TRIAL STATISTICAL ANALYSIS PLAN

Document No.:	**c43291554-01**
BI Trial No.:	1479-0011
Title:	The effect of multiple doses of carbamazepine on the pharmacokinetics of a single oral dose of BI 1810631 in healthy male subjects (an open-label, two-period, fixed-sequence trial) Revised protocol #03 [c40561285-03]
Investigational Product(s):	BI 1810631 (zongertinib)
Responsible trial statistician(s):	[redacted] Phone: +[redacted] Fax: +[redacted]
Date of statistical analysis plan:	03 Jan 2024
Version:	1.0
	Page 1 of 30

1. TABLE OF CONTENTS

[redacted]

[redacted]

LIST OF TABLES

2. LIST OF ABBREVIATIONS

Term	Definition / description
AE	Adverse event
AESI	Adverse events of special interest
ANOVA	Analysis of variance
$AUC_{0-\infty}$	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity
$\%AUC_{tz-\infty}$	Percentage of $AUC_{0-\infty}$ obtained by extrapolation
AUC_{t1-t2}	Area under the concentration-time curve of the analyte in plasma over the time interval t_1 to t_2
AUC_{0-tz}	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 to the last quantifiable data point
BI	Boehringer Ingelheim
BMS	Biomarker parameter analysis set
BP	Blood pressure
carba	Carbamazepine
CI	Confidence interval
CL/F	Apparent clearance of the analyte in plasma after extravascular administration
C_{max}	Maximum measured concentration of the analyte in plasma
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
CYP3A	Cytochrome P450 family 3 subfamily A
DILI	Drug induced liver injury
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
EoS	End of Study (synonym for End of Trial)
F/U	Follow-up
gCV	Geometric coefficient of variation
gMean	Geometric mean
iPD	Important protocol deviation
λ_z	Terminal rate constant of the analyte in plasma
LC-MS/MS	Liquid chromatography with tandem mass spectrometry

Term	Definition / description
MedDRA	Medical Dictionary for Regulatory Activities
MRT_{po}	Mean residence time of the analyte in the body after oral administration
PK	Pharmacokinetic(s)
PKS	Pharmacokinetic parameter analysis set
PR	Pulse rate
Q1	1st quartile
Q3	3rd quartile
R	Reference treatment
REP	Residual effect period
SAE	Serious adverse event
SCR	Screening
T	Test product or treatment
$t_{1/2}$	Terminal half-life of the analyte in plasma
t_{max}	Time from (last) dosing to the maximum measured concentration of the analyte in plasma
TS	Treated set
t_z	Time of last measurable concentration of the analyte in plasma
TSAP	Trial statistical analysis plan
ULN	Upper limit of normal
V_z/F	Apparent volume of distribution during the terminal phase after extravascular administration
zonger	Zongertinib

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 protocol, and to include detailed procedures for executing the statistical analysis of the primary and secondary variables and other data.

This TSAP assumes familiarity with the Clinical Trial Protocol (CTP), including Protocol Amendments. In particular, the TSAP is based on the planned analysis specification as written in CTP Section 7 “Statistical Methods and Determination of Sample Size”. Therefore, TSAP readers may consult the CTP for more background information on the study, e.g., on study objectives, study design and population, treatments, definition of measurements and variables, planning of sample size.

Study data as collected in the 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).

PK parameters will be calculated using Phoenix WinNonlin™ software (version Phoenix 8.1.1 or higher, [redacted].

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 revised CTP.

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.

5. ENDPOINTS

5.1 PRIMARY ENDPOINTS

Primary endpoints are PK endpoints of zongertinib, as defined in **Section 2.1.2 of the CTP**.

