TRIAL STATISTICAL ANALYSIS PLAN

Document No.:	**c44035218-01**
BI Trial No.:	**1479-0019**
Title:	Bioequivalence of zongertinib tablets from two different manufacturers following oral administration in healthy male and female subjects (an open-label, randomised, single-dose, two-period, two-sequence crossover trial)
Investigational Product(s):	Zongertinib (BI 1810631)
Responsible trial statistician(s):	[redacted] Phone: [redacted] Fax: [redacted]
Date of statistical analysis plan:	18 JUL 2024
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2. LIST OF ABBREVIATIONS

Term	Definition / description
$\%AUC_{tz-\infty}$	The Percentage of $AUC_{0-\infty}$ Obtained by Extrapolation
ADS	Analysis Data Set
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine Aminotransferase
ANOVA	Analysis of Variance
AST	Aspartate Aminotransferase
AUC_{0-72h}	Area Under the Concentration-time Curve of the Analyte in Plasma Over the Time Interval from 0 to 72h
$AUC_{0-\infty}$	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
AUC_{t1-t2}	Area Under the Concentration-time Curve of the Analyte in Plasma Over the Time Interval t1 to t2
BI	Boehringer Ingelheim
BMI	Body Mass Index
BP	Blood Pressure
CDR	Clinical Data Repository
CL/F	Apparent Clearance of the Analyte in the Plasma After Extravascular Administration
C_{max}	Maximum Measured Concentration of the Analyte in Plasma
CTCAE	Common Terminology Criteria for Adverse Events
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
DILI	Drug-Induced Liver Injury
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EDMS	Electronic Document Management System
ICH	International Conference of Harmonisation

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Term	Definition / description
iPD	Important Protocol Deviations
λ_z	Terminal Rate Constant in Plasma
MedDRA	Medical Dictionary for Drug Regulatory Activities
MRT_{po}	Mean Residence Time of the Analyte in the Body After Oral Administration
PD	Pharmacodynamic
PK	Pharmacokinetic
PKS	Pharmacokinetic Parameter Analysis Set
PR	Pulse Rate
PT	Preferred Term
R	Reference
RAGe	Report Appendix Generator System
REP	Residual Effect Period
RPM	Report Planning Meeting
SAE	Serious Adverse Event
SOC	System Organ Class
SOP	Standard Operating Procedure
T	Treatment
$t_{1/2}$	Terminal half-life of the Analyte in Plasma
t_{max}	Time from Dosing to Maximum Measured Concentration of the Analyte in Plasma
TMCP	Translational Medicine and Clinical Pharmacology
TMF	Trial Master File
TS	Treated Set
TSAP	Trial Statistical Analysis Plan
ULN	Upper Limit of Normal
V_z/F	Apparent Volume of Distribution During the Terminal Phase After Extravascular Administration
WHO-DD	World Health Organization - Drug Dictionary

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3. INTRODUCTION

As per ICH E9 (9.1), 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, randomisation.

Study data as collected in the electronic case report form (eCRF) will be stored in a trial database within the RAVE electronic data capture (EDC) system. All study data (including external data) will then be uploaded to the 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).

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4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

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

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5. ENDPOINTS

5.1 PRIMARY ENDPOINT(S)

Section 2.1.2 of the CTP:

The following pharmacokinetic parameters will be determined for zongertinib:

- *$AUC_{0\text{-}72h}$ (area under the concentration-time curve of the analyte in plasma over the time interval from 0 to 72h)*
- *C_{max} (maximum measured concentration of the analyte in plasma)*

5.2 SECONDARY ENDPOINT(S)

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 zongertinib:

- *t_{max} (time from dosing to maximum measured concentration of the analyte in plasma)*

