# TRIAL STATISTICAL ANALYSIS PLAN

| | |
|---|---|
| **Document No.:** | **228892_2697669_1.0** |
| **BI Trial No.:** | **1305-0029** |
| **Title:** | Relative bioavailability of two different formulations of nerandomilast and investigation of the food effect on new formulation following oral administration in healthy adult male and female subjects (an open-label, randomised, single-dose, three-way crossover trial)<br>(Protocol Version 1.0 [c43260621-01]) |
| **Investigational Product:** | BI 1015550, nerandomilast |
| **Responsible trial statistician:** | [redacted]<br>Phone: [redacted]<br>Fax: [redacted] |
| **Date of statistical analysis plan:** | 17 JAN 2025 |
| **Version:** | 1.0 |

# 1. TABLE OF CONTENTS

# LIST OF TABLES

# 2. LIST OF ABBREVIATIONS

See Medicine Glossary:
http://glossary

| Term | Definition / description |
|---|---|
| ADA | Anti-drug Antibody |
| ADS | Analysis data set |
| AE | Adverse event |
| AESI | Adverse events of special interest |
| ALT | Alanine Aminotransferase |
| ANOVA | Analysis of Variance |
| AST | Aspartate Aminotransferase |
| $AUC_{0-\infty}$ | Area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity |
| $AUC_{0-tz}$ | Area under the concentration-time curve of the analyte in plasma over the time interval from 0 to the last quantifiable data point |
| BI | Boehringer Ingelheim |
| BMI | Body mass index |
| BP | Blood pressure |
| CDR | Clinical Data Repository |
| CI | Confidence interval |
| $C_{max}$ | Maximum measured concentration of the analyte in plasma |
| CRF | Case report form |
| CSD | Company Standard Displays |
| CT | Concomitant therapy |
| CTP | Clinical Trial Protocol |
| CTR | Clinical Trial Report |
| CV | Arithmetic Coefficient of Variation |
| DILI | Drug induced liver injury |
| ECG | Electrocardiogram |
| eDMS | Electronic documentation management system |
| gCV | Geometric Coefficient of Variation |
| gMean | Geometric Mean |

| Term | Definition / description |
|---|---|
| INR | International Normalization Ratio |
| iPD | Important protocol deviation |
| Max | Maximum |
| MedDRA | Medical Dictionary for Drug Regulatory Activities |
| Min | Minimum |
| N | Number non-missing observations |
| Nobs | Number of observations |
| P10 | 10$^{th}$ percentile |
| P90 | 90$^{th}$ percentile |
| PD | Pharmacodynamic |
| PK | Pharmacokinetic |
| PKS | Pharmacokinetic parameter analysis set |
| PR | Pulse rate |
| PT | Preferred term |
| Q1 | 1$^{st}$ quartile |
| Q3 | 3$^{rd}$ quartile |
| R | Reference treatment |
| RAGe | Report Appendix Generator system |
| REP | Residual Effect Period |
| RPM | Report Planning Meeting |
| SD | Standard Deviation |
| SOC | Primary system organ class |
| T | Test treatment |
| TB | Total bilirubin |
| $t_{max}$ | Time from (last) dosing to the maximum measured concentration of the analyte in plasma |
| [redacted] | |
| TS | Treated set |
| TSAP | Trial Statistical Analysis Plan |
| ULN | Upper Limit of Normal |
| WHO-DD | World Health Organization Drug Dictionary |
| $\lambda_z$ | Terminal rate constant of the analyte in plasma |

# 3. INTRODUCTION

As per ICH E9 (1), the purpose of this document is to provide a more technical and detailed elaboration of the principal features of the analysis described in the protocol, and to include detailed procedures for executing the statistical analysis of the primary and secondary variables and other data.

This trial statistical analysis plan (TSAP) assumes familiarity with the Clinical Trial Protocol (CTP), including Protocol Amendments. In particular, the TSAP is based on the planned analysis specification as written in CTP Section 7 “Statistical Methods and Determination of Sample Size”. Therefore, TSAP readers may consult the CTP for more background information on the study, e.g., on study objectives, study design and population, treatments, definition of measurements and variables, planning of sample size, randomization.

All EDC and non-EDC data for the study are stored on the validated, secured, standardized, and harmonized Clinical Reporting Environment (CRE).

Pharmacokinetic (PK) parameters will be calculated using Phoenix WinNonlin™ software (version 8.1.1 or higher, [redacted] or SAS Version 9.4 (or later version).

