TRIAL STATISTICAL ANALYSIS PLAN

Document No.:	228892_996664
BI Trial No.:	**1479-0015**
Title:	The effect of zongertinib on the pharmacokinetics of dabigatran (part 1) and rosuvastatin, metformin and furosemide administered as a cocktail (part 2) in healthy male subjects (a 2-part, open-label, 2-period, fixed-sequence cross-over trial) (including Protocol Amendment No. 1 [c43424163-02])
Investigational Product:	Zongertinib (BI 1810631)
Responsible trial statistician:	[redacted] Phone: [redacted] Fax: [redacted]
Date of statistical analysis plan:	02 DEC 2024
Version:	1.0
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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
CI	Confidence interval
C_{max}	Maximum measured concentration of the analyte in plasma
CTP	Clinical trial protocol
CTR	Clinical trial report
CV	Arithmetic Coefficient of Variation
DILI	Drug induced liver injury
eDMS	Electronic documentation management system
gCV	Geometric Coefficient of Variation
gMean	Geometric Mean
Max	Maximum
Min	Minimum
N	Number non-missing observations
Nobs	Number of observations
P10	10^{th} percentile
P90	90^{th} percentile
PKS	PK parameter analysis set
Q1	1^{st} quartile
Q3	3^{rd} quartile
QD	Quaque die, once daily
R	Reference treatment

Term	Definition / description
RAGe	Report Appendix Generator system
RPM	Report Planning Meeting
SD	Standard Deviation
T	Test treatment
TS	Treated set
TSAP	Trial Statistical Analysis Plan
ULN	Upper Limit of Normal
t_{max}	Time from (last) dosing to the maximum measured concentration 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.

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 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, except for the following:

In contrast to CTP section 7.2.5, where it is stated: "*Previous and concomitant therapies will be presented per treatment group without consideration of time intervals and treatment periods.*", the concomitant therapies will be presented per treatment group, in addition to the Total column, i.e. one column for 'dabigatran' and one column for 'zongertinib + dabigatran' for Part 1 and 'cocktail' and 'zongertinib + cocktail' for Part 2.

5. ENDPOINTS

5.1 PRIMARY ENDPOINTS

Section 2.1.2 of the CTP:

The following PK parameters will be determined for the probe drugs dabigatran (Part 1)*, rosuvastatin, metformin and furosemide* (Part 2)*:*

- *$AUC_{0-\infty}$ (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 endpoints

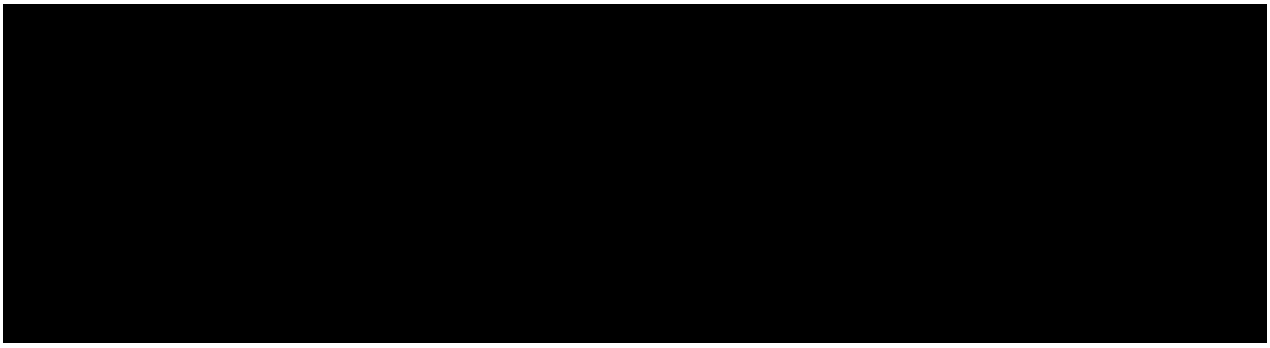
This section is not applicable as no key secondary endpoints have been defined in the CTP.

