has become the primary analysis, dose proportionality will be concluded if 90% confidence intervals for dose normalised Cmax and AUC are contained in the 80 to 125% range of the reference dose.
A reference dose as well as a maximal dose will be fixed by the Sponsor.
Following log-transformation, dose normalised AUC and Cmax will be analysed using a mixed model appropriate to the parallel study design. Each dose will be compared with the reference dose on a pairwise basis, linear contrasts will be used. The geometric mean ratios for each dose level will be compared to the reference dose. If the confidence intervals include unity, then there is no evidence to suggest the relationship between the test dose and the reference dose is not dose proportional. If the lower confidence interval lies only just below 1, this may be an indication that the true response at this level is slightly more than dose proportional compared to the reference dose level.
SAS/MIXED will be used to estimate ANOVA parameters.

[1] ***Note***. For obtaining confidence intervals, the analysis of the raw ratio in the linear regression model relies on the use of Fieller's method, whereas it is straightforward in the power model. Also, the confidence intervals based on the power model are relatively narrower than with the ANOVA model because dose order and values are ignored in the latter [7].

8.2 MAD part

8.2.1 Steady-State

Steady-state will be assessed by visual inspection of the pre-dose concentrations on Days 4, 5, 6 and 7.

8.2.2 General Consideration

The PK parameters will be derived individually for each volunteer from drug concentrations in blood samples. Values below or above the limit of quantification, if any, will be indicated as such and will be taken into account for the calculation of pharmacokinetic parameters after confirming or correcting the relevant value. Blood samples will be taken according to the schedule given in Table 2. (see sec.10.2 below)
Actual blood sampling time points will be used for individual calculations and presentations. Nominal times will be used for calculations and presentations of summarised data.
Descriptive statistics will be calculated for PK parameters on Day 1 ($AUC_{0-\tau}$, C_{max}, t_{max}), on Day 7 at steady-state ($C_{max,ss}$, $t_{max,ss}$, , CL_{ss}/F, V_{ss}/F, Swing, PTF%, C_{trough}, C_{av}, C_{min}), and in addition AUC_{0-last}, λ_Z, $t_{1/2}$, and AUC_{0-inf} using Phoenix WinNonlin 8.3. A non-compartmental model will be assumed for all parameters.
In cases where the λ_z rate is not assigned, the values of AUC_{0-inf} and $t_{1/2}$ will not be estimated and will be reported as "Not calculated".
Graphical images will be given as individual and overlaying (pooled) plots by treatment. Linear and semi-logarithmic views will be produced.
All plasma concentrations and derived PK parameters for each treatment will be listed and summarized descriptively (mean values (arithmetic and geometric), standard deviations, minimum and maximum values, medians, and valid Ns for the calculated variables). Coefficient of variation (CV%) of the arithmetic and geometric mean values will also be presented. 95% CI for arithmetic mean will be given where possible.
Accumulation ratios on the base of C_{max} and on AUC will be calculated.

8.2.3 Computation formulas (MAD)

Pharmacokinetic parameters will be calculated assuming a non-compartmental model as follows:

i) On Day 1 and at steady-state

- $AUC_{0-\tau}$ (h.ng/mL) – Area Under the Curve over a dosing interval, as calculated by the linear trapezoidal method:

$$AUC_{0-\tau} = AUC_{i-1} + \frac{C_i - C_{i-1}}{2} * (t_i - t_{i-1}),$$

where C_i is the value of observed plasma concentration at moment t_i.

- $C_{max,ss}$ (ng/mL) - Maximum plasma concentration at steady state.

- $t_{max,ss}$ (h) – Time until $C_{max,ss}$ is reached.

- Swing(%) - The degree of fluctuation over one dosing interval at steady state: $Swing(\%) = \frac{C_{max,ss} - C_{min,ss}}{C_{min,ss}} \times 100$.

