Boehringer Ingelheim

TRIAL STATISTICAL ANALYSIS PLAN

Document No.:	**c43267449-01**
BI Trial No.:	1479-0006
Title:	A phase I, open-label trial in two parallel parts to investigate mass balance, metabolism, and basic pharmacokinetics of BI 1810631 (C-14) administered as oral solution (part A) and to investigate absolute bioavailability of BI 1810631 administered as film-coated tablet together with an intravenous microtracer dose of BI 1810631 (C-14) (part B) in healthy male volunteers Protocol #01 [c38775190]
Investigational Product(s):	BI 1810631 (zongertinib)
Responsible trial statistician(s):	[redacted] Phone: [redacted] Fax: [redacted]
Date of statistical analysis plan:	15 NOV 2023
Version:	1.0

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2. LIST OF ABBREVIATIONS

Term	Definition / description
ADME	Absorption, distribution, metabolism, and excretion
ADS	Analysis data set
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
$AUC_{0-\infty}$	Area under the concentration-time curve of the analyte over the time interval from 0 extrapolated to infinity
AUC_{0-tz}	Area under the concentration-time curve of the analyte over the time interval from 0 to the last quantifiable time point
BA	Bioavailability
BI	Boehringer Ingelheim
BP	Blood pressure
CARE	Clinical data analysis and reporting environment
CDR	Clinical data repository
CI	Confidence interval
C_{max}	Maximum measured concentration of the analyte in serum
COVID	Coronavirus disease
CRF	Case Report Form, paper or electronic (sometimes referred to as ‘eCRF’)
CTCAE	Common Terminology Criteria for Adverse Events
CTP	Clinical trial protocol
CTR	Clinical trial report
CV	Arithmetic coefficient of variation
DILI	Drug-induced liver injury
ECG	Electrocardiogram
EDC	Electronic data capture
EDMS	Electronic Document Management System
$fe_{faeces,\ 0-tz}$	fraction excreted in faeces as percentage of the administered dose over the time interval from 0 to the last quantifiable time point
$fe_{urine,\ 0-tz}$	fraction excreted in urine as percentage of the administered dose over the time interval from 0 to the last quantifiable time point

Term	Definition / description
gCV	geometric coefficient of variation
gMean	Geometric mean
EudraCT	European union drug regulating authorities clinical trials
ICH	International Conference on Harmonisation
INN	International Nonproprietary Name
iPD	Important protocol deviation
i.v.	intravenous
LLOQ	Lower limit of quantification
MedDRA	Medical Dictionary For Regulatory Activities
PK	Pharmacokinetic(s)
PKS	Pharmacokinetic parameter analysis set
PT	Preferred term
RAGe	Report appendix generator
REP	Residual fffect period
RPM	Report Planning Meeting
SAE	Serious adverse event
SD	Standard deviation
SDL	Subject data listing
SOC	System organ class
TMF	Trial master file
TS	Treated set
TSAP	Trial statistical analysis plan
ULN	Upper limit of normal range

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 revised clinical trial protocol (CTP), and to include detailed procedures for executing the statistical analysis of the primary variables and other data.

This Trial Statistical Analysis Plan (TSAP) assumes familiarity with the CTP and its 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 revised 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, randomisation.

Study data as collected in the Case Report Form (eCRF) will be stored in a trial database within the RAVE EDC system. All study data also including external data will then be uploaded to the CDR data warehouse.

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).

Pharmacokinetic (PK) parameters will be calculated using Phoenix WinNonlin™ software (version Phoenix 8.1.1, [redacted]

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.

All analyses described in this TSAP are in accordance with the statistical methods described in the CTP.

5. ENDPOINTS

5.1 PRIMARY ENDPOINT(S)

Part A (ADME part):

Primary endpoints are the following PK parameter of mass balance and total recovery of [^{14}C]-radioactivity in urine and faeces after oral single dose administration of zongertinib (C- 14), as defined in **Section 2.1.2 of the CTP**:

- *$fe_{urine,\ 0\text{-}tz}$ (fraction excreted in urine as percentage of the administered dose over the time interval from 0 to the last quantifiable time point)*
- *$fe_{faeces,\ 0\text{-}tz}$ (fraction excreted in faeces as percentage of the administered dose over the time interval from 0 to the last quantifiable time point)*

Part B (absolute BA part):

Primary endpoint is the following PK parameter in plasma for [^{14}C]zongertinib after intravenous administration and for zongertinib after oral administration, as defined in **Section 2.1.2 of the CTP**:

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

5.2 SECONDARY ENDPOINT(S)

5.2.1 Key secondary endpoint(s)

Not applicable.

