TRIAL STATISTICAL ANALYSIS PLAN

Document No.:	**c43255293-01**
BI Trial No.:	**1484-0003**
Title:	Effect of itraconazole on the pharmacokinetics of a single [redacted] dose of BI 1584862 in healthy male subjects (an open-label, two-period, fixed-sequence design study) (revised protocol including Protocol Amendment No.1 [c40933306-02]).
Investigational Product:	BI 1584862
Responsible trial statistician:	[redacted] Phone: [redacted] Fax:
Date of statistical analysis plan:	11 DEC 2023
Version:	1.0

1. TABLE OF CONTENTS

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2. LIST OF ABBREVIATIONS

See Medicine Glossary:
http://glossary

Term	Definition / description
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
BMI	Body mass index
BP	Blood pressure
CI	Confidence interval
C_{max}	Maximum measured concentration of the analyte in plasma
CSD	Company Standard Displays
CTP	Clinical trial plan
CTR	Clinical trial report
CV	Arithmetic Coefficient of Variation
DILI	Drug induced liver injury
gCV	Geometric Coefficient of Variation
gMean	Geometric Mean
ITZ	Itraconazole
Max	Maximum
Min	Minimum
N	Number non-missing observations
P10	10^{th} percentile
P90	90^{th} percentile
PKS	PK parameter analysis set
PR	Pulse rate
Q1	1^{st} quartile
Q3	3^{rd} quartile

Term	Definition / description
QD	Quaque die, once daily
R	Reference treatment
RPM	Report Planning Meeting
RAGe	Report Appendix Generator system
SD	Standard Deviation
T	Test treatment
TS	Treated Set
TSAP	Trial Statistical Analysis Plan
ULN	Upper Limit of Normal

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.

Study data (including data entered in the RAVE EDC system and external data provided by suppliers) will be stored in a Clinical Data Repository (CDR).

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, by [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 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.

To emphasize that the previous and concomitant therapies will be presented by treatment sequence ('BI / ITZ+BI'), the respective sentence of CTP Section 7.2.5 has been rephrased in the TSAP (see Section 7.2) from "*Previous and concomitant therapies will be presented per treatment group without consideration of time intervals and treatment periods"* to "*Previous and concomitant therapies will be presented* for the overall treatment sequence ('BI / ITZ+BI') *without consideration of time intervals and treatment periods".*

5. ENDPOINTS

5.1 PRIMARY ENDPOINTS

Section 2.1.2 of the CTP:

The following pharmacokinetic parameters will be determined for BI 1584862:

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

5.2 SECONDARY ENDPOINTS

5.2.1 Key secondary endpoint

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 BI 1584862:

- *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)*

Safety and tolerability endpoints

Section 2.2.2.3 of the CTP:

Safety and tolerability of treatment with BI 1584862 and itraconazole will be assessed based on:

- *Adverse events (including clinically relevant findings from the physical examination)*
- *Safety laboratory tests*
- *12-lead ECG*
- *Vital signs (blood pressure, pulse rate)*

6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENTS

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

This trial is designed as an open-label, two-treatment, two-period, fixed sequence design trial in 14 healthy male subjects with a wash-out phase of [redacted] between the single dose administrations of BI 1584862 in the two periods.

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 1584862, [redacted]	BI
T	Itraconazole oral solution, 200 mg, qd + BI 1584862, [redacted]	ITZ+BI

The sequence for "R-T" is named "BI / ITZ+BI" accordingly.

Section 1.2.3 of the CTP:
The Residual Effect Period (REP, the period after the last dose with measurable drug levels and/or pharmacodynamic effects still likely to be present) of BI 1584862 is conservatively assumed to be [redacted], i.e. a minimum observation period of at least 10-fold estimated t1/2 has been selected for treatment period 1 (BI 1584862 alone, treatment reference).
When given together with itraconazole (Treatment T), it is expected [redacted].
For the use of itraconazole in Treatment T, the REP is defined as 8 days after last administration of itraconazole in Period 2.