- PTF% - Peak to Trough Fluctuation within a complete dosing interval at steady state: $PTF(\%) = \frac{C_{max,ss} - C_{min,ss}}{C_{av}} \times 100$.
- CL_{ss}/F (L/h) – Apparent total body clearance following extravascular administration: $CL_{ss} / F = \frac{Dose}{AUC_{0-\tau}}$.
- V_{ss}/F - Apparent volume of distribution: $V_{ss} / F = \frac{CL_{ss} / F}{\lambda_z}$, where λ_z is terminal elimination rate constant estimated from corresponding single dose.
- $C_{through}$ - Concentration reached immediately before the last dose is administered.
- C_{av} - Average concentration over a dosing interval: $C_{av} = \frac{AUC_{0-\tau}}{\tau}$.

- $C_{min,ss}$ - Minimum observed concentration over a dosing interval.

ii) After Day 7: formulae are similar to those given in sec. 8.1.2 for single dose.

8.2.4 Accumulation ratios

Two accumulation ratios will be computes:

i) $Ra(AUC) = \frac{AUC_{\tau}}{AUC_{\tau 1}}$, $AUC_{\tau 1}$ is AUC for single dose on the dosing interval;

ii) $Ra(C_{max}) = \frac{C_{max,ss}}{C_{max}}$, C_{max} is maximal concentration for single dose.

8.2.5 Dose proportionality (MAD)

On Day 7, dose-proportionality for PK parameters of OT and B-OT ($AUC_{0-\tau}$, and $C_{max,ss}$) will be assessed by the power model [6]. The slope and the associated 90% CI will be reported. The same approach will be applied as for SAD (sec.8.1.3).

9. EVALUATION OF EFFICACY PARAMETERS

Not applicable.

10. EVALUATION OF PHARMACODYNAMIC PARAMETERS

The exploratory endpoints of the study are to evaluate the pharmacodynamics (PD) by measuring the transketolase activity in erythrocytes (SAD part of the study) or white blood cells (MAD part of the study).
All pharmacodynamic results will be presented and explored according to the dose administrated after the end of SAD and MAD parts of the study. If PD results are available at the end of the SAD and MAD part of the study, these will be listed where applicable.

10.1 SAD part

Descriptive statistics (n, arithmetic mean, standard deviation [SD], maximum, median, and minimum) will be reported for each time point. Individual and mean concentration time data will also be plotted.
LoQ and missing concentrations will be treated as is stated in section 5.9.1.
Blood samples will be taken according to the schedule given in Table 1.

Table 1. PK/PD SAMPLING TIMEPOINTS: SAD Part

PK sample timepoint (hr.)	Allowed time deviation	PD sample timepoint (hr.)	Allowed time deviation
Pre-dose (35 min before dosing)	+/- 5 min	Pre-dose (35 min before dosing)	+/- 5 min
0.25	+/- 5 min	-	-
0.5	+/- 5 min	-	-
0.75	+/- 5 min	-	-
1.0	+/- 5 min	1.0	+/- 5 min
1.5	+/- 5 min	-	-
2	+/- 5 min	2.0	+/- 5 min
4	+/- 10 min	4.0	+/- 10 min
8	+/-15 min	8.0	+/-15 min
12	+/- 30 min	12	+/- 30 min
24	+/- 1 hr	24	+/- 1hr
36	+/- 1 hr	-	-
48	+/- 1hr	48	+/- 1hr
72	+/- 1hr	72	+/- 1hr
168	+/- 2 hr	168	+/- 2 hr

10.2 MAD part

Descriptive statistics (n, arithmetic mean, standard deviation [SD], maximum, median, and minimum) will be reported for each time point. Individual and mean concentration time data will also be plotted.
LoQ and missing concentrations will be treated as is stated in section 5.9.1.

Blood samples will be taken according to the schedule given in Table 2.