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

5.2 SECONDARY ENDPOINT

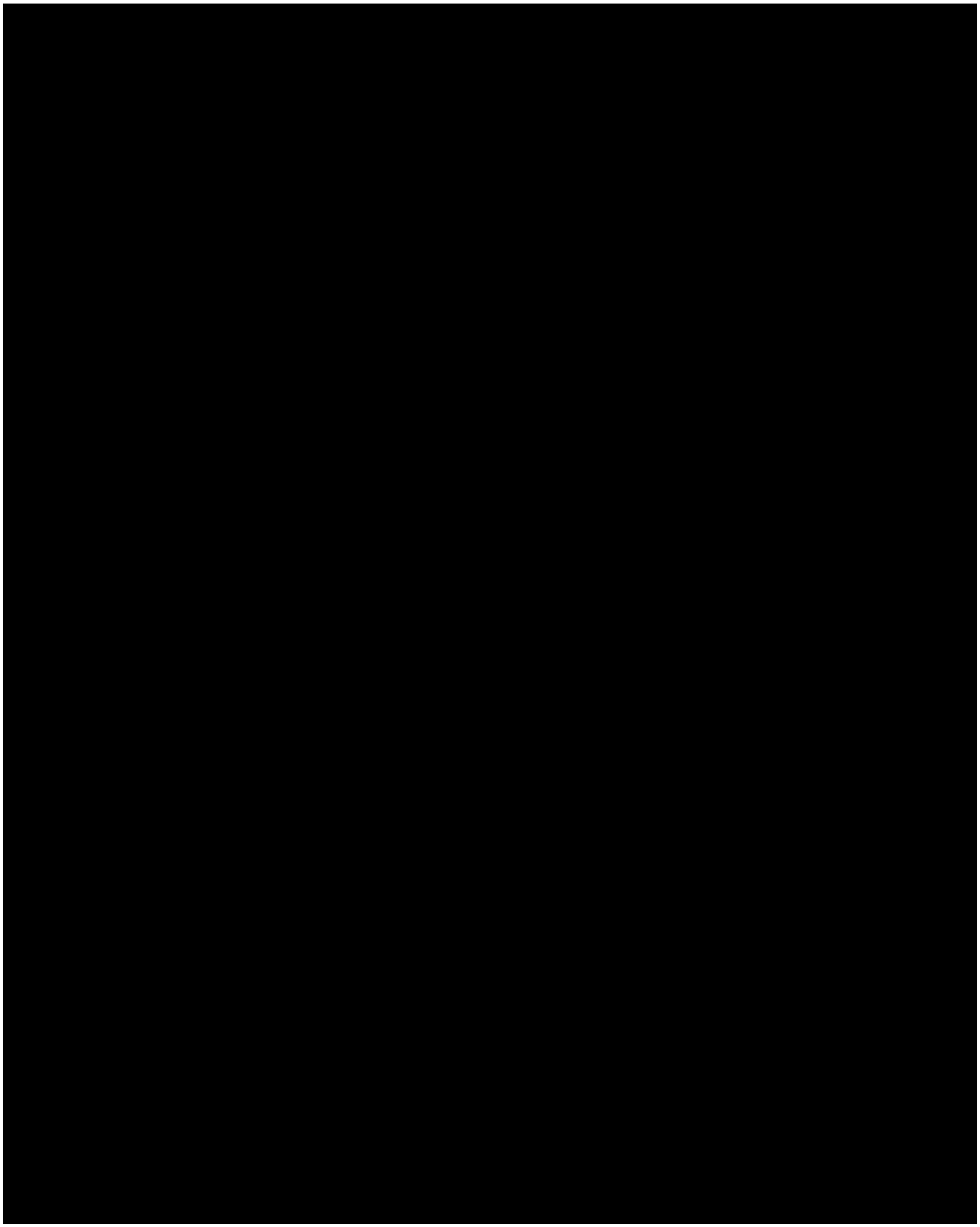
5.2.1 Key secondary endpoint

Not applicable.

5.2.2 Secondary endpoint

Secondary endpoint is the PK endpoint of zongertinib, as defined in **Section 2.1.3 of the CTP:**

- *AUC_{0-tz} (area under the concentration-time curve of the analyte in plasma over the time interval from 0 to the last quantifiable data point)*



6. GENERAL ANALYSIS DEFINITIONS

6.1 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.**

This is a two-period trial with a fixed sequence R-T. In Period 1 subjects will receive zongertinib alone (Reference treatment (R)) whereas in Period 2 carbamazepine plus zongertinib (Test treatment (T)) will be administered.

For treatment R in Period 1, each subject will receive:

- 60 mg zongertinib administered as film-coated tablet on Day 1 of Visit 2,

and for treatment T in Period 2, each subject will receive:

- Multiple doses of 200 mg carbamazepine administered in the evening for 4 days (Day -18 to Day -15 of Visit 3), of 400 mg carbamazepine administered in the evening for 7 days (Day -14 to Day -8 of Visit 3) and 600 mg carbamazepine administered in the evening for 13 days (Day -7 to Day 6 of Visit 3) as extended release tablets.
- 60 mg zongertinib as film-coated tablet in the morning on Day 1 of Visit 3

Morning doses of zongertinib are administered in fasted state. Carbamazepine will be administarted after dinner.