5.2.2 Secondary endpoint(s)

Part A:

Secondary endpoints are the PK parameters of zongertinib and [^{14}C]-radioactivity (assessed by [^{14}C]zongertinib-EQ) in plasma, as defined in **Section 2.1.3 of the CTP**:

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

Part B:

Secondary endpoints are the PK parameters of [^{14}C]zongertinib in plasma after intravenous administration and for zongertinib after oral administration, as defined in **Section 2.1.3 of the CTP**:

- C_{max}
- $AUC_{0\text{-}tz}$

[redacted]

6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENT(S)

For basic study information on the treatment to be administered, and selection of dose, **cf. Section 4 of the CTP**. For information of overall trial design, **cf. Section 3.1 of the CTP**.

In Part A, subjects will receive a single oral solution of [redacted] zongertinib (C-14) containing a radioactive dose of approximately 3.7 MBq (Test 1 (T1)).

In Part B, subjects will receive at first a film-coated tablet of [redacted] zongertinib [redacted] (Test 2 (T2)) followed by i.v. infusion of [redacted] zongertinib (C-14) solution 2 h later (Reference (R)).

CTP Section 1.2.3: *The Residual Effect Period (REP) of a single dose of BI 1810631 is conservatively estimated as* [redacted].

For statistical analysis of AEs, the following analysis phases are defined for each subject.

Table 6.1: 1 Analysis phases for statistical analysis of AEs, and actual treatment for analysis of laboratory data and vital signs for part A

Study analysis phase	**Label**	**Start (inclusive)**	**End (exclusive)**
Screening[1]	**Screening**	Date of informed consent	Date/time of administration of study drug (test treatment T1)
On treatment	**zongertinib sol**	Date/time of administration of study drug (test treatment T1)	Date/time of administration of study drug + residual effect period [redacted] or 12:00 a.m. on day after subject's trial termination date, whichever occurs first
Follow-up	**F/U**	Date/time of administration of study drug + residual effect period [redacted]	12:00 a.m. on day after subject's trial termination 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.

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

Study analysis phase	**Label**	**Start (inclusive)**	**End (exclusive)**
Screening[1]	**Screening**	Date of informed consent	Date/time of administration of test treatment (T2)
On treatment	**zongertinib tab + iv**	Date/time of administration of test treatment (T2, film-coated tablet)	Date/time of administration of the last treatment (T2 or R) + residual effect period [redacted] or 12:00 a.m. on day after subject's trial termination date, whichever occurs first
Follow-up	**F/U**	Date/time of administration of last treatment (T2 or R) + residual effect period [redacted]	12:00 a.m. on day after subject's trial termination 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.

AE summary tables will present results for the on-treatment phase only. All AEs will be listed.

Safety laboratory data, vital signs and PK parameters will be analysed 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 phase as defined in Table 6.1: 1 and Table 6.1: 2. No distinction will be made between on- or off-treatment assessments of a post-baseline visit in the by-visit-summaries of vital signs.

More details on the technical implementation of these analyses are provided in the ADS Plan of this TSAP.

6.2 IMPORTANT PROTOCOL DEVIATIONS

Consistency check listings (for identification of deviations from 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 PD (iPD). For definition of iPDs, and for the process of

identification of these, refer to the BI reference document "Identify and Manage Important Protocol Deviations (iPD)" (2) and the DV domain template.

If any iPDs are identified, they are to be summarised into categories and will be captured in the decision log. Categories which are considered to be iPDs in this trial are defined in the DV domain template. If the data show other iPDs, the definition in the DV domain template will be supplemented accordingly by the time of the RPM.

iPDs will be summarised and listed. Which kind of iPDs could potentially lead to exclusion from which analysis set is specified in the DV domain template. The decision on exclusion of subjects from analysis sets will be made at the latest at the RPM, after discussion of exceptional cases and implications for analyses.

Non-important COVID-19 related PDs will only be listed.

Handling of iPDs in analysis is included in the DV domain specifications and stored within the TMF in EDMS.

6.3 INTERCURRENT EVENTS

This Section is not applicable.

6.4 SUBJECT SETS ANALYSED

The treated set (TS) and pharmacokinetic parameter analysis set (PKS) will be used as defined in the **CTP, Section 7.2.1.1**.