Table 2. PK/PD SAMPLING TIMEPOINTS: MAD Part

Day	PK sample timepoint (hr.)	Allowed time deviation	PD sample timepoint (hr.)	Allowed time deviation
1	Pre-dose (35 min before dosing)	+/- 5 min	Pre-dose (35 min before dosing)	+/- 5 min
	0.25	+/- 5 min	-	-
	0.5	+/- 5 min	-	-
	0.75	+/- 5 min	-	-
	1.0	+/- 5 min	1.0	+/- 5 min
	1.5	+/- 5 min	-	-
	2	+/- 5 min	2.0	+/- 5 min
	4	+/- 10 min	4.0	+/- 10 min
	8	+/-15 min	8.0	+/-15 min
	12	+/- 30 min	12	+/- 30 min
2	Pre-dose (24 hr after last dosing)	+/- 30 min	Pre-dose (24 hr after last dosing)	+/- 30min
3	Pre-dose (24 hr after last dosing)	+/- 30 min	-	
4	Pre-dose (24 hr after last dosing)	+/- 30 min	Pre-dose (35 min before dosing) - - - 1.0 - 2.0 4.0 8.0 12.0	+/- 30 min
5	Pre-dose (24 hr after last dosing)	+/- 30 min	Pre-dose (24 hr after last dosing)	
6	Pre-dose (24 hr after last dosing)	+/- 30 min	-	
7	Pre-dose (24 hr after last dosing)	+/- 10 min	Pre-dose (24 hr after last dosing)	+/- 10 min
	0.25	+/- 5 min	-	-
	0.5	+/- 5 min	-	-

Day	PK sample timepoint (hr.)	Allowed time deviation	PD sample timepoint (hr.)	Allowed time deviation
	0.75	+/- 5 min	-	-
	1.0	+/- 5 min	1.0	+/- 5 min
	1.5	+/- 5 min	-	-
	2	+/- 5 min	2.0	+/- 5 min
	4	+/- 10 min	4.0	+/- 10 min
	8	+/-15 min	8.0	+/-15 min
	12	+/- 30 min	12	+/- 30 min
8	24 hr after last dosing	+/- 30 min	24 hr after last dosing	+/- 30 min
11	96 hr after last dosing	+/- 4hr	-	-
14	168 hr after last dosing	+/- 4hr	-	-

11. EVALUATION OF SAFETY PARAMETERS

The common adverse events and adverse drug reactions, if any, laboratory test changes and other safety parameters (vital signs, 12-lead ECG) will be identified and classified by study groups.
Serious adverse events, if any, will be identified and classified by study groups.

11.1 Adverse Events

Adverse events, if any, will be summarized according to the treatment arm and tabulated by MedDRA System Organ Class and Preferred Term, as well as by relationship to treatment. Serious adverse events and deaths will be listed by patient. The Preferred Term and the corresponding Body Systems for each occurrence of adverse event will be determined and recorded.
The summaries of related events will include those events determined by the investigator to be related (certainly related, probable, or possible) and not related (unlikely or unrelated) to study medication. Events for which causality was unknown will be included in the summary as related.

11.1.1 Brief summary of adverse events

Tables and Listings will be presented for the adverse events. The AE listing will contain: verbatim term, system organ class, start and stop date, duration of AE, outcome, severity, relation to the study drug, action taken, concomitant therapy. The column “Adverse Event” in all the listings will contain the verbatim term obtained from the CRF pages. Listings will include TEAEs and Non-TEAEs with TEAEs respective Non-TEAEs indicated.

11.1.2 Display of Adverse Events

Adverse events will be summarized by intensity (Mild, Moderate and Severe) and relationship to study drug (Unrelated, Unlikely, Possible, Probable and Certain). Wherever relationship to study drug is reported as certainly related, possible or probable, the adverse event will be considered as related to study drug. Adverse events for which assessment of causality have not been completed will also be taken into account as related adverse events. All other adverse events will be considered as not related to study drug. All the percentages will be calculated with respect to the number of patients in the respective treatment group.
Number and percent of distinct adverse events reported during the study will be displayed in tables. The overall incidence and summary of TEAEs will be presented by System Organ Class (SOC) and Preferred Term (PT) and also broken down further by maximum severity.

11.1.3 Analysis of Adverse Events

Summary statistics will be presented for adverse events. These data will be presented per treatment group by counts and percentages. Number (%) of patients with at least one adverse event will be tabulated. The tables will represent the number and percentage of patients with at least one adverse event by preferred term in each treatment group.
For TEAEs leading to discontinuation of study medication, summaries of incidence rates (frequencies and percentages) by SOC and PT will be prepared. For serious TEAEs, a summary of serious TEAEs by SOC and PT will be prepared.