5.2.2 Secondary endpoint

Section 2.1.3 of the CTP:

The following PK parameter will be determined for the probe drugs dabigatran (Part 1)*, rosuvastatin, metformin and furosemide* (Part 2)*:*

- *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

Both parts:

Section 2.2.2.2 of the CTP:

Safety and tolerability of zongertinib, dabigatran-etexilate, rosuvastatin, metformin and furosemide 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)*

5.4 OTHER VARIABLES

Both parts:

Section 5.2.1 of the CTP:

At screening, the medical examination will include demographics, height and body weight, smoking and alcohol history (alcohol history not mandatory to be entered into case report form (*CRF*) *or to be reported), relevant medical history and concomitant therapy, review of inclusion and exclusion criteria, review of vital signs (*blood pressure, pulse rate*), 12-lead ECG, laboratory tests, and a physical examination. Demographics information includes trial subject`s age on the day of informed consent, subject's sex at birth, and ethnicity and race in order to sufficiently characterize the trial population and to support possible subgroup analyses if needed. At the end of trial examination, it will include review of vital signs, 12-lead ECG, laboratory tests, and a physical examination.*

BMI will be calculated as weight [kg] / (0.01 * height [cm])^2.

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.

This trial is designed as a 2-part, non-randomised, open-label, 2-period fixed-sequence crossover trial in 32 healthy male subjects (16 subjects in Part 1 and 16 subjects in Part 2 of the trial) enrolled at a single site in order to compare the test treatments (T) to the reference treatments (R). Reference treatment will always be followed by the Test treatment in a fixed sequence. In Part 1, periods 1 and 2 are separated by a wash-out interval of at least 7 days. In Part 2, no washout interval between periods is required.

For details of dosage and formulation see Table 6.1: 1 and Table 6.1: 2 below.

Part 1:

Table 6.1: 1 Part 1: Treatments and labels used in the analysis

Treatment		**Short label**
A	Dabigatran-etexilate, tablet, 150 mg, single dose	Dabigatran
B	Zongertinib, tablet, 2*60 mg (=120 mg), single dose + dabigatran-etexilate, tablet, 150 mg, single dose	Zongertinib + Dabigatran

Part 2:

Table 6.1: 2 Part 2: Treatments and labels used in the analysis

Treatment		**Short label**
C	Rosuvastatin, tablet, 10 mg, single dose + metformin, solution, 1000 mg / 5 mL, 0.05 mL, single dose + furosemide, solution, 10 mg/mL, 0.1 mL, single dose	Cocktail
D	Zongertinib, tablet, 2*60 mg (=120 mg), qd for 12 days + rosuvastatin, tablet, 10 mg, single dose + metformin, solution, 1000 mg / 5 mL, 0.05 mL, single dose + furosemide, solution, 10 mg/mL, 0.1 mL, single dose	Zongertinib + Cocktail

For PK analysis in Part 2, test and reference formulations have to be distinguished. The following labels will be used (Section 15.5 and Appendix 16.1.13.3):

rosuvastatin (R1), zongertinib + rosuvastatin (T1)

metformin (R2), zongertinib + metformin (T2)

furosemide (R3), zongertinib + furosemide (T3)

Section 1.2.6 of the CTP:

The Residual Effect Period (REP) of zongertinib is [redacted]. This is the period after the last dose during which measurable drug levels and/or pharmacodynamic effects are still likely to be present. The REP for dabigatran is 3 days, the REP for rosuvastatin is 6 days, the REP for metformin is 2 days and the REP for furosemide is 2 days.

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

Part 1:

- **Screening**
    - Ranging from 0:00 h on day of informed consent until time of first drug administration.
- **On-treatment** (labelled with short label)

  "dabigatran":
    - Ranging from drug administration of dabigatran-etexilate in treatment period 1 until first drug administration (zongertinib) in treatment period 2 OR until 3 days (72 h) after treatment administration in period 1, whatever occurs first.

  "zongertinib":
    - Ranging from drug administration of zongertinib in treatment period 2 until drug administration of dabigatran-etexilate OR until [redacted] after treatment administration of zongertinib in period 2, whatever occurs first.