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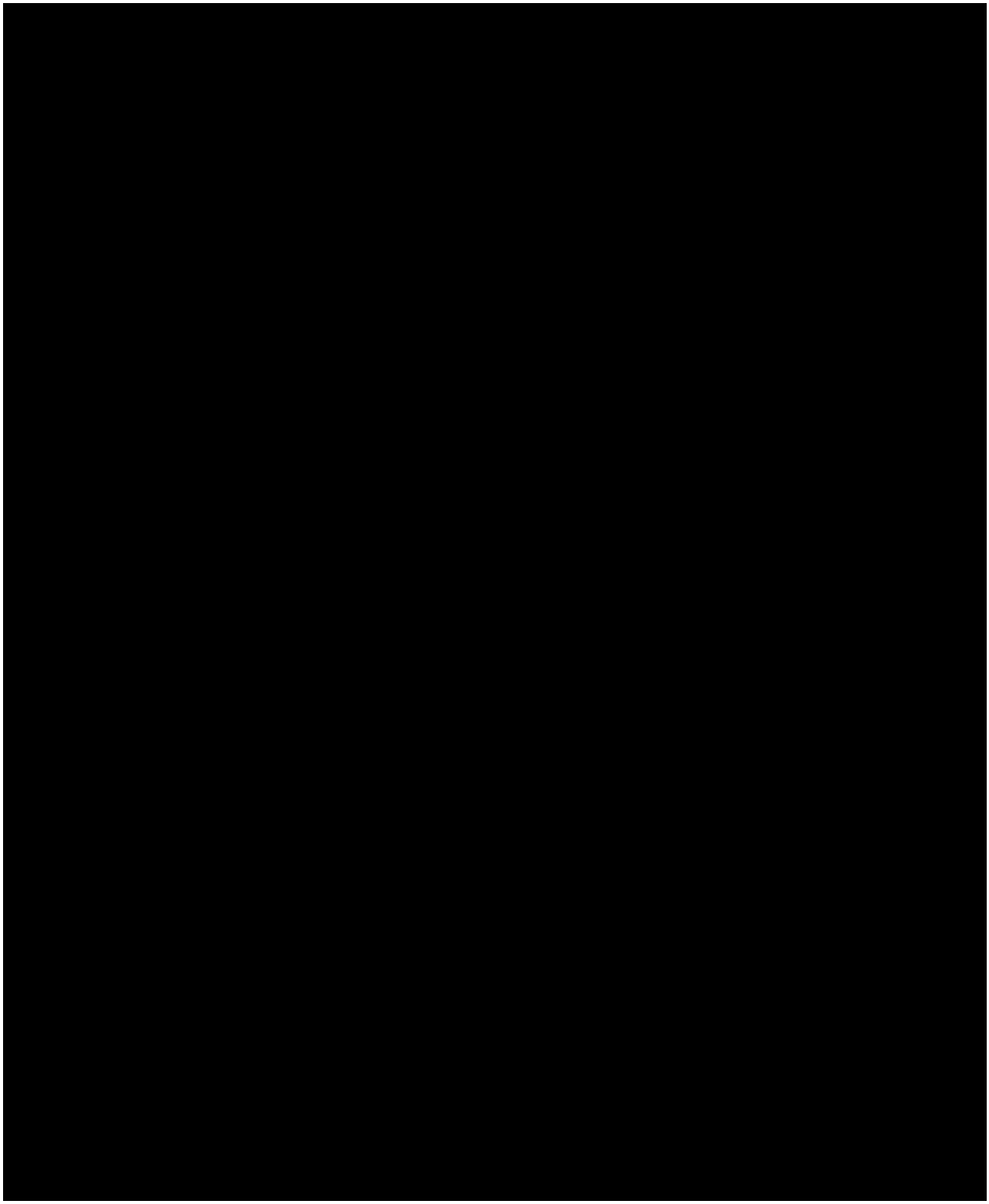

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6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENT(S)

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

Section 3.1 of the CTP:

The trial will be performed as an open-label, randomized, single-dose, two period, two sequence crossover trial in healthy male and female subjects in order to compare the test treatment (T) to the reference treatment (R).

The subjects will be randomly allocated to the 2 treatment sequences (T-R or R-T).

There will be a washout period of [redacted] *between the treatments.*

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

Table 6.1:1 Treatments and labels used in the analysis

Treatment	Label	Short label
T	[redacted] zongertinib tablet manufactured by [redacted] administered [redacted]	Test treatment
R	[redacted] zongertinib tablet manufactured by [redacted] administered to subjects [redacted]	Reference treatment

It is planned to include a total of 56 healthy male and female subjects in the trial.