11.1.4 Listing of adverse events by patient

There will be provided a listing of the adverse events by treatment.

11.2 Clinical Laboratory Evaluation

All laboratory evaluations and abnormalities will be listed separately for each treatment arm. The number (%) of patients with clinical abnormalities pertaining to the laboratory parameters will be further summarized. Clinical significance of the values will also be listed.

11.2.1 Analysis of Abnormal Laboratory Value

Abnormal values (if any) will be summarized as incidents by treatment group for each test.

11.2.2 Evaluation of Each Laboratory Examination

Summary statistics (i.e. n, mean, standard deviation, median, minimum and maximum) for all laboratory parameters for each treatment group will be given. Frequency tables (number and percentage) will be presented for all categorical variables.

11.3 Vital Signs

Vital signs will be tabulated by treatment groups. Descriptive statistics will be provided and clinical significance will be summarized. No formal statistical tests will be performed. Summary results will be shown in table, and individual data will be listed.

11.4 Concomitant Therapy

The individual results will be given by treatment group. The ATC/DDD Index classification will be used for all concomitant medication with respect to the Anatomical-Therapeutic-Chemical (ATC) classification (Chemical sub-group), ATC code and drug generic name. Summaries will be given where appropriate.

12. GENERAL CONVENTIONS

This section details general conventions to be followed while presenting the tables, listings and figures. The following conventions will be applied to all data presentations and analyses.

- All tables and listings will be displayed in **Courier New 10 pt font** (where possible).
- The size of paper will be A4. Single spacing should be used for all text.
- The font color should be black. No bolding, underlining italics or subscripting will be used.
- All tables, listings and figures will have header sections.
- If needed, some of the tables, listings and figures could have footnote sections.
- Page numbering will appear bottom right and be of form “Page X of Y”.
- The outputs have to be created as per the templates that will be provided along with this analysis plan, in case no changes are needed.
- Treatment groups will be labelled according to dose applied.
- Summary tables and figures will contain a footnote that references any data listings or tables associated with the table (e.g. Source: Listing XX.X.XX).
- The footnotes of tables and listings will be displayed in a separate line of the table or listing, respectively, while the footnote of the figures will be part of the figure display.
- All mean, median, minimum and maximum values will be formatted to one decimal place. Standard deviation will be formatted to two decimal places. More than two decimal places will be represented for results where two decimal places do not render useful information (say, plasma concentrations or terminal rate constant).
- All p-values will be formatted to four decimal places. More than four decimal places will be used for results where three decimal places do not render useful information.
- 95% CI values will be formatted to two decimal places.
- The number and percentage of responses will be presented in the form XX (Y.Y) where the percentage is in the parentheses.
- All summary tables will include the total number of subjects in the population that is being analyzed. This information will be given in the column headings in each table.
- All listings will be ordered by treatment group, subject number, and visit number (if applicable).
- Date variables will be formatted as DD/MM/YYYY for presentation, if available.
- Tables, figures and listings will be presented both in landscape and portrait orientation depending on the data displayed.
- Tables, figures and listings design will follow (where possible) recommendations from [4].

13. COMPUTATIONS

All mathematical computations, data manipulations, hypotheses tests, model fitting, table generation and graphical presentations will be done by SAS® [3], current version. WinNonlin® package [1] will be used for the pharmacokinetic parameters' calculation.

