TRIAL STATISTICAL ANALYSIS PLAN

Document No.:	**c43422553-01**
BI Trial No.:	**1479-0010**
Title:	Relative bioavailability of BI 1810631 following oral administration [redacted] in healthy male subjects (an open-label, randomised, single-dose, two-way crossover trial) Including Protocol Amendment 1 [c40254926-02] Including Protocol Amendment 2 [c40254926-03]
Investigational Product(s):	BI 1810631 (zongertinib)
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2. LIST OF ABBREVIATIONS

Term	Definition / description
ADS	Analysis data set
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
ANOVA	Analysis of variance
AST	Aspartate aminotransferase
$AUC_{0\text{-}tz}$	Area under the concentration-time curve of the analyte in plasma over the time from 0 to the last quantifiable data point
BI	Boehringer Ingelheim
BMI	Body mass index
CARE	Clinical data analysis and reporting environment
CDR	Clinical data repository
CI	Confidence interval
C_{max}	Maximum measured concentration of the analyte in plasma
COVID	Coronavirus disease
CRF	Case report form, paper or electronic (sometimes referred to as ‘eCRF’)
CSD	Company standard displays
CTCAE	Common Terminology Criteria for Adverse Events
CTP	Clinical trial protocol
CTR	Clinical trial report
DILI	Drug Induced Liver Injury
ECG	Electrocardiogram
EDC	Electronic data capture
EDMS	Electronic document management system
EudraCT	European union drug regulating authorities clinical trials
[redacted]	[redacted]
ICH	International Conference on Harmonisation
iPD	Important protocol deviation
INN	International nonproprietary name
MedDRA	Medical Dictionary for Drug Regulatory Activities

Term	Definition / description
PK	Pharmacokinetic(s)
PKS	Pharmacokinetic parameter analysis set
PT	Preferred term
RAGe	Report appendix generator
REP	Residual effect period
RPM	Report planning meeting
SDL	Subject data listings
SOC	System organ class
SOP	Standard operating procedure
[redacted]	
TMF	Trial master file
TS	Treated set
TSAP	Trial statistical analysis plan
ULN	Upper limit of normal
WHO-DD	World Health Organization - Drug Dictionary

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 clinical trial protocol (CTP), 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 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 electronic data capture (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

At the time of writing the CTP no international nonproprietary name (INN) was available and therefore BI 1810631 was used throughout the document. Since this trial is conducted at a later stage of clinical development the INN “zongertinib” has already been assigned and will be used instead of BI 1810631 from now on.

Previous and concomitant therapies will be presented per treatment sequence instead of treatment group (Section 7.2). The definition in CTP Section 7.2.5 “*Previous and concomitant therapies will be presented per treatment group without consideration of time intervals and treatment periods.*”.

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

5. ENDPOINTS(S)

5.1 PRIMARY ENDPOINT(S)

Section 2.1.2 of the CTP:

The following pharmacokinetic parameters will be determined for BI 1810631 (zongertinib)*:*

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

5.2 SECONDARY ENDPOINT(S)

5.2.1 Key secondary endpoint(s)

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

5.2.2 Secondary endpoint(s)

Section 2.1.3 of the CTP:

The following pharmacokinetic parameter will be determined for BI 1810631 (zongertinib)*:*

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

5.3 FURTHER ENDPOINT(S)

Pharmacokinetic (PK) endpoints:

Other pharmacokinetic parameters of zongertinib are further study endpoints. For more details see **CTP Section 2.2.2.1**.

Safety and tolerability:

Section 2.2.2.2 of the CTP:

Safety and tolerability of BI 1810631 (zongertinib) *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* [BP]*, pulse rate* [PR]*)*

6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENT(S)

For basic study information on treatment and selection of doses, please see **CTP Sections 3 and 4.**

The trial is designed as a randomised, open-label, two-period, two-sequence crossover trial in healthy male subjects with a washout period of [redacted] between the administrations of zongertinib. The treatments will be [redacted] of zongertinib administered to subjects in the [redacted] zongertinib administered to subjects in the [redacted] In total, it was planned that 16 healthy male subjects are randomly allocated to the 2 treatment sequences T-R or R-T.

[redacted]

Section 1.2.3 of the CTP:

The Residual Effect Period (REP) [redacted] *This is the period after the last dose during which measurable drug levels and/or pharmacodynamic effects are still likely to be present.*

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

Study analysis phase	Short Label	Start (inclusive)	End (exclusive)
Screening[1]	**Screening**	Date of informed consent	Date/time of administration of study drug
On treatment	**zongertinib** [redacted] **zongertinib** [redacted]	Date/time of administration of study drug	Date/time of administration of study drug in the respective treatment + [redacted] Or Date/time of the next administration of study drug (if any) Or 12:00 a.m. on day after last contact date (whichever occurs first)
Follow up	**F/U zongertinib** [redacted] **F/U zongertinib** [redacted]	Date/time of administration of study drug [redacted]	Date/time of administration of study drug in the next treatment period, if applicable Or Date/time of trial termination (12:00 a.m. on day after last contact date)

[1] See Section 6.7 for definition of baseline, which will be used in the statistical analyses of safety laboratory data and vital signs.