The statistical analyses will be performed within the validated working environment CARE, including SAS™ (current Version 9.4, b [redacted], and a number of SAS™-based tools (e.g., macros for the analyses of AE data or laboratory data; Report Appendix Generator system (RAGe) for compilation/formatting of the Clinical Trial Report (CTR) appendices).

# 4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

All analyses as planned in the CTP will be performed and are described in more detail in this TSAP.

# 5. ENDPOINTS

## 5.1 PRIMARY ENDPOINTS

**Section 2.1.2 of the CTP:**

*The following pharmacokinetic parameters will be determined for nerandomilast:*

- *$AUC_{0\text{-}tz}$ (area under the concentration-time curve of the analyte in plasma over the time interval from 0 to the last quantifiable data point)*
- *$C_{max}$ (maximum measured concentration of the analyte in plasma)*

## 5.2 SECONDARY ENDPOINTS

### 5.2.1 Key secondary endpoints

This section is not applicable as no key secondary endpoints have been defined in the CTP.

### 5.2.2 Secondary endpoint

**Section 2.1.3 of the CTP:**

*The following pharmacokinetic parameter will be determined for nerandomilast:*

- *$AUC_{0\text{-}\infty}$ (area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity)*

# 6. GENERAL ANALYSIS DEFINITIONS

## 6.1 TREATMENTS

For basic study information on treatments to be administered, assignment of treatment groups, selection of doses, refer to CTP Sections 3 and 4.

**Section 3.1 of the CTP:**

*The trial will be performed as a randomised, open-label, three-way crossover trial in healthy male and female subjects in order to compare the test treatment 1 (T1) to the reference treatment (R) and to compare test treatment 2 (T2) to test treatment 1 (T1).*

[…]

*The subjects will be randomly allocated to one of the 3 treatment sequences: R-T1-T2, T1-T2-R, or T2-R-T1. There will be a washout period of at least 7 days between the treatments (referring to day 1). In each treatment period (1, 2, 3), the subject is planned to receive 1 single dose of medication (R, T1, or T2).*

It is planned to include 15 healthy male and female subjects in the trial.

For details of dosage and formulation see Table 6.1: 1 below.

Table 6.1: 1 Treatments and labels used in the analysis

| Treatment | | Short label |
|---|---|---|
| R | BI 1015550 (nerandomilast), film-coated tablet, formulation C1 (adult), 1 x 18 mg, once, in fasting state | Nera 18 mg C1 fasted (R) |
| T1 | BI 1015550 (nerandomilast), film-coated tablet, paediatric formulation, 18 x 1 mg (= 18 mg), once, in fasting state | Nera 18 mg ped fasted (T1) |
| T2 | BI 1015550 (nerandomilast), film-coated tablet, paediatric formulation, 18 x 1 mg (= 18 mg), once, in fed state | Nera 18 mg ped fed (T2) |

**Section 1.2.1 of the CTP:**

*The Residual Effect Period (REP) of nerandomilast is 7 days. This is the period after the last dose with measurable drug levels and / or pharmacodynamic effects still likely to be present.*

Based on this, the following study phases will be defined for the analysis of adverse events (AEs) and vital signs:

- **Screening**
  - Ranging from 0:00 h on day of informed consent until time of first drug administration.

- **On-treatment** (labelled with short label)

  - Ranging from time of respective drug administration until 7 days (168 h) thereafter OR until next drug administration OR until trial termination (0:00 h on the day after trial termination), whatever occurs first.

- **Follow-up** (labelled "F/U")
  - Ranging from the end of REP until the next drug administration OR until trial termination (0:00 h on the day after trial termination), whatever occurs first.

**Section 7.2.5 of the CTP:**

*Note that AEs occurring after the last per protocol contact but entered before database lock will be reported to Pharmacovigilance only and will not be captured in the trial database.*

The following AE displays will be provided in the CTR:

In Section 9.3 and Appendix 10.5.1.8 (for ClinicalTrials.gov and EudraCT only) of the CTR displays, the on-treatment phase will be analysed (labelled with the short label of the study treatments as in Table 6.1: 1). The screening and follow-up phases will not be included in this analysis.

The following totals will be provided in addition for AE outputs for Section 9.3:

- a total over all on-treatment phases (**"Total"**)

In Section 9.4 and Appendix 10.6 (Listings) of the CTR displays, the screening period, as well as the follow-up phases will additionally be included and no totals will be provided.