14. REFERENCES

1. Phoenix WinNonlin 8.3. Certara, L.P., 210 North Tucker Boulevard Suite 350, St. Louis, MO 63101 USA,1998-2020.
2. SAS Institute Inc., SAS 9.4 Help and Documentation, Cary, NC: SAS Institute Inc., 2002-2017.
3. EMA/CPMP/EWP/QWP/1401/98 Rev.1/Corr**, "GUIDELINE ON THE INVESTIGATION OF BIOEQUIVALENCE", London, UK.
4. PhUSE/CSS, „Analyses and Displays Associated to Non-Compartmental Pharmacokinetics – With a Focus on Clinical Trials", White Paper, Standard Scripts for Analysis and Programming Working Group, 2014.
5. ICH Harmonised Tripartite Guideline, ICH E3 "Structure and content of clinical study reports", 1996.
6. Smith, B.P., Vandenhende, F.R., deSante, K.A., Welch, P.A., Callaghan, J.T., and Forgne, S.T. 2000. Confidence interval criteria for assessment of dose proportionality. Pharmaceutical Research, 17, 1278–1283.
7. Low, Gordon, "Dose proportionality" in Encyclopaedia of Biopharmaceutical Statistics, 4th Edition 2018, CRC Press.

LIST OF SUMMARY TABLES AND PLOTS

I. SAD Part

I.I Tables and Figures

Demographic Data

Table I.14.1.1 Patient Disposition
Figure I.14.1.1 Patient Disposition
Table I.14.1.2 Demographics

Pharmacokinetic and Pharmacodynamic Data

Pharmacokinetics

Table I.14.2.1 Summary of Plasma Concentrations (ng/mL) versus Nominal Sampling Times

Table I.14.2.2 Summary of Pharmacokinetic Parameters

Table I.14.2.3 Statistical Analysis for Pharmacokinetic Parameters

Figure I.14.2.1 Arithmetic means concentration-time plot per treatment

Figure I.14.2.2 Geometric means concentration-time plot per treatment

Figure I.14.2.3 Individual concentration-time profiles - PK

Figure I.14.2.4 Overlaying individual concentration-time profiles – PK

Pharmacodynamics

Table I.14.2.4 Pharmacodynamic Tests: Summary of (ng/mL) versus Nominal Sampling Time

Table I.14.2.5 Summary of Pharmacodynamic Parameters

Figure I.14.2.3 Arithmetic means concentration-time plot per treatment

Figure I.14.2.4 Geometric means concentration-time plot per treatment

Figure I.14.2.5 Individual concentration-time profiles - PD

Figure I.14.2.6 Overlaying individual concentration-time profiles – PD

Safety Data and Adverse events

Table I.14.3.1 Overall Incidence of Treatment Emergent Adverse Events

Table I.14.3.2 Treatment Emergent Adverse Events, by SOC and PT

Table I.14.3.3 Related Treatment Emergent Adverse Events, by SOC and PT

Table I.14.3.4 Treatment Emergent Serious Adverse Events, by SOC and PT

Table I.14.3.5 Summary of Hematology Parameters - Actual Values and Change from Baseline

Table I.14.3.6 Summary of Biochemistry Parameters - Actual Values and Change from Baseline

Table I.14.3.7 Summary of Urinalysis Parameters

Table I.14.3.8 Summary of Vital Signs: Actual Values and Change from Baseline

Table I.14.3.9 Overall ECG Assessment

Table I.14.3.10 Concomitant Therapy by ATC code (if appropriate)

I.II Individual Listings

Listing I.16.2.1.1 Listing of Subjects in Analysis Populations

Listing I.16.2.1.2 Subject Disposition

Listing I.16.2.1.3 Withdrawals from study

Listing I.16.2.1.4 Protocol deviations

Listing I.16.2.4.1 Demographics

Listing I.16.2.4.2 Prior and Concomitant Medications

Listing I.16.2.5.1 Exposure to Study Drug

Listing I.16.2.5.2 Individual PK Blood Sampling Times and Concentrations

Listing I.16.2.5.3 Individual PD Blood Sampling Times and Concentrations

Listing I.16.2.6.1 Pharmacokinetic Parameters

Listing I.16.2.6.2 Pharmacodynamic Parameters

Listing I.16.2.7.1 Adverse Events

Listing I.16.2.7.2 Serious Adverse Events

Listing I.16.2.7.3 Adverse Events Related to Treatment

Listing I.16.2.7.3 Adverse Events with Fatal Outcome

Listing I.16.2.7.3 Adverse Events Leading to Withdrawal

Listing I.16.2.8.1 Clinical Laboratory Evaluations: Hematology, Biochemistry, Serology, and Urinalysis Parameters Including Absolute Changes from Baseline (where applicable)