  "zongertinib + dabigatran":
    - Ranging from drug administration of dabigatran-etexilate in treatment period 2 until [redacted] after treatment administration of zongertinib in period 2 OR until trial termination (0:00 h on the day after trial termination), whatever occurs first.
- **Follow-up** (labelled "F/U")
    - Ranging from 3 days (72 h) after treatment administration of dabigatran-etexilate in period 1 until first drug administration in treatment period 2 OR ranging from [redacted] after treatment administration of zongertinib in period 2 until trial termination (0:00 h on the day after trial termination).

Part 2:

- **Screening**

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

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

  "cocktail":

  - Ranging from drug administration of cocktail in treatment period 1 until first drug administration of zongertinib in treatment period 2 OR until 6 days (144 h; i.e., REP of rosuvastatin) after treatment administration in period 1, whatever occurs first.

  "zongertinib":

  - Ranging from first drug administration of zongertinib in treatment period 2 until drug administration of cocktail OR until [redacted] after last treatment administration of zongertinib in period 2, whatever occurs first.

  "zongertinib + cocktail":

  - Ranging from drug administration of cocktail in treatment period 2 until [redacted] after last treatment administration of zongertinib in period 2 OR until trial termination (0:00 h on the day after trial termination), whatever occurs first.

- **Follow-up** (labelled "F/U")

  - Ranging from 6 days (144 h) (i.e., longest REP of the three drugs in cocktail) after treatment administration of cocktail in period 1 until first drug administration in treatment period 2 or until trial termination (0:00 h on the day after trial termination), whatever occurs first, OR ranging from [redacted] after last treatment administration of zongertinib in period 2 until trial termination (0:00 h on the day after trial termination).

Both parts:

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 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: 1 and Table 6.1: 2). The screening and follow-up phases will not be included in this analysis.

In Appendix 16.1.13.1.8 (for ClinicalTrials.gov and EudraCT only) both trial parts will be displayed together.

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

- a total over all on treatment phases involving zongertinib (BI 1810631) (**"BI Total"**) (both parts)
- a total over all on treatment phases involving dabigatran-etexilate (**"Dabigatran Total"**) (only part 1)
- a total over all on treatment phases involving cocktail (**"Cocktail Total"**) (only part 2)
- a total over all on-treatment phases (**"Total"**) (both parts)

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 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 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 DV domain sheet, 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 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.*

[redacted]

Section 7.2.1.2 of the CTP:

The PK *parameters listed in* CTP *Section 2.1 and 2.2.2 for probe substrates dabigatran (Part 1), and rosuvastatin, metformin, and furosemide (Part 2) and zongertinib (Part 2) will be calculated according to the relevant BI internal procedures.*

Plasma [redacted] *concentration data and parameters of a subject will be included in the statistical 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 RPM) 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 [redacted] *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 [redacted] *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.*

[…]

Only concentration values within the validated concentration range and actual sampling times will be used for the calculation of PK *parameters. Concentrations used in the* PK *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 endpoints/analysis	TS	PKS
Primary/secondary [redacted] PK endpoints		X
[redacted]		
Safety assessments	X	
Disposition	X	
Demographic/baseline parameters	X	
iPDs	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

Part 1:

The baseline value for vital signs is defined as the last measurement before first drug administration in each treatment period.

Part 2:

The baseline value for vital signs is defined as the last measurement before cocktail administration in first treatment period and before first zongertinib administration in second period.

The baseline value for laboratory analysis is defined as the last measurement before first zongertinib administration in second treatment period.

Both parts:

Section 6.1 of the CTP:

The tolerance time for ambulatory dosing (and other scheduled procedures) from Day -9 to Day -1 in period 2 of Part 2 of the trial is ± 120 minutes.

If not stated otherwise in the CTP *Flow Chart, the acceptable deviation from the scheduled time for vital signs, ECG, and laboratory tests will be ± 60 min during in-house confinement. During ambulatory visits the acceptable deviation from the scheduled time for vital signs, ECG, and laboratory tests will be ± 120 min.*

[…]

For planned blood sampling times [redacted]*, 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* PK *parameters. Beyond the planned time of 48 hours after drug administration the tolerance time of ± 120 min will be allowed for blood sampling times.*

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

If not stated otherwise, Part 1 and Part 2 will be analysed separately. For Part 1 and Part 2 of the trial, the same analyses will be performed if applicable.