For detailed information on the handling of the treatments refer to Technical TSAP ADS (analysis data set) plan and Analysis Data Reviewers guide.

## 6.2 IMPORTANT PROTOCOL DEVIATIONS

Data discrepancies and deviations from the CTP will be identified for all treated subjects. Consistency check listings (for identification of deviations of time windows) and a list of protocol deviations (e.g. deviations in drug administration, in blood sampling times, etc.) will be provided to be discussed at the Report Planning Meeting (RPM). At this meeting, all manual deviations identified at the sites by the Clinical Research Associates (CRAs) and deviations too complex to program will be reviewed by the trial team to decide which are considered important. For definition of important protocol deviations (iPD), and for the process of identification of these, refer to the Boehringer Ingelheim (BI) SOP "Identify and Manage Important Protocol Deviations (iPD)" (2).

IPD categories will be suggested in the iPD specification file, iPDs will be identified no later than in the RPM, and the iPD categories will be updated as needed.

If any iPDs are identified, they are to be summarised into categories and will be captured in the iPD specification file (DV domain) (3) and in the decision log (4). Both documents will be stored within the TMF in eDMS.

The iPDs will be summarized and listed in the CTR.

## 6.3 INTERCURRENT EVENTS

This section is not applicable.

## 6.4 SUBJECT SETS ANALYSED

**Section 7.2.1.1 of the CTP:**

*Statistical analyses will be based on the following analysis sets:*

- *Treated set (TS): The treated set includes all subjects who were treated with at least one dose of trial drug. The treated set will be used for safety analyses.*
- *Pharmacokinetic parameter analysis set (PKS): This set includes all subjects in the treated set (TS) who provide at least one PK endpoint that was defined as primary or secondary and was not excluded due to a protocol deviation relevant to the evaluation of PK or due to PK non-evaluability (as specified* below*). Thus, a subject will be included in the PKS, even if he/she contributes only one PK parameter value for one period to the statistical assessment. Descriptive and model-based analyses of PK parameters will be based on the PKS.*

**Section 7.2.1.2 of the CTP:**

*The pharmacokinetic parameters listed in* CTP *Section 2.1 and 2.2.2 for drug nerandomilast will be calculated according to the relevant BI internal procedures.*

*Plasma concentration data and parameters of a subject will be included in the statistical pharmacokinetic (PK) analyses if they are not flagged for exclusion due to a protocol deviation relevant to the evaluation of PK (to be decided no later than in the Report Planning Meeting) or due to PK non-evaluability (as revealed during data analysis, based on the criteria specified below). Exclusion of a subject's data will be documented in the CTR.*

*Important protocol deviations may be*

- *Incorrect trial medication taken, i.e. the subject received at least one dose of trial medication the subject was not assigned to*
- *Incorrect dose of trial medication taken*
- *Use of restricted medications*

*Plasma concentrations and/or parameters of a subject will be considered as non-evaluable, if for example*

- *The subject experienced emesis that occurred at or before two times median $t_{max}$ of the respective treatment (Median $t_{max}$ is to be determined excluding the subjects experiencing emesis),*
- *A predose concentration is >5% $C_{max}$ value of that subject*
- *Missing samples/concentration data at important phases of PK disposition curve*

*Plasma concentration data and parameters of a subject which are flagged for exclusion will be reported with its individual values but will not be included in the statistical analyses. Descriptive and inferential statistics of PK parameters will be based on the PKS.*

*Only concentration values within the validated concentration range and actual sampling times will be used for the calculation of pharmacokinetic parameters. Concentrations used in the pharmacokinetic calculations will be in the same format provided in the bioanalytical report, (that is, to the same number of decimal places provided in the bioanalytical report).*

Table 6.4: 1 Subject sets analysed

| | **Subject analysis set** | |
|---|---|---|
| Class of endpoint/analysis | TS | PKS |
| Primary and secondary endpoints | | X |
| Analysis of further PK parameters | | X |
| Safety assessments | X | |
| Disposition | X | |
| Demographic/baseline characteristics | X | |
| Important protocol deviations | X | |
| Exposure | X | |

[redacted]

## 6.6 HANDLING OF MISSING DATA AND OUTLIERS

Handling of missing data and outliers will be performed as described in the CTP, Section 7.3.

It is not planned to impute missing values for safety parameters. Nevertheless, missing or incomplete AE dates are imputed according to BI standards (see “Handling of Missing and Incomplete AE Dates” (5)).