CTP Section 1.2.3: *The Residual Effect Period (REP) of single doses of* [zongertinib] (*BI 1810631*) *is conservatively estimated as 14 days. This is the period after the last dose during which measurable drug levels and/or pharmacodynamic effects are still likely to be present. The REP of carbamazepine is defined as 8 days.*

For statistical analysis of AEs, the following analysis phases are defined for each subject. Analysis phases for active treatments are defined separately for Period 1 and Period 2.

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

Study analysis phase	Label	Start (inclusive)	End (exclusive)
Screening[1]	**Screening**	Date of informed consent	Date/time of first administration of zongertinib
On treatment	**zongertinib**	Date/time of first administration of zongertinib	Date/time of first administration of zongertinib + REP (14 days * 24 hours) or Date/time of first administration of carbamazepine or 12:00 a.m. on day after subject's trial termination date, whichever occurs earlier
Follow-up	**F/U zongertinib**	Date/time of first administration of zongertinib + REP (14 days * 24 hours)	Date/time of first administration of carbamazepine or 12:00 a.m. on day after subject's trial termination date, whichever occurs earlier.
On treatment	**zonger + carba loading**	Date/time of first administration carbamazepine	Date/time of first administration of zongertinib + REP (14 days * 24 hours).
On treatment	**carba loading**	Date/time of first administration of zongertinib + REP (14 days * 24 hours)	Date/time of second administration of zongertinib (Visit 3, Day 1)
On treatment	**zonger + carba**	Date/time of second administration of zongertinib (Visit 3, Day 1)	(Date/time of second administration of zongertinib (Visit 3, Day 1) + REP (14 days * 24 hours) or Date/time of last administration of carbamazepine + REP (8 days * 24 hours), whichever occurs later) or 12:00 a.m. on day after subject's trial termination date, whichever occurs earlier.
Follow-up	**F/U zonger + carba**	Date/time of last administration of zongertinib + REP (14 days * 24 hours) or Date/time of last administration of carbamazepine + REP (8 days * 24 hours), whichever occurs later	12:00 a.m. on day after 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 displays in CTR Section 15.3, Appendix 16.1.13.1.8. will present results for the on-treatment phase only defined in Table 6.1: 1. Screening will not be included in this analysis.

All AEs will be listed, based on the “actual treatment” defined in these tables.

In AE tables in CTR Section 15.3 (but not in displays for ClinicalTrials.gov or EudraCT), the following totals will be provided in addition:

- "Total zongertinib ", defined as the total over all on-treatment phases involving zongertinib (either as zongertinib as administrated in this phase or the REP of zongertinib administration overlaps with this phase)
- "Total carbamazepine ", defined as the total over all on-treatment phases involving carbamazepine
- "Total on-trt", defined as the total over all on-treatment phases.

In the safety laboratory as well as vital sign tabels and figures, the data will be presented by trial period. The first period will be labeled ‘zongertinib’. The on-treatment phases ‘zonger + carba loading’, ‘carba loading’, and ‘zonger + carba’ will be part of the second period labeled ‘zongertinib + carba’.

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)" (9.2) and the DV domain template.

If any iPDs are identified, they are to be summarized 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 summarized 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. If the data show other iPDs, this table will be supplemented accordingly by the time of the RPM.

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

The documentation of the iPD categories and how to handle iPDs in the analysis are done in the DV domain specifications, which is stored within the TMF in EDMS.

6.3 INTERCURRENT EVENTS

This Section is not applicable.

6.4 SUBJECT SETS ANALYSED

The treated set (TS), the pharmacokinetic parameter analysis set (PKS) and the biomarker parameter analysis set (BMS) 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	BMS
Disposition	X		
iPDs	X		
Primary endpoints		X	
Secondary endpoint		X	
Further PK endpoints		X	
Drug-drug interaction biomarker endpoints			X
Safety parameters	X		
Demographic/baseline characteristics, concomitant diseases, concomitant medications and concomitant procedures	X		
Treatment exposure	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 (9.4)

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 (9.5) and (9.6).