Section 7.2.5 of the CTP:

Note that AEs occurring after the last per protocol contact but entered before data base 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 report:

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). 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 **("Total on treatment")**

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. The labelling of the actual treatment in listings corresponds to the labelling of study phases

defined above. Single exception is the Follow-up phase where the actual treatment will be labelled “F/U <short label>”.

Safety laboratory data and vital signs will be analysed based on treatment groups with clear differentiation between baseline (cf. Section 6.7) and on-treatment measurements. Measurements will be considered on-treatment, if they were taken within the on-treatment phases as defined in Table 6.1: 2.

For detailed information on the handling of the treatments refer to Technical TSAP analysis data set (ADS) 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, it will be decided whether a discrepant data value can be used in analyses or whether it must be corrected in the clinical database. Each protocol deviation must be assessed to determine whether it is an important protocol deviation (iPD).

For definition of 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 trial master file (TMF) in electronic document management system (EDMS).

The iPDs will be summarised and listed in the CTR. Non-important COVID-19 related protocol deviations will only be listed.

6.3 INTERCURRENT EVENTS

Section is not applicable since no intercurrent events were defined in the CTP.

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/she contributes only one PK parameter value for one period to the statistical assessment. Descriptive and model-based analyses of PK parameters will be based on the PKS.*

Section 7.2.1.2 of the CTP:

The pharmacokinetic parameters listed in Section 2.1 and 2.2.2 for drug BI 1810631 (zongertinib) *will be calculated according to the relevant BI internal procedures.*

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

Important protocol deviations may be:

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

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

- *The subject experienced emesis that occurred at or before two times median t_{max} of the respective treatment (Median t_{max} is to be determined excluding the subjects experiencing emesis),*
- *A predose concentration of BI 1810631* (zongertinib) *is >5% C_{max} value of that subject*
- *Missing samples/concentration data at important phases of PK disposition curve*

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

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

Table 6.4: 1 Subject sets analysed

	Subject set	
Class of analysis	TS	PKS
Primary endpoints		X
Secondary endpoint		X
Further PK endpoints		X
Analyses of 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**.

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 (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 (6) and (7).

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

Section 7.2.5 of the CTP:

For laboratory data and vital signs baseline is defined as the last measurement prior to trial medication intake of respective treatment period.

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

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.

Model-based 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 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 (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. Listings will be sorted by subject number, visit and time point (if visit/ time point is applicable in the respective listing). AE listings will be sorted by assigned treatment (see Section 7.8.1 below for details). The listings will be contained in Appendix 16.2 (Subject data listings (SDL)) of the CTR.

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

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

For plasma and urine concentrations as well as for all PK parameters the following descriptive statistics will additionally be calculated:

CV	arithmetic coefficient of variation
gMean	geometric mean
gCV	geometric coefficient of variation

For PK parameters the following descriptive statistics will additionally be calculated:

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.

Tabulations of frequencies for categorical data will include all possible categories and will display the number of observations in a category as well as the percentage (%) relative to the respective treatment group (unless otherwise specified, all subjects in the respective subject set whether they have non-missing values or not).

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.

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

Exclusion of PK concentrations

The ADS "ADPC" (PK concentrations per time-point or per time-interval) contains column variables ACEX or 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 report, based on the TS. The data will be summarised by treatment sequence and in total.

7.2 CONCOMITANT DISEASES AND MEDICATION

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

Concomitant diseases and non-drug therapies will be coded according to the most recent version of the coding system of the Medical Dictionary for Drug Regulatory Activities (MedDRA). Concomitant medication 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 per treatment group without consideration of time intervals and treatment periods.

Previous and concomitant therapies will be presented per treatment sequence instead of treatment group.

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 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 will be decided no later than at the RPM.