Missing data and outliers of PK data are handled according to BI standards (see “Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics” (6) and “Noncompartmental Pharmacokinetic / Pharmacodynamic Analyses of Clinical Studies” (7)).

PK parameters that cannot be reasonably calculated based on the available drug concentration-time data will not be imputed.

## 6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

Baseline for vital signs is defined as the last measurement before drug administration in each treatment period.

**Section 6.1 of the CTP:**

*Study measurements and assessments scheduled to occur 'before' trial medication administration on Day 1 are to be performed and completed within a 3 h-period prior to the trial drug administration.*

*If not stated otherwise in the* CTP *Flow Chart, the acceptable deviation from the scheduled time for vital signs, AE questioning and laboratory tests will be ± 60 min.*

*If scheduled in the* CTP *Flow Chart at the same time as a meal, blood sampling, vital signs, and 12-lead ECG recordings have to be done first. Furthermore, if several measurements including venipuncture are scheduled for the same time, venipuncture should be the last of the measurements due to its inconvenience to the subject and possible influence on physiological parameters. In all periods subjects may have their dinner together.*

*For planned blood sampling times, refer to the* CTP *Flow Chart. While these nominal times should be adhered to as closely as possible, the actual sampling times will be recorded and used for the determination of pharmacokinetic parameters. Starting from 58h after dosing a tolerance of ± 120 minutes is given for all procedures.*

*If a subject misses an appointment, it will be rescheduled if possible. The relevance of measurements outside the permitted time windows will be assessed no later than at the Report Planning Meeting.*

Adherence to time windows will be checked via the consistency check listings at the RPM.

Unscheduled measurements of laboratory data and vital signs data will be assumed to be repeat measurements of the most recent scheduled measurement (e.g. for follow-up or confirmation of a particular value). Therefore, unscheduled measurements will be assigned to the planned time point of the previous scheduled measurement.

# 7. PLANNED ANALYSIS

Safety analysis (refer to Section 7.8) will be performed by [redacted] and will be presented in Sections 9.1 to 9.4 of the CTR and in Appendix 10.6 and 10.5.1.

Inferential statistical analyses of PK endpoints (refer to Section 7.4 and Section 7.5.2) will also be performed by [redacted] and will be presented in Section 9.5 of the CTR and in Appendix 10.5.3.

Descriptive data analysis of PK endpoints and concentrations will be performed by the [redacted] at [redacted] The results will be presented in Section 9.6 of the CTR and Appendix 10.5.5.

The format of the listings and tables will follow the BI standards (see "Standards for Reporting of Clinical Trials and Project Summaries" (8)) with the exception of those generated for PK-calculations following BI standards for PK/PD analysis (9).

The individual values of all subjects will be listed, sorted by treatment sequence, subject number, visit and time point. The listings will be included in Appendix 10.6 of the CTR.

For end-of-text tables, the set of summary statistics for non-PK parameters is:

| | |
|---|---|
| N | number non-missing observations |
| Mean | arithmetic mean |
| SD | standard deviation |
| Min | minimum |
| Median | median |
| Max | maximum |

For analyte concentrations and PK parameters, the following descriptive statistics will additionally be calculated:

| | |
|---|---|
| Nobs | number of observations |
| CV | arithmetic coefficient of variation |
| gMean | geometric mean |
| gCV | geometric coefficient of variation |
| P10 | $10^{th}$ percentile |
| Q1 | $1^{st}$ quartile |
| Q3 | $3^{rd}$ quartile |
| P90 | $90^{th}$ percentile |

The data format for descriptive statistics of concentrations will be identical to the data format of the respective concentrations. The descriptive statistics of PK parameters will be calculated using the individual values with the number of decimal places as provided by the evaluation program. Then the individual values as well as the descriptive statistics will be reported with three significant digits in the CTR.

Descriptive statistics of PK parameters will be calculated if $n \geq 2$.

The gMeans and gMean ratio based on the inferential statistics will be reported with maximum of 2 decimal places.

Tabulations of frequencies for categorical data will include all possible categories available in the CRF and will display the number of observations in a category, as well as the percentage

(%). The precision for percentages should be one decimal point, unless the denominator is smaller than 100 (in all treatment columns), in which case percentages are given in integer numbers. The category 'missing' will be displayed only if there are actually missing values.

Units of variables should be given in the titles or column/row descriptors in brackets (e.g. (mg)).