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

Table 6.1: 2 Analysis phases for statistical analysis of AEs, and actual treatment for analysis of laboratory data

Study analysis phase	Short Label	Start	End
Screening	**Screening**	0:00h on date of informed consent	Date/time of administration of BI 1584862 in treatment period 1
On treatment	**BI**	Date/time of administration of BI 1584862 alone in treatment period 1	[redacted] after date/time of administration of BI 1584862 in treatment period 1 [redacted] OR Trial termination (0:00 h on the day after trial termination)
Follow-up	**FU BI**	[redacted] after date/time of administration of BI 1584862 in treatment period 1 [redacted]	Date/time of first administration of itraconazole alone in treatment period 2 OR Trial termination (0:00 h on the day after trial termination) – whatever occurs first
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
Follow-up	**FU ITZ-2**	8 days (192 h) after [redacted] administration of itraconazole in period 2 (End of REP of itraconazole)	Trial termination (0:00 h on the day after trial termination)

Section 7.2.5 of the CTP:
Note that AEs occurring after the last per protocol contact but entered before data base lock the trial will be reported to Pharmacovigilance only and will not be captured in the trial database.

The following AE displays will be provided in the Clinical Trial Report (CTR):

In Section 15.3 and Appendix 16.1.13.1.8 (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 treatment as in Table 6.1: 2). The screening and follow-up phases will not be included in this analysis.

The following totals will be provided in addition for Section 15.3:

- A total over all on treatment phases involving BI 1584862 **("BI Total")**
- A total over all on treatment phases involving ITZ **("ITZ Total")**
- a total over all on treatment phases (**"Total"**)

In Section 15.4 and Appendix 16.2 (Listings) of the CTR displays, the screening period, as well as the follow-up phases will additionally be included.

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 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).

Important protocol deviation (iPD) categories are pre-specified in the iPD specification file (DV domain) (3). 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 in* Section 7.2.1.2 of the CTP*). Thus, a subject will be included in the PKS, even if he 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.*

Table 6.4: 1 Subject sets analysed

	Subject set	
Class of analysis	TS	PKS
Primary/secondary and [redacted]		X
Safety, treatment exposure & iPD	X	
Disposition, demographics & baseline conditions	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**:

Section 7.3.1 of the CTP: *It is not planned to impute missing values for safety parameters.*

The only exceptions where imputation might be necessary for safety evaluation are AE dates. Missing or incomplete AE dates are imputed according to BI standards (see "Handling of Missing and Incomplete AE Dates") (5).

Section 7.3.2 of the CTP:

Handling of missing PK data will be performed according to the relevant BI internal procedures.

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

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)).

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

The baseline value for laboratory and vital signs analyses is defined as the last measurement before [redacted] BI 1584862 or itraconazole drug administration in each treatment period. [redacted]

Time windows are defined in **Section 6.1 of the CTP**. 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 15.1 to 15.4 of the CTR and in Appendix 16.2 and 16.1.13.1.

Inferential statistical analyses of PK endpoints (refer to Section 7.4) will also be performed by [redacted] and will be presented in Section 15.5 of the CTR and in Appendix 16.1.13.3.

Descriptive data analysis of PK endpoints and concentrations will be performed by the department of [redacted] at [redacted] and will be presented in Section 15.6 of the CTR and in Appendix 16.1.13.5.

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 and visit and time point. The listings will be included in Appendix 16.2 of the CTR.

The following standard descriptive statistical parameters will be displayed in summary tables of continuous variables:

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 (if needed):

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.

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 (%). Percentages will be given in integer numbers due to the small sample size of <100. Percentages will be based on all subjects in the respective subject set whether they have non-missing values or not. 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.
- ‘DESC STATS’ the value will be excluded from descriptive evaluations per planned time point/time interval.
- ‘HALF LIFE’, the value will be excluded from half-life calculation (and, as a consequence, any calculation that relies on λ_z) only; the value is included for all other analyses.

If ACEXCO contains the addition ‘TIME VIOLATION’ or ‘TIME DEVIATION’ the value can be used for further analyses based on actual times. Excluded concentration itself will be listed in the CTR associated with an appropriate flag.

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

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Only descriptive statistics are planned for this section of the CTR, based on the TS.
The data will be summarised by the overall treatment sequence.

7.2 CONCOMITANT DISEASES AND MEDICATION

Only descriptive statistics are planned for this section of the CTR, 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.