Table 6.4: 1 Subject sets analysed

	Subject set	
Class of analysis	Treated set	PKS
Primary endpoints		X
Secondary and further PK endpoints		X
Further safety endpoints & treatment exposure	X	
Disposition	X	
iPDs	X	
Demographic/baseline endpoints	X	

[redacted]

6.6 HANDLING OF MISSING DATA AND OUTLIERS

CTP Section 3.3.4: *If a subject is removed from or withdraws from the trial prior to the first administration of trial medication, the data of this subject will not be entered in the case report form (CRF) and will not be reported in the clinical trial report (CTR). If a subject is removed from or withdraws from the trial after the first administration of trial medication, this will be documented and the reason for discontinuation must be recorded in the CRF; in addition, trial data will be included in the CRF and will be reported in the CTR*

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

One exception where imputation might be necessary for safety evaluation is AE dates. Missing or incomplete AE dates are imputed according to BI standards (3).

CTP Section 7.3.2: *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 (4) and (5).

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

The last available value determined prior to study drug administration will be defined as baseline.

Time windows are defined in Section 6.1 of the CTP. Adherence to time windows will be checked at the RPM.

7. PLANNED ANALYSIS

The format of the listings and tables will follow the BI guideline "Reporting of clinical trials and project summaries" (6).

The individual values of all subjects will be listed. Listings will be sorted by treatment or subject number and visit (if visit 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 (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 serum 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 serum concentrations will be identical with 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. Percentages will be rounded to integer numbers. The category missing will be displayed if and only if there actually are missing values. Percentages will be based on all subjects in the respective subject set whether they have non-missing values or not.

No formal interim analysis is planned.

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Only descriptive statistics are planned for this section of the CTR. These will be based on the TS.

7.2 CONCOMITANT DISEASES AND MEDICATION

Concomitant diseases will be coded according to the most recent version of MedDRA. Concomitant medication will be coded according to the most recent version of the World Health Organisation - Drug Dictionary. Concomitant non-drug therapies will be coded according to the most recent version of MedDRA.

A medication will be considered concomitant to a dose group, 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).

CTP Section 7.2.5: *Previous and concomitant therapies will be presented per treatment group without consideration of time intervals and treatment periods*.

Only descriptive statistics based on the TS are planned for this section of the CTR.

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

7.3 TREATMENT COMPLIANCE

Treatment compliance will not be analysed as a specific endpoint. Any deviations from complete intake will be addressed in the RPM (cf. Section 6.2) 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

Part A:

CTP Section 7.2.2: *The primary endpoints (refer to Section 2.1.2) will be calculated according to the relevant BI internal procedures. The analysis will be descriptive in nature.*

These will be based on the PKS.

CTP Section 7.2.2: *To avoid underestimation of the total recovery of [^{14}C], the excretion during the non-sampling phase of the study will be estimated using linear interpolation between the observed 24-h sampling periods before and after the non-sampling period for urine and faeces respectively.*

Part B:

CTP Section 7.2.2: *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 the other effect '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, ..., 7*

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) for the dose-normalized 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 PK parameter described as the primary endpoint (see Section 5.1) will be the dose-normalized PK parameter.

This analysis will be based on the PKS.

Exclusion of PK parameters

The ADS ADPP 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 are based on PK parameter values which are not flagged for exclusion, i.e. with APEX equal to "Included".

CTP 7.2.1: *Plasma, urine and faeces 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*.

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. 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 only; the value is included for all other analyses. 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"(4) and "Description of Analytical Transfer Files and PK/PD Data Files" (5).

[redacted]

7.4.4 Supplementary analysis

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

The analysis of secondary PK endpoints will be based on the PKS.

CTP Section 7.2.3: *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*.

As for the primary endpoint analysis, the PK parameters described as secondary endpoints (see Section 5.2.2) will be the dose-normalized PK parameters.

Exclusion of PK parameters and exclusion of plasma concentrations are handled as described in Section 7.4.1.

7.6 FURTHER OBJECTIVE ANALYSIS

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

7.6.1 Further pharmacokinetic endpoints

CTP Section 7.2.4.1*: Further PK endpoints will be analysed descriptively.*

The analysis of standard PK parameters is performed according to BI standards (4).

7.6.2 Safety parameters

Safety endpoints and tolerability will be analysed as described in Section 7.8 of this TSAP.

7.7 EXTENT OF EXPOSURE

Since only a single dose is administered per subject, a listing will be sufficient to give account of the extent of exposure.

7.8 SAFETY ANALYSIS

All safety analyses will be performed on the TS.

7.8.1 Adverse Events

AEs will be coded with the most recent version of MedDRA.

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.

For further details on summarization of AE data, please refer to "Analysis and Presentation of Adverse Event Data from Clinical Trials" (7) and "Handling of missing and incomplete AE dates" (3).