Exclusion of PK parameters

The ADS "ADPP" (PK parameters) contains column variables APEX and APEXCO indicating inclusion/exclusion (APEX) of a PK parameter and an analysis flag comment (APEXCO). All analyses based on the PKS will include parameters only if they are not flagged for exclusion, that is APEX is equal to "Included".

Exclusion of PK concentrations

The ADS "ADPC" (PK concentrations per time-point or per time-interval) contains column variables ACEX and ACEXCO indicating inclusion/exclusion (ACEX) of a concentration and an analysis flag comment (ACEXCO). Exclusion of a concentration depends on the analysis flag comment ACEXCO. For example, if ACEXCO is set to 'ALL CALC', the value will be excluded for all types of analyses based on concentrations. If ACEXCO is set to 'DESC STATS' the value will be excluded from descriptive evaluations per planned time point/time interval. If ACEXCO contains the addition 'TIME VIOLATION' or 'TIME DEVIATION' the value can be used for further analyses based on actual times. If ACEXCO is set to 'HALF LIFE', the value will be excluded from half-life calculation (and, as a consequence, any calculation that relies on $\lambda_z$) only; the value is included for all other analyses.

Further details are given in "Noncompartmental Pharmacokinetic / Pharmacodynamic Analyses of Clinical Studies" (7) and "Description of Analytical Transfer Files, PK/PD Data files and ADA files" (10).

## 7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Only descriptive statistics are planned for this section of the report, based on the TS.
The data will be summarised by treatment sequence and in total.

## 7.2 CONCOMITANT DISEASES AND MEDICATION

Frequency tables are planned for this section of the report, based on the TS.

Concomitant diseases and non-drug therapies will be coded according to the version defined in the decision log (4) of the coding system of the Medical Dictionary for Drug Regulatory Activities (MedDRA). Concomitant medications will be coded according to the most recent version of the World Health Organization Drug Dictionary (WHO-DD). The coding version number will be displayed as a footnote in the respective output.

**Section 7.2.5 of the CTP:**

*Previous and concomitant therapies will be presented per treatment without consideration of treatment periods.*

A therapy will be considered concomitant to the study treatment, if it

- is ongoing at the time of study drug administration, or

- starts within the on-treatment phase of the respective treatment (see Section 6.1 for a definition of treatments and study phases).

The diagnoses, non-drug therapies and medications will be listed. Subjects without any concomitant diagnoses or concomitant therapies will be marked with a “No” in the respective column.

The relevance of the concomitant therapies to the evaluation of PK data will be decided no later than at the RPM.

## 7.3 TREATMENT COMPLIANCE

**Section 4.3 of the CTP:**

*Compliance will be assured by administration of all trial medication in the trial centre under supervision of the investigating physician or a designee. The measured plasma concentrations of trial medication will provide additional confirmation of compliance.*

It is not intended to list the compliance separately. Any deviations from complete intake will be addressed in the RPM and described in the CTR.

## 7.4 PRIMARY OBJECTIVE ANALYSIS

Independent of the main objectives stated in the CTP, this section describes further details of the primary endpoint analyses outlined in the CTP.

### 7.4.1 Main analysis

**Section 7.2.2 of the CTP:**

*Primary analyses*

*The two main objectives of this trial, see* CTP *Section 2.1.1, will be analysed according to the statistical model described below. However, the statistical model will be applied only to data that contribute to the particular comparison of interest.*

*The statistical model used for the analysis of the primary endpoints will be an analysis of variance (ANOVA) model on the logarithmic scale. That is, the PK endpoints will be log-transformed (natural logarithm) prior to fitting the ANOVA model. This model will include effects accounting for the following sources of variation: sequence, subjects within sequences, period and treatment. The effect 'subjects within sequences' will be considered as random, whereas the other effects will be considered as fixed.*

*The model is described by the following equation:*

$$y_{ijkm} = \mu + \zeta_i + s_{im} + \pi_j + \tau_k + e_{ijkm}$$ *, where*

$y_{ijkm}$ *= logarithm of response measured on subject m in sequence i receiving treatment k in period j,*

$\mu$ *= the overall mean,*

$\zeta_i$ *= the* $i^{th}$ *sequence effect, i = 1, 2, 3,*

*$s_{im}$ = the effect associated with the $m^{th}$ subject in the $i^{th}$ sequence, m = 1, 2, ..., 5,*

*$\pi_j$ = the $j^{th}$ period effect, j = 1, 2, 3,*

*$\tau_k$ = the $k^{th}$ treatment effect, k = 1, 2, 3,*

*$e_{ijkm}$ = the random error associated with the $m^{th}$ subject in sequence i who received treatment k in period j,*