Section 1.2.2 of the CTP:

The Residual Effect Period (REP) of single doses of BI 1810631 (zongertinib) *is conservatively estimated as 14 days. This is the period after the last dose during which measurable drug levels and/or pharmacodynamic* (PD) *effects are still likely to be present.*

Based on this, the study phases in Table 6.1:2 will be defined for the analysis of adverse events (AEs):

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Table 6.1:2 Definition of analysing treatment periods for safety analysis

Analysis phase	Label	Start Date	End Date
Screening	Screening	Date/time of informed consent	Date/time of first drug administration
On-treatment	Test treatment, Reference treatment	Date/time of zongertinib administration (T/R) in the respective treatment period	Date/time of next zongertinib administration (R/T) OR date/time of the drug administration [redacted], whichever is earlier.
Follow-up	F/U	Date/time of the zongertinib administration (T/R) [redacted]	Date/time of next zongertinib administration (R/T), if applicable OR Date/time of EoS visit (last per protocol contact date).

Section 7.2.5 of the CTP:

Note that AEs occurring after the last per protocol contact 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:

AE displays in CTR Section 15.3 and Appendix 16.1.13.1.8 (for ClinicalTrials.gov and EudraCT) will present results for the on-treatment phase (as defined in Table 6.1:2) only. Screening and follow-up phase will not be included in this analysis.

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

- **"Total on-trt"**, defined as the total over all on-treatment phases involving zongertinib

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.

More details 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 randomised subjects.

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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 important protocol deviations (iPD), and for the process of identification of these, refer to the Boehringer Ingelheim (BI) Standard Operating Procedure (SOP) “Identify and Manage Important Protocol Deviations (iPD)” (9.2).

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) (9.3) and in the decision log (9.4). Both documents will be stored within the trial master file (TMF) in electronic document management system (EDMS).

The iPDs will be summarised by sequence and listed in the CTR.

6.3 INTERCURRENT EVENTS

This section is not applicable.

6.4 SUBJECT SETS ANALYSED

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

- *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.*

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Table 6.4:1 Subject sets analysed

	Subject set	
Class of analysis	TS	PKS
Disposition	X	
iPDs	X	
Primary PK endpoints		X
Secondary PK endpoint		X
Further PK endpoints		X
Safety & treatment exposure	X	
Demographic & baseline	X	

[redacted]

6.6 HANDLING OF MISSING DATA AND OUTLIERS

Section 3.3.4 of the CTP:

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.

Section 7.3.1 of the CTP:

It is not planned to impute missing values for safety parameters.

Missing or incomplete AE dates are imputed according to BI standards (9.5).

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 (9.6) and (9.7).

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6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

For all parameters if not specified otherwise, the last non-missing value determined prior to dosing of the trial medication of the respective treatment period will be defined as baseline.

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.

Time windows *for vital signs, ECG, and laboratory tests* are defined in Section 6.1 of the CTP:
If not stated otherwise in the Flow Chart, the acceptable deviation from the scheduled time for vital signs, ECG, and laboratory tests will be ± 30 min.

Details about acceptable deviations from the scheduled time for PK sampling, safety laboratory sampling and vital signs are given in Table 6.7:1. Adherence to time windows will be checked at the RPM.

Table 6.7:1 Time windows for safety laboratory, vital signs, and PK sampling

Day	Planned time (relative to drug administration) [h:min]	Event and comment	Time Windows for Safety laboratory and vital signs	PK blood zongertinib	Time Windows for PK
-21 to -1		Screening (SCR)			
-1	-13:00	Admission to trial site			
1	-2:00	Allocation to treatment (visit 2 only)	-3h	x	- 3 h (prior to drug administration)
	0:00	Drug administration: zongertinib			
	0:30			x	± 5 min
	1:00			x	± 5 min
	1:30			x	± 5 min
	2:00	[redacted]		x	± 5 min
	2:30			x	± 5 min
	3:00			x	± 5 min
	3:30			x	± 5 min

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Day	Planned time (relative to drug administration) [h:min]	Event and comment	Time Windows for Safety laboratory and vital signs	PK blood zongertinib	Time Windows for PK
	4:00	[redacted]		x	± 5 min
	5:00	[redacted]			
	6:00			x	± 15 min
	8:00			x	± 15 min
	10:00			x	± 15 min
	11:00	[redacted]			
	12:00			x	± 15 min
2	24:00		± 30 min	x	± 60 min
	36:00			x	± 60 min
3	48:00	Discharge from trial site		x	± 60 min
4	72:00	Ambulatory visit		x	± 120 min
15 to 18		End of study (EoS) examination			

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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.