In the remaining document ‘therapy’ will be used for non-drug therapies and concomitant medications

Section 7.2.5 of the CTP:
Previous and concomitant therapies will be presented for the overall treatment sequence (‘BI / ITZ+BI’) *without consideration of time intervals and treatment periods.*

A therapy will be considered concomitant to a treatment, if it

- is ongoing at the time of study drug administration, or
- starts within the analysis phase of the respective treatment (see Section 6.1 for a definition of treatments and analysis phases).

The diagnoses and therapies 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

Treatment compliance will not be analysed as a specific endpoint, but judged by observed analyte concentrations, cf. **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.

Treatment exposure to BI 1584862 is defined as the number of doses and total dose of BI 1584862 per subject.

Treatment exposure to itraconazole is defined as the number of doses and total dose of itraconazole per subject.

Any deviations from complete [redacted] will be addressed in the RPM and described in the CTR.

7.4 PRIMARY OBJECTIVE ANALYSIS

7.4.1 Main analysis

Section 7.2.2 of the CTP:
The statistical model used for the analysis of the primary and secondary *endpoints (refer to* Section 5.1 and Section 5.2.2*) 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: subjects and treatment. The effect 'subjects' will be considered as random, whereas 'treatment' will be considered as fixed. The model is described by the following equation:*

$y_{km} = \mu + s_m + \tau_k + e_{km}$, *where*

y_{km} = *logarithm of response measured on subject m receiving treatment k,*

μ = *the overall mean,*

s_m = *the effect associated with the* m^{th} *subject, m = 1, 2, ..., n*

τ_k = *the* k^{th} *treatment effect, k = 1, 2,*

e_{km} = *the random error associated with the* m^{th} *subject who received treatment k.*

where $s_m \sim N(0, \sigma_B^2)$ *i.i.d.,* $e_{km} \sim N(0, \sigma_W^2)$ *i.i.d. and* s_m, e_{km} *are independent random variables and n is the total number of subjects included in the trial.*

Point estimates for the ratios of the geometric means (test/reference) for the primary endpoints […] *and their two-sided 90% confidence intervals (CIs) will be provided.*

