TRIAL STATISTICAL ANALYSIS PLAN

Document No.:	**c44585921-01**
BI Trial No.:	**1479-0014**
Title:	The effect of multiple doses of zongertinib on the single-dose pharmacokinetics of midazolam, omeprazole and repaglinide in healthy male subjects (an open-label, 2-period, fixed-sequence trial) (including Protocol Amendments No.1-3 [c42988075-04])
Investigational Product:	Zongertinib (BI 1810631)
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Date of statistical analysis plan:	25 OCT 2024
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	Page 1 of 29

1. TABLE OF CONTENTS

LIST OF TABLES

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
BMS	Biomarker parameter analysis set
CI	Confidence interval
C_{max}	Maximum measured concentration of the analyte in plasma
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
Max	Maximum
Min	Minimum
N	Number non-missing observations
P10	10^{th} percentile
P90	90^{th} percentile
PK	Pharmacokinetic(s)
PKS	PK parameter analysis set
PTM	Planned time point
Q1	1^{st} quartile
Q3	3^{rd} quartile
QD	Quaque die, once daily

Term	Definition / description
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.

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 WinNonlinTM 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.

5. ENDPOINTS

5.1 PRIMARY ENDPOINTS

Section 2.1.2 of the CTP:
The following pharmacokinetic parameters will be determined for the probe drugs midazolam, repaglinide and omeprazole:

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

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 the probe drugs midazolam, repaglinide and omeprazole:

- *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)*

6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENTS

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

The trial will be performed as an open-label, two-period fixed sequence design trial in healthy male subjects. Sixteen subjects are planned to be included in the trial. They are assigned to a fixed sequence, including two reference treatments (R1, R2) followed by a washout phase of at least 3 days and four test treatments (T1, T2, T3, T4).

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
R1	Repaglinide, 0.5 mg tablet, qd	Repa (R1)
R2	Midazolam, 1 mg as oral solution, po, qd + Omeprazole, 20 mg tablet, qd	Mida+Ome (R2)
T1	Zongertinib, 2*60 mg tablet, qd + Repaglinide, 0.5 mg tablet, qd	Zonger+Repa (T1)
T2	Zongertinib, 2*60 mg tablet, qd + Midazolam, 1 mg as oral solution, po, qd + Omeprazole, 20 mg tablet, qd (following predosing with zongertinib over 1 day)	Zonger+Mida+Ome (T2)
Z	Zongertinib, 2*60 mg tablet, qd	Zonger
T3	Zongertinib, 2*60 mg tablet, qd + Repaglinide, 0.5 mg tablet, qd (following predosing with zongertinib over 13 days)	Zonger+Repa (T3)
T4	Zongertinib, 2*60 mg tablet, qd + Midazolam, 1 mg as oral solution, po, qd + Omeprazole, 20 mg tablet, qd (following predosing with zongertinib over 14 days)	Zonger+Mida+Ome (T4)

Section 1.2.5 of the CTP:
The Residual Effect Period (REP) of zongertinib is conservatively estimated as 14 days. This is the period after the last dose during which measurable drug levels and/or pharmacodynamics effects are still likely to be present.
The REP for omeprazole is 48 hours, the REP for repaglinide is 12 hours, the REP for midazolam is 24 hours.

When two trial drugs are administered together, we conservatively assume that the respective on-treatment phase is given by the longer REP of the two drugs starting at the time point, when both treatments have been administered.

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

Table 6.1: 2 Analysis phases (screening and on-treatment) for statistical analysis of AEs, and actual treatment for analysis of laboratory data, vital signs

Study analysis phase	**Treatment (Short label)**	**Start**	**End***
Screening	Screening (**Screening**)	0:00h on day of informed consent	Date/time of first trial drug administration
On treatment	Repaglinide alone (**Repa (R1)**)	Date/time of administration of repaglinide in Period 1	*Date/time of administration of Mida+Ome in Period 1 OR date/time of trial termination**, whatever occurs first.
	Midazolam+ Omeprazole (**Mida+Ome (R2)**)	Date/time of administration of Mida+Ome in Period 1	48 h after date/time of administration of Mida+Ome in Period 1 OR date/time of trial termination**, whatever occurs first.
	Zongertinib+ Repaglinide (**Zonger+Repa (T1)**)	Date/time of first administration of Zonger+Repa in Period 2	Date/time of first administration of treatment Zonger+Mida+Ome in Period 2 OR 14 days after date/time of administration of Zonger+Repa in Period 2 OR date/time of trial termination**, whatever occurs first.