7.3 TREATMENT COMPLIANCE

Section 4.3 of the CTP:

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

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

7.4 PRIMARY OBJECTIVE ANALYSIS

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

7.4.1 Main analysis

Section 7.2.2 of the CTP:

Primary analyses

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

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

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

μ = *the overall mean,*

ζ_i = *the* i^{th} *sequence effect, i = 1, 2,*

s_{im} = *the effect associated with the* m^{th} *subject in the* i^{th} *sequence, m = 1, 2, ..., 8*

π_j = *the* j^{th} *period effect, j = 1, 2,*

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

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

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

Point estimates for the ratios of the geometric means (test/reference) for the primary endpoints (see Section 2.1) 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 Company Standard Displays (CSD) macros based on the PKS. The following SAS code can be used:

```
PROC MIXED DATA=indata METHOD=REML;
        CLASS subject treatment sequence period;
        MODEL logpk = treatment sequence period / DDFM=KR;
        RANDOM subject(sequence);
        LSMEANS treatment / PDIFF CL ALPHA=0.1;
        ESTIMATE 'T-R' treatment -1 1;
RUN;
```

7.4.4 Supplementary analysis

This section is not applicable.

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 2.1.3) 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.

[redacted]

Safety and tolerability endpoints

Refer to Section 7.8 for a description of the analysis of safety and tolerability.

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 treated set.

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. All withdrawals will be documented and the reason for withdrawal recorded.

7.8.1 Adverse Events

AEs will be coded using the most recent version of 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 Table 6.1: 1.

An overall summary of AEs will be presented. This overall summary will include summary statistics for the class of adverse events of special interest (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 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).

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 treatment, maximum CTCAE grade, SOC and PT.

The system organ classes will be sorted alphabetically, PTs will be sorted in descending order by frequency (within SOC). The MedDRA version number will be displayed as a footnote in the respective output. AEs will be displayed by maximum CTCAE grade using the categorisation “All grades”, “Grade 1”, “Grade 2”, “Grade 3”, “Grade 4” and “Grade 5”.

For disclosure of AE data on ClinicalTrials.gov, the frequency of subjects with non-serious AEs occurring with an incidence of greater than 5 % (in preferred terms) 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, the frequency of non-serious AEs with an incidence of greater than 5 % (in preferred terms) and the frequency of SAEs will be summarised.

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 support of lay summaries, the frequency of participants with drug-related SAEs 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 (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 (checked at the RPM at the latest).

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

The analyses of vital signs (blood pressure, pulse rate) will be descriptive in nature. Descriptive statistics of vital signs over time and for the difference from baseline (see Section 6.7) will be provided.

Clinically relevant findings in vital signs data 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” (when they occurred during screening) or will be reported as AEs (when they occurred during treatment), and will be analysed as such. No separate listing or analysis of ECG data will be prepared.

7.9 OTHER ANALYSIS

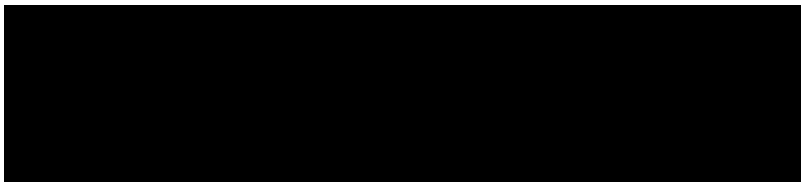
Not applicable.

8. TIMEPOINT OF RELEASE OF TREATMENT INFORMATION

The treatment information will be loaded into the trial database after randomisation.

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 / owning department "Med Clinical Development & Operations", DMS for controlled documents.
3.	*KM Asset BI-KMED-BDS-TMP-0059:* "iPD specification document (sdtm-dv-domain-specification)", current version; KMED
4.	*BI-VQD-12682-S-G_50-415_AD-03:* "Clinical Trial Analysis Decision Log (template)", current version, group / owning department "Med Biostatistics & Data Sciences", DMS for controlled documents.
5.	*KM Asset BI-KMED-BDS-HTG-0035:* "Handling of missing and incomplete AE dates", current version; KMED
6.	*KM Asset BI-KMED-TMCP-HTG-0025:* "Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics", current version; KMED
7.	*KM Asset BI-KMED-TMCP-MAN-0014:* "Noncompartmental Pharmacokinetic / Pharmacodynamic Analyses of Clinical Studies", current version; KMED
8.	*KM Asset BI-KMED-BDS-HTG-0045:* "Standards for Reporting of Clinical Trials and Project Summaries", current version; KMED
9.	*KM Asset BI-KMED-TMCP-OTH-0003*: "Graphs and Tables for Clinical Pharmacokinetics and Pharmacodynamic Noncompartmental Analyses", current version; KMED
10.	*KM Asset BI-KMED-TMCP-MAN-0010:* "Description of Analytical Transfer Files, PK/PD Data Files and ADA files", current version; KMED
11.	*KM Asset BI-KMED-BDS-HTG-0041:* "Analysis and Presentation of Adverse Event Data from Clinical Trials – Display Template", current version; KMED
12.	*KM Asset 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.	*KM Asset 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	**15-JAN-24**	[redacted]	None	This is the final TSAP.