It is not planned to impute missing values for biomarker data.

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

The last non-missing value determined prior to first zongertinib administration will be defined as baseline.

For biomarkers (related to 6β-OH cortisol / cortisol ratio and 4β-OH cholesterol), the baseline value is defined as the last measurement before administration of carbamazepine in treatment period 2.

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" (9.7).

The individual values of all subjects will be listed. Listings will be sorted by treatment or sequence group, 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 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	10^{th} percentile
Q1	1^{st} quartile
Q3	3^{rd} quartile
P90	90^{th} 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 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.

The analysis of standard PK parameters is performed according to BI standards (9.5).

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 Section 7.2.1.2: *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 […].*

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.

Exclusion of Biomarker concentrations

The ADS ADYC (Biomarker concentrations per time-point or per time-interval) contains column variables ACEX and ACEXCO indicating inclusion/exclusion (ACEX) of a concentration and an 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. Excluded concentration itself will be listed in the CTR associated with an appropriate flag.

CTP Section 7.2.1.3: *Biomarker data and parameters of a subject will be included in the statistical biomarker analyses if they are not flagged for exclusion due to a protocol deviation relevant to the evaluation of biomarkers (to be decided no later than in the Report Planning Meeting) or due to non-evaluability […].*

Further details are given in "Noncompartmental Pharmacokinetic / Pharmacodynamic Analyses of Clinical Studies" (9.5) and "Description of Analytical Transfer Files and PK/PD Data Files" (9.6).

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

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

7.2 CONCOMITANT DISEASES AND MEDICATION

Concomitant diseases and non-drug therapies will be coded according to the most recent version of MedDRA. Concomitant medication and drug therapies will be coded according to the most recent version of the World Health Organisation - Drug Dictionary. The coding version number will be displayed as a footnote in the respective output.

A drug or non-drug 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).

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 are planned for this section of the CTR.

The relevance of the concomitant therapies to the evaluation of PK and Biomarker 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 Report Planning Meeting (cf. Section 6.2) and described in the CTR.

7.4 PRIMARY OBJECTIVE ANALYSIS

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

7.4.1 Main analysis

The relative bioavailability of zongertinib in plasma when given as a single oral dose (R) or together with multiple dose of carbamazepine (T) will be evaluate as defined in the CTP for the primary and secondary endpoints specified in Section 5.1 and Section 5.2.2 .

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 effects will be considered as fixed. The model is described by the following equation:*

$$y_{km} = \mu + s_m + \tau_k + e_{km}, \text{ where}$$

y_{km} = logarithm of response measured on subject m in receiving treatment k,

μ = the overall mean,

s_m = the effect associated with the m^{th} subject, m = 1, 2, ..., 16

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

e_{km} = the random error associated with the m^{th} subject 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 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.

All primary endpoints will also be analysed descriptively.

[redacted]

7.5 SECONDARY OBJECTIVE ANALYSIS

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

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 same statistical model as stated in Section 7.4.1 and Section 7.4.2 will be repeated for the secondary endpoint.

The secondary endpoint will also be analysed descriptively.

[redacted]

7.7 EXTENT OF EXPOSURE

Descriptive statistics of exposure of zongertinib and carbamazepin are planned for this section of the report. These will be based on the TS.

7.8 SAFETY ANALYSIS

All safety analyses will be performed on the treated set and will be descriptive in nature, **cf. Section 7.2.5 of the CTP**.

7.8.1 Adverse Events

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

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.

For further details on summarization of AE data, please refer to "Analysis and Presentation of Adverse Event Data from Clinical Trials" (9.8) and "Handling of missing and incomplete AE dates" (9.4).

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 on the recorded time of AE onset, as defined in Table 6.1: 1. For details on the treatment definition, see Section 6.1..

CTP Section 7.2.5: *Relevant ECG findings will be reported as AEs.*

CTP Section 5.2.5.1: *Clinically relevant findings of the neurological examination during the trial will be reported as adverse events (AEs).*

CTP Section 5.2.5.2: *Clinically relevant findings of the skin inspection during the trial will be reported as adverse events (AEs).*

CTP Section 5.2.5.3: *All C-SSRS reports of suicidal ideation type 4 or 5 and all reports of suicidal behaviour must be reported as SAEs by the investigator.*

For each negative report (suicidal ideation type 1, 2, or 3) after start of the trial, the investigator is to decide based on clinical judgment whether it represents an AE as defined in the protocol, and if it is considered an AE then it must be reported accordingly.