Table 6.1: 2 Analysis phases (screening and on-treatment) for statistical analysis of AEs, and actual treatment for analysis of laboratory data, vital signs - continued

Study analysis phase	**Treatment (Short label)**	**Start**	**End***
On treatment	Zongertiunib+ Midazolam+ Omeprazole (**Zonger+Mida+Ome (T2)**)	Date/time of first administration of Zonger+Mida+Ome in Period 2	Date/time of first administration of Zonger+Mida+Ome in Period 2 + 48 h OR date/time of trial termination**, whatever occurs first.
	Zongertininb (**Zonger**)	Date/time of first administration of Zonger+Mida+Ome in Period 2 + 48 h	Date/time of second administration of Zonger +Repa in Period 2 OR 14 days after date/time of last administration of Zongertinib alone in Period 2 OR date/time of trial termination**, whatever occurs first.
	Zongertinib + repaglinide (**Zonger+Repa (T3)**)	Date/time of second administration of Zonger+Repa in Period 2	Date/time of second administration of Zonger+Mida+Ome in Period 2 OR 14 days after date/time of second administration of Zonger +Repa in period 2 OR date/time of trial termination**, whatever occurs first.
	Zongertinib + midazolam + omeprazole (**Zonger+Mida+Ome (T4)**)	Date/time of second administration of Zonger+Mida+Ome in period 2	14 days after date/time of second administration of Zonger+Mida+Ome in Period 2 OR date/time of trial termination**, whatever occurs first.

* In order to enable valid comparisons between T1/T3 with R1, the R1 period was extended to 24 hours.
**Date/time of trial termination is defined as 0:00 h on the day after trial termination.

Follow-up phases:
Follow-up phases (labelled "**F/U**") range from the end of respective REP until administration of next treatment OR until trial termination (0:00 h on the day after trial termination). Actual treatments in AE listings will be labelled "F/U <previous treatment>".

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 Clinical Trial Report (CTR):

In Section 15.3 and Appendix 16.1.13.1.8 (for ClinicalTrials.gov) of the CTR displays, the on treatment phases will be analysed (labelled with the short label of the study treatment 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 Section 15.3:

- A total over all on treatment phases involving Zongertinib (BI 1810631) **("BI Total")**
- A total over all on treatment phases involving Repaglinide **("Repa Total")**
- A total over all on treatment phases involving Midazolam and Omeprazole **("Mida+Ome Total")**
- An overall 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 will be suggested in the DV domain sheet, iPDs will be identified no later than in the Report Planning Meeting, 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

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 the following subsection 'Pharmacokinetics'). 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.*
- *Biomarker parameter analysis set (BMS): This set includes all subjects in the treated set (TS) who provide at least one evaluable measure of* [redacted] *without protocol deviations relevant to the evaluation of the biomarker (as specified in the* CTP *subsection 'Biomarkers'). Listing of the biomarker will be based on the BMS.*

Table 6.4: 1 Subject sets analysed

	Subject analysis set		
Class of endpoint	TS	PKS	BMS
Analyses of PK endpoints (primary, secondary and further)		X	
Analyses of biomarker endpoints			X
Further safety assessments	X		
Disposition	X		
Demographic/baseline parameters	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.

Missing or incomplete AE dates are imputed according to BI standards (see BI-KMED-BDS-HTG-0035) (5).

Missing data and outliers of PK/Biomarker 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

For laboratory data and vital signs, baseline is defined as measurement prior to first drug administration in each period.

Section 6.1 of the CTP:
Study measurements and assessments scheduled to occur 'before' trial medication administration on Day 1 and Day 2 of Visit 2 as well as Day 1, Day 2, Day 3, Day 14 and Day 15 of Visit 3 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.*

If not stated otherwise in the CTP *Flow Chart, the acceptable deviation from the scheduled time for vital signs, safety laboratory tests (excluding blood glucose testing) and ECG will be ± 30 min. For glucose testing the acceptable deviation from the scheduled time is ± 10 min.*

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 and Section 7.5.2) 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 [redacted] and will be presented in Section 15.6 of the CTR and in Appendix 16.1.13.5.

Listings of Biomarker concentrations will be performed by the [redacted] and will be presented in Appendix 16.1.13.6.

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	10th percentile
Q1	1st quartile
Q3	3rd quartile
P90	90th 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".

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 report, based on the TS.
The data will be summarised in total.

7.2 CONCOMITANT DISEASES AND MEDICATION

Frequency tables are planned for this section of the report, based on the TS.
Concomitant diseases will be coded using the coding system of the Medical Dictionary for Drug Regulatory Activities (MedDRA). Medications will be coded using the World Health Organization Drug Dictionary (WHO-DD). The coding version number will be displayed as a footnote in the respective output.
The diagnoses and medications will be listed. Subjects without any concomitant diagnoses or concomitant therapies will be marked with a “No” in the respective column.

Section 7.2.5 of the CTP:
Previous and concomitant therapies will be presented per treatment sequence without consideration of time intervals and treatment periods. A total column will be displayed only.