*where $s_{im} \sim N(0, \sigma_B^2)$ i.i.d., $e_{ijkm} \sim N(0, \sigma_W^2)$ i.i.d. and $s_{im}$, $e_{ijkm}$ are independent random variables.*

*Point estimates for the ratios of the geometric means (T1/R respectively T2/T1) for the primary endpoints (see Section 5.1) and their two-sided 90% confidence intervals (CIs) will be provided.*

*For each endpoint, the difference between the expected means for log(T1)-log(R) respectively log(T2)-log(T1) will be estimated by the difference in the corresponding adjusted means (Least Squares Means). Additionally their two-sided 90% confidence intervals will be calculated based on the residual error from the ANOVA and quantiles from the t-distribution. These quantities will then be back-transformed to the original scale to provide the point estimate and 90% CIs for each endpoint.*

The implementation for this analysis will be accomplished by using the CSD macros based on the PKS. The following SAS code can be used:

```
PROC MIXED DATA=indata METHOD=REML;
        CLASS subject treatment sequence period;
        MODEL logpk = treatment sequence period / DDFM=KR;
        RANDOM subject(sequence);
        LSMEANS treatment / PDIFF CL ALPHA=0.1;
RUN;
```

[redacted]

## 7.5 SECONDARY OBJECTIVE ANALYSIS

Independent of the main objectives stated in the CTP, this section describes further details of the secondary endpoint analyses.

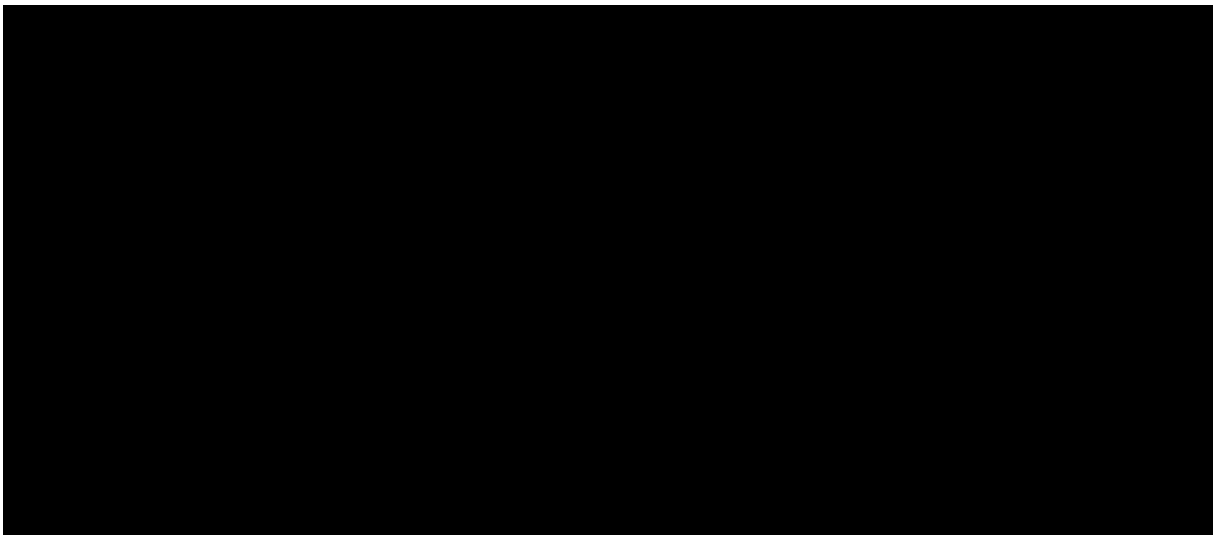
### 7.5.1 Key secondary objective analysis

This section is not applicable as no key secondary endpoint has been specified in the protocol.

### 7.5.2 Secondary objective analysis

**Section 7.2.3 of the CTP:**

*The secondary endpoint (refer to Section 5.2.2) will be calculated according to the relevant BI internal procedures and will be assessed statistically using the same methods as described for the primary endpoints (refer to Section 7.4).*



## 7.7 EXTENT OF EXPOSURE

Descriptive statistics are planned for this section of the report, based on the TS. The date and time of drug administration will be listed for each subject.

## 7.8 SAFETY ANALYSIS

All safety analyses will be performed on the TS.