Listing I.16.2.8.2 Electrocardiogram Results

Listing I.16.2.8.3 Vital Signs Values Including Absolute Changes from Baseline

Listing I.16.2.8.4 Physical examination

Listing I.16.2.8.5 RT-PCR Test

II. MAD Part

II.1 Tables and Figures

Demographic Data

Table II.14.1.1 Patient Disposition
Figure II.14.1.1 Patient Disposition
Table II.14.1.2 Demographics

Pharmacokinetic and Pharmacodynamic Data

Pharmacokinetics

Table II.14.2.1 Summary of Plasma Concentrations (ng/mL) versus Nominal Sampling Times
Table II.14.2.2 Summary of Pharmacokinetic Parameters
Table II.14.2.3 Statistical Analysis for Pharmacokinetic Parameters
Figure II.14.2.1 Pre-dose Arithmetic means concentration-time plot per treatment
Figure II.14.2.2 Arithmetic means concentration-time plot per treatment
Figure II.14.2.3 Geometric means concentration-time plot per treatment
Figure II.14.2.4 Individual concentration-time profiles - PK
Figure II.14.2.5 Overlaying individual concentration-time profiles – PK

Pharmacodynamics

Table II.14.2.4 Pharmacodynamic Tests: Summary of (ng/mL) versus Nominal Sampling Time
Table II.14.2.5 Summary of Pharmacodynamic Parameters
Figure II.14.2.3 Arithmetic means concentration-time plot per treatment
Figure II.14.2.4 Geometric means concentration-time plot per treatment
Figure II.14.2.5 Individual concentration-time profiles - PD
Figure II.14.2.6 Overlaying individual concentration-time profiles – PD

Safety Data and Adverse events

Table II.14.3.1 Overall Incidence of Treatment Emergent Adverse Events
Table II.14.3.2 Treatment Emergent Adverse Events, by SOC and PT
Table II.14.3.3 Related Treatment Emergent Adverse Events, by SOC and PT
Table II.14.3.4 Treatment Emergent Serious Adverse Events, by SOC and PT
Table II.14.3.5 Summary of Hematology Parameters - Actual Values and Change from Baseline

Table II.14.3.6 Summary of Biochemistry Parameters - Actual Values and Change from Baseline

Table II.14.3.7 Summary of Urinalysis Parameters

Table II.14.3.81 Summary of Vital Signs: Actual Values and Change from Baseline

Table II.14.3.12 Overall ECG Assessment

Table II.14.3.13 Concomitant Therapy by ATC code (if appropriate)

II.2 Individual Listings

Listing II.16.2.1.1 Listing of Subjects in Analysis Populations

Listing II.16.2.1.2 Subject Disposition

Listing II.16.2.1.3 Withdrawals from study

Listing II.16.2.1.4 Protocol deviations

Listing II.16.2.4.1 Demographics

Listing II.16.2.4.2 Prior and Concomitant Medications

Listing II.16.2.5.1 Exposure to Study Drug

Listing II.16.2.5.2 Individual PK Blood Sampling Times and Concentrations

Listing II.16.2.5.3 Individual PD Blood Sampling Times and Concentrations

Listing II.16.2.6.1 Pharmacokinetic Parameters

Listing II.16.2.6.2 Pharmacodynamic Parameters

Listing II.16.2.7.1 Adverse Events

Listing II.16.2.7.2 Serious Adverse Events

Listing II.16.2.7.3 Adverse Events Related to Treatment

Listing II.16.2.7.3 Adverse Events with Fatal Outcome

Listing II.16.2.7.3 Adverse Events Leading to Withdrawal

Listing II.16.2.8.1 Clinical Laboratory Evaluations: Hematology, Biochemistry, Serology, and Urinalysis Parameters Including Absolute Changes from Baseline (where applicable)

Listing II.16.2.8.2 Electrocardiogram Results

Listing II.16.2.8.3 Vital Signs Values Including Absolute Changes from Baseline

Listing II.16.2.8.4 Physical examination

Listing II.16.2.8.5 RT-PCR Test