The relevance of the concomitant therapies to the evaluation of PK 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 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 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: 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.*

Point estimates for the ratios of the geometric means (test/reference: T1/R1, T2/R2, T3/R1, T4/R2) 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% 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.
Separate models will be applied for each comparison / gMean ratio.

[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 endpoints (refer to Section 5.2) 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.

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.

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.

According to the clinical study protocol, 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. *An elevation of AST (aspartate aminotransferase) and/ or ALT (alanine aminotransferase) ≥3-fold ULN combined with an elevation of total bilirubin ≥2x ULN measured in the same blood sample, or in samples drawn within 30 days of each other, OR*
  2. *Aminotransferase (ALT, and/or AST) elevations ≥10-fold ULN* […]

According to ICH E3 (13), in addition to deaths and serious adverse events, 'other significant' AEs need to be listed in the clinical trial report. 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).

An overall summary of adverse events 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 adverse events and for subjects with AESIs. In addition, the frequency of subjects with AEs will be summarised by CTCAE grade, treatment, primary system organ class (SOC) and preferred term (PT).

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

For disclosure of adverse events on EudraCT and ClinicalTrials.gov, 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 EudraCT/ ClinicalTrials.gov
- Non-serious Adverse Events for disclosure on EudraCT/ ClinicalTrials.gov
- Serious Adverse Events for disclosure on EudraCT/ ClinicalTrials.gov

Frequencies of subjects with serious and 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.

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).

For post-dose measurements, descriptive statistics 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). The baseline value is defined as the last measurement before first drug administration in each period. For laboratory parameters which are available at screening and in period 2 only, last measurement before trial drug administration in second period will be flagged as baseline.

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

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 period.

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 first drug administration in each period will be used.

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 adverse events.

No separate listing or analysis of ECG data 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 AE and will be summarised as such.

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

7.9.1 Biomarker analyses

Section 7.2.4 of the CTP:
Biomarker analyses

[redacted] *will only be listed in the CTR. Other analysis will be reported outside of this report.*

Analysis for liquid biopsy

If data allows correlation between CL/F of probe substrates and mRNA, protein expression or enzyme activity of respective PK protein in small extracellular vesicle in plasma will be explored outside of the CTR.

7.9.2 PK / PD analyses

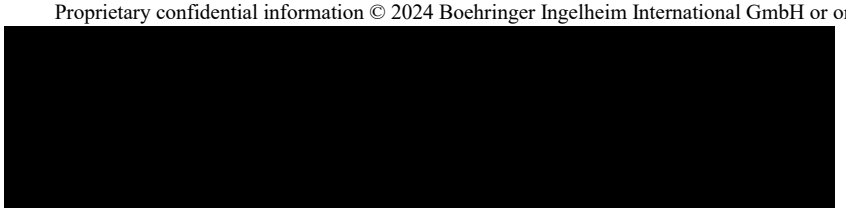
No PK/PD analysis is planned.

8. TIMEPOINT OF RELEASE OF TREATMENT INFORMATION

The treatment information will be loaded into the trial database 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.	*001-MCS-40-413:* "Identify and Manage Important Protocol Deviations (iPD)", current version, Group "Clinical Operations", IDEA for CON.
3.	*BI-KMED-BDS-TMP-0059*: "iPD specification document (sdtm-dv-domain-specification)", template, current version, KMED.
4.	*001-MCS-50-415_RD-03:* "Clinical Trial Analysis Decision Log (template) Decision Log", current version, Group "Biostatistics & Data Sciences", IDEA for CON.
5.	*BI-KMED-BDS-HTG-0035:* "Handling of Missing and Incomplete AE Dates", current version; KMED.
6.	*BI-KMED-TMCP-HTG-0025:* "Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics", current version; KMED.
7.	*BI-KMED-TMCP-MAN-0014:* "Noncompartmental Pharmacokinetic / Pharmacodynamic Analyses of Clinical Studies", current version; KMED.
8.	*BI-KMED-BDS-HTG-0045*: "Standards for Reporting of Clinical Trials and Project Summaries", current version; KMED.
9.	*BI-KMED-TMCP-OTH-0003*: "Graphs and Tables for Clinical Pharmacokinetics and Pharmacodynamic Noncompartmental Analyses", current version, KMED.
10.	*BI-KMED-TMCP-MAN-0010*: "Description of Analytical Transfer Files and PK/PD Data Files", current version; KMED.
11.	*BI-KMED-BDS-HTG-0041*: "Analysis and Presentation of Adverse Event Data from Clinical Trials – Display Template", current version; KMED.
12.	*BI-KMED-BDS-HTG-0066*: "Analysis and Presentation of AE data from clinical trials", current version, 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; KMED.



11. HISTORY TABLE

Table 11: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
1.0	**25-OCT-24**	[redacted]	None	This is the final TSAP.