Statistical model-based analysis of PK endpoints (refer to Section 7.4) will be performed by [redacted] and will be presented in Section 15.5 of the CTR and Appendix 16.1.13.3.

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

The format of the listings and tables will follow the BI guideline "Reporting of clinical trials and project summaries" (9.8) with the exception of those generated for PK-calculations following BI standards for PK/PD analysis (9.9).

The individual values of all subjects will be listed. Listings will be sorted by treatment or sequence group, subject number and visit. The listings will be included in Appendix 16.2 of the CTR.

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

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

For plasma 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 plasma 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

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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 sequence. The percentages are given in integer numbers, because the sample size and denominator is smaller than 100. The category missing will be displayed only if there are actually missing values.

Exclusion of PK concentrations and parameters

Section 7.2.1.2 of the CTP:

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*
- *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 tmax of the respective treatment (Median tmax is to be determined excluding the subjects experiencing emesis),*
- *A predose concentration is >5% Cmax 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).

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7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Only descriptive statistics are planned for this section of the report.

This section of the report will be based on the TS.

7.2 CONCOMITANT DISEASES AND MEDICATION

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

Concomitant diseases and non-drug therapies will be coded according to the most recent version at the time of DBL of the coding system of the Medical Dictionary for Drug Regulatory Activities (MedDRA). Concomitant medication will be coded according to the most recent version at the time of DBL of the World Health Organization - Drug Dictionary (WHO-DD). The coding version number will be displayed as a footnote in the respective output.

A medication 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).

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 sequence without consideration of time intervals and treatment periods.

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

7.3 TREATMENT COMPLIANCE

Section 4.3 of the CTP

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

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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

Bioequivalence will be investigated on the primary PK endpoints $AUC_{0\text{-}72h}$ and C_{max} for zongertinib.
The statistical model used for the analysis of the primary endpoints of the trial will be an analysis of variance (ANOVA) model on the logarithmic scale as described in the **CTP, section 7.2.2**.

The data analysis will be implemented using SAS PROC MIXED, based on the PKS. The following pseudo SAS code will be applied.

```
PROC MIXED DATA=indata;
 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;
```

Point estimates of the treatment difference, the ratios of the geometric means for the primary endpoints, and their two-sided 90% confidence intervals will be provided. For the comparison Test versus Reference, the point estimate for each relevant PK parameter will be compared to the acceptance interval 80.00% to 125.00%.

Section 7.2.2 of the CTP

Bioequivalence is considered established if the 90% confidence intervals of the geometric means for the primary endpoints are contained in the pre-defined acceptance range, see Section 7.1. (of the CTP)

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[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

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

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 descriptively.

Note: The secondary endpoint is defined in Section 5.2.2.

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 Safety and tolerability endpoints

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

7.6.2 Pharmacokinetic endpoints

The analysis of further endpoints will be based on the PKS.

Section 7.2.4.1 of the CTP:

Further PK endpoints will be analysed descriptively.

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7.7 EXTENT OF EXPOSURE

Descriptive statistics are planned for this section of the report based on the TS. The date and time of drug administration will be listed for each subject.

7.8 SAFETY ANALYSIS

All safety analyses will be performed on the TS.

The safety data for treated subjects who failed to complete the 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” (9.10), “Analysis and Presentation of AE data from clinical trials” (9.11) and "Handling of missing and incomplete AE dates" (9.5) 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.

An overall summary of AEs will be presented with additional entry for subjects with AEs by highest CTCAE grade. This overall summary will comprise summary statistics for the class of other significant AEs according to ICH E3 (9.12) and 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

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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 (9.12), in addition to Deaths and serious AEs, "other significant" AEs need to be listed in the CTR. These will be any non-serious AE that led to an action taken with study drug (e.g. discontinuation or dose reduced or interrupted).