The safety data for treated subjects who failed to complete the trial (dropouts or withdrawals) will be reported as far as their data are available. All withdrawals will be documented and the reason for withdrawal recorded.

**Section 7.2.5 of the CTP:**

*For all analyses, the treatment actually administered (= treatment at onset) to the subject will be used (any deviations from the randomised treatment will be discussed in the minutes of the Report Planning Meeting).*

### 7.8.1 Adverse Events

AEs will be coded using MedDRA. The coding version number will be displayed as a footnote in the respective output.

Unless otherwise specified, the analyses of AEs will be descriptive in nature. All analyses of AEs will be based on the number of subjects with AEs and NOT on the number of AEs. BI standards as presented in "Analysis and Presentation of Adverse Event Data from Clinical Trials – Display Template" (11) and "Analysis and Presentation of Adverse Event data from clinical trials" (12) will be applied.

The analysis of AEs will be based on the concept of treatment emergent AEs. That means that all AEs will be assigned to 'screening', 'on-treatment' or 'follow-up' phases as defined in Section 6.1. AEs will be analysed based on actual treatments, as defined in Table 6.1: 1.

According to the CTP, adverse events of special interest (AESI) will be analysed:

**Section 5.2.6.1.4 of the CTP:**

*The following are considered as AESIs:*

- *Potential severe DILI*

  *A potential severe Drug Induced Liver Injury (DILI) that requires follow-up is defined by the following alterations of hepatic laboratory parameters:*

  1. *AST (aspartate aminotransferase) and/ or ALT (alanine aminotransferase) elevation ≥3x ULN and TB (total bilirubin) ≥2x ULN measured at the same visit, or in samples drawn within 30 days of each other, OR*
  2. *AST and/ or ALT elevation ≥3x ULN and INR ≥1.5x ULN measured at the same visit, or in samples drawn within 30 days of each other, OR*
  3. *AST and/ or ALT elevation ≥3x ULN with new onset, or worsening of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/ or eosinophilia (>5%), OR*
  4. *AST and/ or ALT elevation ≥5x ULN*

According to ICH E3 (13), in addition to deaths and serious AEs, 'other significant' AEs need to be listed in the CTR. These will be any non-serious AE that led to an action taken with study drug (e.g. discontinuation or dose reduced or interrupted).

An overall summary of AEs will be presented.

The frequency of subjects with AEs will be summarised by treatment, primary system organ class (SOC) and preferred term (PT). Separate tables will be provided for subjects with serious AEs, for subjects with drug-related AEs, for subjects with drug-related serious AEs, for subjects with other significant AEs (according to ICH E3), for subjects with AESIs and for subjects with AEs leading to discontinuation. In addition, the frequency of subjects with AEs will be summarised by worst intensity, treatment, primary SOC and PT.

The system organ classes will be sorted by default alphabetically, PTs will be sorted by descending frequency (within SOC).

For disclosure of AEs on ClinicalTrials.gov and EudraCT, additional information not included in a standard AE analysis will be performed. The following three entries will be created:

- Adverse Events per arm for disclosure on CTgov/EudraCT
- Non-serious Adverse Events (>5%) for disclosure on CTgov/EudraCT
- Serious Adverse Events for disclosure on CTgov/EudraCT

### 7.8.2 Laboratory data

The analyses of laboratory data will be descriptive in nature and will be based on BI standards as presented in "Handling, Display and Analysis of Laboratory Data" (14). Analyses will be based on normalised values, which means transforming to a standard unit and a standard reference range. The original values will be analysed if the transformation into standard unit is not possible for a parameter.

Laboratory data will be analysed qualitatively via comparison of laboratory data to their reference ranges. Values outside the reference range will be highlighted in the listings.

Clinically relevant findings in laboratory data will be reported as baseline conditions (at screening) or as AEs (during the trial) if judged clinically relevant by the investigator, and will be analysed as such.

It is the investigator's responsibility to decide whether a lab value is clinically significantly abnormal or not (at the RPM at the latest).

### 7.8.3 Vital signs

Descriptive statistics over time including change from baseline will be performed for vital signs (blood pressure, pulse rate). In the listing the change from baseline will also be displayed.

For post-dose measurements of vital signs, descriptive statistics will be calculated by planned time point based on the first value of the subject at that planned time point (or assigned to that planned time point). For baseline value, see Section 6.7.

Clinically relevant findings will be reported as baseline conditions (at screening) or as AEs (during the trial) if judged clinically relevant by the investigator, and will be analysed as such.