For each primary endpoint, the difference between the expected mean for log response of the test treatment – log response of the reference treatment 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;
   MODEL logpk = treatment / DDFM=KR;
   RANDOM subject;
   LSMEANS treatment / PDIFF CL ALPHA=0.1;
   ESTIMATE 'T-R' treatment 1 -1;
RUN;
```

7.4.4 Supplementary analysis

No supplementary analysis is planned.

7.5 SECONDARY OBJECTIVE ANALYSIS

7.5.1 Key secondary objective analysis

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

7.5.2 Secondary objective analysis

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

7.7 EXTENT OF EXPOSURE

Descriptive statistics of number of doses and calculated total doses of BI 1584862 and itraconazole are planned for this section of the CTR 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 study (dropouts or withdrawals) will be reported as far as their data are available.

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 assigned 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 AE 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 and Table 6.1: 2.

An overall summary of adverse events will be presented. This overall summary will comprise summary statistics for the class of AESIs.

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:

  - *An elevation of AST (aspartate aminotransferase) and/or ALT (alanine aminotransferase) ≥3-fold ULN combined with an elevation of total bilirubin ≥2-fold ULN measured in the same blood sample, or in samples drawn within 30 days of each other, or*
  - *Aminotransferase (ALT, and/or AST) elevations ≥10-fold ULN*

  These lab findings constitute a hepatic injury alert and the subjects showing these lab abnormalities need to be followed up according to the 'DILI checklist' provided in the ISF. In case of clinical symptoms of hepatic injury (icterus, unexplained encephalopathy, unexplained coagulopathy, right upper quadrant abdominal pain, etc.) without lab results (ALT, AST, total bilirubin) available, the Investigator should make sure that these parameters are analysed, if necessary in an unscheduled blood test.. Should the results meet the criteria of hepatic injury alert, the procedures described in the DILI checklist should be followed.

The investigator had to classify on the eCRF whether an observed AE was an AESI or not.

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

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 investigator-defined drug-related AEs, for subjects with investigator-defined drug-related serious adverse events, 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 system organ class (SOC) and preferred term (PT).

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

In addition, for disclosure of AE data on ClinicalTrials.gov, frequencies of subjects with non-serious AEs that had an incidence of > 5% (in preferred terms) for at least one treatment will be summarised by treatment, primary SOC and PT. The frequency of subjects with SAEs will also be summarised.

For disclosure of AE data in the EudraCT register, the frequency of AEs and the frequency of non-serious AEs with an incidence of greater than 5 % (in preferred terms) and the frequency of SAEs will be summarized.

7.8.2 Laboratory data

The analyses of laboratory data will be descriptive in nature and will be based on BI standards outlined 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 flagged in the data listings.

It is the Investigator's responsibility to decide whether a lab value is clinically significant abnormal or not. Clinically significant abnormal laboratory values are identified either in the Investigator's comments or at the Report Planning Meeting at the latest. They will be reported as baseline conditions (prior to first administration of study treatment) or as AEs (after first administration of study treatment).

Descriptive statistics of laboratory data including change from baseline will be calculated by planned time point based on the worst value of the subject at that planned time point (or assigned to that planned time point).

7.8.3 Vital signs

Descriptive statistics over time including change from baseline will be performed for vital signs (blood pressure and 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, the last measurement before drug administration in each treatment period will be used.

Clinically relevant findings in vital signs will be reported as baseline conditions (prior to first administration of study treatment) or as AEs (after first administration of study treatment) if judged clinically relevant by the investigator, and will be analysed as such.

7.8.4 ECG

ECG recordings will be checked by the investigator for pathological results. Clinically relevant abnormal findings for ECG will be listed under 'Relevant Medical History / Baseline Conditions' (prior to first administration of study treatment) or will be reported as AEs (after first administration of study treatment), and will be analysed as such. 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. if a condition already exists before first administration of study treatment) or as AE (if condition emerges after first administration of study treatment) and will be summarised as such.

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

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

Not applicable due to open label fashion of the trial as described in the CTP Section 4.1.5. The treatment information will be loaded into the trial database at trial initiation.

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_40-413:* "Identify and Manage Important Protocol Deviations (iPD)", current version, Group "Clinical Operations", KMED.
3.	*BI-KMED-BDS-TMP-0059*: "iPD specification document (sdtm-dv-domain-specification)", template, current version, Group "Clinical Operations", KMED.
4.	*001-MCS-50-415_RD-03:* "Clinical Trial Analysis Decision Log (template)", current version, Group "Biostatistics & Data Sciences", KMED.
5.	*BI-KMED-BDS-HTG-0035:* "Handling of Missing and Incomplete AE Dates", current version, Group "Biostatistics & Data Sciences" KMED.
6.	*BI-KMED-TMCP-HTG-0025:* "Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics", current version ;, Group "Translational Medicine Clinical Pharmacology", KMED.
7.	*BI-KMED-TMCP-MAN-0014:* "Noncompartmental Pharmacokinetic / Pharmacodynamic Analyses of Clinical Studies", current version, Group "Translational Medicine Clinical Pharmacology", KMED.
8.	*BI-KMED-BDS-HTG-0045*: "Standards for Reporting of Clinical Trials and Project Summaries", current version, Group "Biostatistics & Data Sciences", KMED.
9.	*BI-KMED-TMCP-OTH-0003*: "Graphs and Tables for Clinical Pharmacokinetics and Pharmacodynamic Noncompartmental Analyses", current version, Group "Translational Medicine Clinical Pharmacology", KMED.
10.	*BI-KMED-TMCP-MAN-0010*: "Description of Analytical Transfer Files and PK/PD Data Files", current version, Group "Translational Medicine Clinical Pharmacology", KMED.
11.	*BI-KMED-BDS-HTG-0041*: "Analysis and Presentation of Adverse Event Data from Clinical Trials – Display Template", current version, Group "Biostatistics & Data Sciences", KMED.
12.	*BI-KMED-BDS-HTG-0066*: "Analysis and Presentation of AE data from clinical trials", current version, Group "Biostatistics & Data Sciences", KMED.
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 "Biostatistics & Data Sciences", KMED.

11. HISTORY TABLE

Table 11: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
1.0	**11-DEC-23**	[redacted]	None	This is the final TSAP.