A separate table will be provided for subjects with other significant AEs and a flag for serious and non-serious will be included in the respective listing.

The frequency of subjects with AEs will be summarised by maximum CTCAE grade, treatment, primary system organ class (SOC) and preferred term (PT). AEs which were considered by the investigator to be drug related will be summarised separately.

Separate tables will be provided for subjects with SAEs, for subjects with drug-related AEs, for subjects with drug-related serious adverse events, for subjects with AESIs and for subjects with other significant AEs (according to ICH E3 (9.12)).

In addition, the frequency of subjects with AEs will be summarised by highest CTCAE grade, treatment, primary SOC and PT.

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

Separate tables will be provided for subjects with:

- All AEs
- Serious AEs (SAEs)
- AESI
- Severe AEs, i.e. AEs with CTCAE grade ≥ 3.
- Related AEs (any drug-related, to zongertinib by [redacted] to zongertinib by [redacted]

Reported fatal AEs will be listed.

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 PTs) will be summarised by treatment, primary SOC and PT. The frequency of subjects with SAEs will also be summarised.

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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 PTs) and the frequency of SAEs will be summarised.

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 "Display and Analysis of Laboratory Data" (9.13).

Analyses will be based on normalised values, which mean 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.

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 first value of the subject at that planned time point (or assigned to that planned time point). For baseline value, the last measurement before drug administration in each treatment period will be used, if not specified otherwise.

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

Abnormal findings will be reported as baseline conditions (at screening) or as AEs (during the trial) if judged clinically relevant by the investigator.

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7.9 OTHER ANALYSIS

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

This section is not applicable as no biomarker analysis has been specified in the protocol.

7.9.2 PK / PD analyses

This section is not applicable as no specific PK/PD analysis has been specified in the protocol.

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8. TIMEPOINT OF RELEASE OF TREATMENT INFORMATION

The treatment information will be loaded into the trial database at trial initiation, i.e., the database will be handled open-label in accordance with the CTP.

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9. REFERENCES

9.1	*CPMP/ICH/363/96:* "Statistical Principles for Clinical Trials", ICH Guideline Topic E9, Note For Guidance on Statistical Principles for Clinical Trials, current version.
9.2	*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.
9.3	*BI-KMED-BDS-TMP-0059:* "iPD specification document (sdtm-dv-domainspecification)", template, current version, group/owning department "Clinical Operations", DMS for controlled documents..
9.4	*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.
9.5	*BI-KMED-BDS-HTG-0035:* "Handling of missing and incomplete AE dates", current version, group/owning department "Med Biostatistics & Data Sciences", DMS for controlled documents.
9.6	*BI-KMED-TMCP-MAN-0014:* "Noncompartmental Pharmacokinetic / Pharmacodynamic Analyses of Clinical Studies", current version, group/owning department "Med Translational Medicine Clinical Pharmacology", DMS for controlled documents..
9.7	*BI-KMED-TMCP-MAN-0010:* "Description of Analytical Transfer Files, PK/PD Data Files and ADA files", current version, group/owning department "Med Translational Medicine Clinical Pharmacology", DMS for controlled documents..
9.8	*BI-KMED-BDS-HTG-0045:* "Standards for Reporting of Clinical Trials and Project Summaries", current version, group/owning department "Med Biostatistics & Data Sciences", DMS for controlled documents.
9.9	*BI-KMED-TMCP-OTH-0003*: "Graphs and Tables for Clinical Pharmacokinetics and Pharmacodynamic Noncompartmental Analyses", current version, group/owning department "Med Translational Medicine Clinical Pharmacology", DMS for controlled documents.
9.10	*BI-KMED-BDS-HTG-0041:* "Analysis and Presentation of Adverse Event Data from Clinical Trials – Display Template", current version; KMED
9.11	*BI-KMED-BDS-HTG-0066:* "Analysis and Presentation of AE data from clinical trials", current version; KMED
9.12	*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.

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9.13	*BI-KMED-BDS-HTG-0042:* "Handling, Display and Analysis of Laboratory Data", current version; KMED

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11. HISTORY TABLE

Table 11: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
1.0	**18-Jul-24**	[redacted]	None	This is the final TSAP.