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 [redacted] endpoints (refer to Section 7.4 and Section 7.5.2) will also be performed by [redacted] and will be presented in Section 15.5 and 15.7 of the CTR and in Appendix 16.1.13.3 and 16.1.13.6, respectively.

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

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 16.2 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≥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”.

Section 7.2.1.2 of the CTP:

Plasma [redacted] *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* […].

Exclusion of PK concentrations

The ADS “ADPC” (PK concentrations per time-point [redacted]) 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 λ_z) only; the value is included for all other analyses.

[redacted]

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.

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 group without consideration of time intervals and treatment periods.

In contrast to the protocol, the concomitant therapies will be presented per treatment group, in addition to the Total column, i.e. one column for ‘dabigatran’ and one column for ‘zongertinib + dabigatran’ for Part 1 and ‘cocktail’ and ‘zongertinib + cocktail’ for Part 2.

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 phase).

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 and/or urinary excretion 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:

The statistical model used for the analysis of the primary endpoints (refer to Section 5.1) *will be an analysis of variance (ANOVA) model on the logarithmic scale. That is, the PK endpoints will be logtransformed (natural logarithm) prior to fitting the ANOVA model. This model will include effects accounting for the following sources of variation: subject and treatment. The effect 'subject' 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 receive 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.*

Point estimates for the ratios of the geometric means (test/reference) 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(T)-log(R) will be estimated by the difference in the corresponding adjusted means (Least Squares Means). Additionally their two-sided 90% CIs 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;
RUN;
```

[redacted]

In addition to the model based approach all parameters will be calculated and analysed descriptively.

[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 assessed statistically using the same methods as described for the primary endpoints* (refer to Section 7.4).

[redacted]

[redacted]

Part 2:

[redacted]

Safety endpoints and tolerability endpoints

For a description of the analysis of safety and tolerability, please refer to Section 7.8.

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.

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 and Table 6.1: 2.

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:

  - *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.

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 AESIs and for subjects with AEs leading to discontinuation. In addition, the frequency of subjects with AEs will be summarised by CTCAE grade, treatment, primary SOC and PT.

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

In addition, frequencies of subjects with non-serious AEs that had an incidence of > 5% for at least one treatment will be summarised by treatment, primary SOC and PT, for both trial parts together.

For disclosure of AEs on EudraCT, additional information not included in a standard AE analysis will be performed, for both trial parts together. The following three entries will be created:

- Adverse Events per arm for disclosure on EudraCT
- Non-serious Adverse Events for disclosure on EudraCT
- Serious Adverse Events for disclosure on 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 flagged in the data 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).

Only Part 2:

Descriptive statistics of laboratory data including change from baseline 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.

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. In addition, the time profiles of median and (Min, Max) will be displayed graphically by treatment group.

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.

7.9.2 PK / PD analyses

No PK/PD analysis is planned.

8. TIMEPOINT OF RELEASE OF TREATMENT INFORMATION

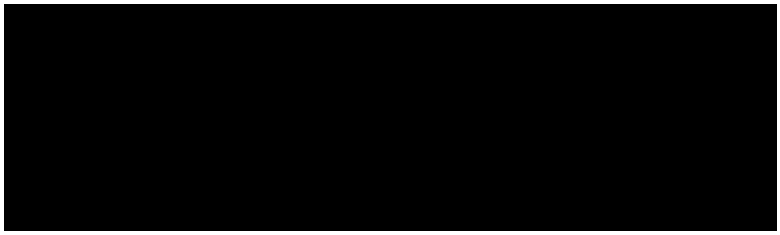
Not applicable due to open-label fashion of the trial as described in the CTP Section 4.1.5.

The treatment information will be loaded into the trial database during trial conduct.

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, PK/PD Data files and ADA 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 Adverse Event 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	**02-DEC-24**	[redacted]	None	This is the final TSAP.