### 7.8.4 ECG

Clinically relevant abnormal findings will be reported as AEs.

No separate listing or analysis of continuous ECG monitoring will be prepared.

## 7.9 OTHER ANALYSIS

Physical examination

Physical examination findings will be reported as relevant medical history/baseline condition (i.e., a condition already existent before intake of trial drug) or as AEs and will be summarised as such.

No separate listing or analysis of physical examination findings will be prepared.

Meal intake

Data regarding high-fat, high-calorie meal intake will only be listed.

### 7.9.1 Biomarker analyses

No biomarker analysis is planned.

### 7.9.2 PK / PD analyses

No PK/PD analysis is planned.

# 8. TIMEPOINT OF RELEASE OF TREATMENT INFORMATION

The treatment information will be loaded into the trial database as requested during the trial conduct, since this is an open-label phase I healthy volunteer trial.

# 9. REFERENCES


| | |
|---|---|
| 1. | *CPMP/ICH/363/96:* "Statistical Principles for Clinical Trials", ICH Guideline Topic E9, Note For Guidance on Statistical Principles for Clinical Trials, current version. |
| 2. | *BI-VQD-12045-S-G_40-413:* “Identify and Manage Important Protocol Deviations (iPD)”, current version, group / owning department: “Med Clinical Development & Operations”, DMS for controlled documents. |
| 3. | *BI-VQD-189393-S-G_40-413_AD-01*: “iPD Specification Document (pdf of template)”, current version, group / owning department: “Med Clinical Development & Operations”, DMS for controlled documents. |
| 4. | *BI-VQD-12682-S-G_50-415_AD-03*: “Clinical Trial Analysis Decision Log (template with annotations)”, current version, group / owning department: “Biostatistics & Data Sciences”, DMS for controlled documents. |
| 5. | *BI-KMED-BDS-HTG-0035*: “Handling of Missing and Incomplete AE Dates”, current version, group / owning department: “Biostatistics & Data Sciences”, DMS for controlled documents. |
| 6. | *BI-KMED-TMCP-HTG-0025*: “Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics”, current version, group / owning department: “Translational Medicine Clinical Pharmacology”, DMS for controlled documents. |
| 7. | *BI-KMED-TMCP-MAN-0014*: “Noncompartmental Pharmacokinetic / Pharmacodynamic Analyses of Clinical Studies”, current version, group / owning department: “Translational Medicine Clinical Pharmacology”, DMS for controlled documents. |
| 8. | *BI-KMED-BDS-HTG-0045*: “Standards for Reporting of Clinical Trials and Project Summaries”, current version, group / owning department: “Biostatistics & Data Sciences”, DMS for controlled documents. |
| 9. | *BI-KMED-TMCP-OTH-0003*: “Graphs and Tables for Clinical Pharmacokinetic and Pharmacodynamic Noncompartmental Analyses and Anti-Drug Antibody Reporting”, current version, group / owning department: “Translational Medicine Clinical Pharmacology”, DMS for controlled documents. |
| 10. | *BI-KMED-TMCP-MAN-0010*: “Description of Analytical Transfer Files, PK/PD Data files and ADA files”, current version, group / owning department: “Translational Medicine Clinical Pharmacology”, DMS for controlled documents. |

| | |
|---|---|
| 11. | *BI-KMED-BDS-HTG-0041*: "Analysis and Presentation of Adverse Event Data from Clinical Trials – Display Template", current version, group / owning department: "Biostatistics & Data Sciences", DMS for controlled documents. |
| 12. | *BI-KMED-BDS-HTG-0066*: "Analysis and Presentation of Adverse Event Data from Clinical Trials", current version, group / owning department: "Biostatistics & Data Sciences", DMS for controlled documents. |
| 13. | *CPMP/ICH/137/95*: "Structure and Content of Clinical Study Reports", ICH Guideline Topic E3; Note For Guidance on Structure and Content of Clinical Study Reports, current version, EMA webpage. |
| 14. | *BI-KMED-BDS-HTG-0042*: "Handling, Display and Analysis of Laboratory Data", current version, group / owning department: "Biostatistics & Data Sciences", DMS for controlled documents. |

# 11. HISTORY TABLE

Table 11: 1 History table

| Version | Date (DD-MMM-YY) | Author | Sections changed | Brief description of change |
|---|---|---|---|---|
| 1.0 | **17-JAN-25** | [redacted] | None | This is the final TSAP. |