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 phase and follow-up phase as defined in Section 6.1. AEs will be analysed based on actual treatments, as defined in Table 6.1: 1 and Table 6.1: 2 .

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

CTP Section 5.2.6.1.4: 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*

[redacted]

[redacted]

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

According to ICH E3 (8), 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. AEs which were considered by the investigator to be drug related will be summarised and listed separately. Separate tables will also be provided for subjects with SAEs and subjects with AESIs. [redacted]

The SOCs and preferred terms within SOCs will be sorted by descending frequency over all treatment groups.

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 preferred term. 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.

For support of lay summaries, the frequency of subjects with drug-related SAEs will be summarised by treatment, primary SOC and preferred term.

7.8.2 Laboratory data

The analyses of laboratory data will be descriptive in nature and will be based on BI standards "Display and Analysis of Laboratory Data" (9).

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.

Descriptive statistics of laboratory values over time and for the difference from baseline (see Section 6.7) will be provided. Frequency tables of changes between baseline and last value on treatment with respect to the reference range will be presented.

Unscheduled measurements of laboratory 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. Descriptive statistics 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).

Laboratory data will be compared to their reference ranges. Values outside the reference range will be highlighted in the listings.

Clinically relevant findings in laboratory data will be reported as baseline conditions (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.

7.8.3 Vital signs

The analyses of vital signs (blood pressure and 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.

Unscheduled measurements of vital signs will be assigned to planned time points in the same way as described above for laboratory data. However, for vital signs, descriptive statistics will be calculated by planned time point based on the last value of the subject at that planned time point (or assigned to that planned time point). An unscheduled measurement more than 20 minutes after the time of the scheduled measurement of that planned time point will be listed, but will not be used in calculation of descriptive statistics. These measurements are

interpreted as off-schedule vital signs measurements, taken for other reasons. If the time of measurement is missing for a scheduled measurement, the scheduled measurement will be used in calculation of descriptive statistics (as time difference between scheduled and unscheduled cannot be assessed).

If the time of measurement is missing for an unscheduled measurement, this measurement will be listed but will be ignored for the calculation of descriptive statistics.

7.8.4 ECG

Abnormal findings in ECG 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. No separate listing or analysis of ECG data will be prepared.

7.8.5 Other

7.8.5.1 Physical examination

Physical findings will be reported as relevant medical history/baseline condition (if a condition already exists before first administration of study treatment) or as AE (if condition emerges after first administration of study treatment) and will be summarised as such. No separate listing or analysis of physical examination findings will be prepared.

7.8.5.2 Body weight

Body weight will only be listed.

7.8.5.3 Local tolerability

Part B only: Local findings assessed as clinically relevant by the investigator must be recorded as AE.

Local tolerability (absence or presence of "swelling", "induration", "heat", "redness", "pain", or "other findings") will be summarised by frequency of subjects with local findings with counts and percentages overall (i.e. over all on-treatment time points, cf. Section 6.1) as well as by time point.

7.9 OTHER ANALYSIS

Not applicable.

8. TIMEPOINT OF RELEASE OF TREATMENT INFORMATION

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

9. REFERENCES

1	CPMP/ICH/363/96: "Statistical Principles for Clinical Trials", ICH Guideline Topic E9; Note For Guidance on Design, Conduct, Analysis and Evaluation of Clinical Trials, current version
2	BI-VQD-12045_40-413: "Identify and Manage Important Protocol Deviations (iPD)", current version; DMS for controlled documents
3	KM Asset BI-KMED-BDS-HTG-0035: "Handling of missing and incomplete AE dates", current version; DMS for controlled documents
4	KM Asset BI-KMED-TMCP-MAN -0014: "Noncompartmental PK/PD Analyses of Clinical Studies", current version; DMS for controlled documents
5	KM Asset BI-KMED-TCMP-MAN-0010: "Description of Analytical Transfer Files, PK/PD Data Files and ADA files", current version; DMS for controlled documents
6	KM Asset BI-KMED-BDS-HTG-0045: "Standards for Reporting of Clinical Trials and Project Summaries", current version; DMS for controlled documents
7	KM Asset BI-KMED-BDS-HTG-0066: "Analysis and Presentation of Adverse Event Data from Clinical Trials", current version; DMS for controlled documents
8	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
9	KM Asset BI-KMED-BDS-HTG-0042: "Handling, Display and Analysis of Laboratory Data", current version; DMS for controlled documents

11. HISTORY TABLE

Table 11: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
1.0	**15-NOV-23**	[redacted]	None	This is the final TSAP.