CTP Section 5.2.6.1.4: *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*

Haematologic toxicities (grades refer to CTCAE grading):
- *Grade 5*
- *Grade 4 except for lymphopenia (including, but not limited to Grade 4 anaemia, Grade 4 thrombocytopenia and Grade 4 neutropenia)*
- *Anaemia of any grade requiring blood transfusion*
- *Febrile neutropenia*
- *Grade 3 neutropenia with documented infection and/or lasting >3 days*
- *Neutropenia of any grade requiring treatment with growth factors*
- *Grade 3 thrombocytopenia*
- *Thrombocytopenia of any grade requiring platelet transfusion*

Any ≥Grade 3 non-haematologic toxicity with the following exceptions (grades refer to CTCAE grading):

- *Grade 3 vomiting/nausea or diarrhea which persists for less than 48 hours after start of adequate treatments*
- *Grade 3 fever*
- *Grade 3 fatigue that persists <7 days*
- *Grade 3 rash that resolves to ≤Grade 1 within 2 weeks*
- *Any Grade 3 laboratory abnormality which is not considered clinically relevant by the investigator, resolves spontaneously or responds to conventional medical intervention*
- *Grade 3 or higher electrolyte abnormality that lasts up to 72 hours, is not clinically complicated, and resolves spontaneously or responds to conventional medical interventions*

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

According to ICH E3 (9.3), in addition to Deaths and serious AEs, 'other significant' AEs need to be listed in the clinical trial report. These will be any non-serious AE that led to an action taken with study drug (e.g. discontinuation or dose reduced or interrupted). An overall summary of AEs will be presented. This overall summary will comprise summary statistics for the class of AESIs.
The frequency of participants with AEs will be summarised by treatment, primary SOC and preferred term. Separate tables will be provided for participants with

- AEs, which were considered by the investigator to be drug related
- SAEs
- AESIs
- AEs leading to treatment discontinuation
- AEs summarized by maximum CTCAE grade.

SAEs, AESIs and other significant AEs will be listed seperatly.

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

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

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 summarized.

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

7.8.2 Laboratory data

The analyses of laboratory data will be descriptive in nature and will be based on BI standards “Handling, Display and Analysis of Laboratory Data” (9.9).

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 participant 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.

In general, clinically significant abnormal laboratory values are only those identified either in the Investigator's comments or at the Report Planning Meeting at the latest. With regard to laboratory abnormal values identified at the site it is the Investigator's responsibility to decide whether a lab value is clinically significantly abnormal or not. Those will be reported as baseline conditions (prior to first administration of study treatment) or as AEs (after first administration of study treatment).

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.

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.

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 post-baseline time point based on the last value of the participant at that planned time point (or assigned to that planned time point). If the time of measurement is missing for a scheduled post-baseline measurement (e.g. for follow-up visits) 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 post-baseline measurement, this measurement will be listed but will be ignored for the calculation of descriptive statistics.

In descriptive statistics of the Screening visit the planned time points will be used. However, if an unscheduled measurement on the same day as the screening visit exists then the unscheduled assessment will be used in descriptive statistics of Screening visit.

7.8.4 ECG

ECG recordings will be checked by the investigator for pathological results. Clinically relevant abnormal findings in ECG will be reported as baseline conditions (at screening) or as AEs (after first administration of study treatment) 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 Others

7.8.5.1 Neurological examinations

The physical neurological examination will be performed as described in **Section 5.2.5.1 of the CTP**.

Findings will only be reported as AEs as described in Section 7.8.1.

7.8.5.2 Skin inspection

A visual inspection of the skin will be performed as described in **Section 5.2.5.2 of the CTP**. Findings will only be reported as AEs as described in Section 7.8.1.

7.8.5.3 Suicidality assessment (C-SSRS)

C-SSRS interview will be performed as described in **Section 5.2.5.3 of the CTP**.
Results will be listed and findings will be reported as AEs as described in Section 7.8.1.

7.8.5.4 Physical examination

Physical examination 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 summarized as such. No separate listing or analysis of physical examination findings will be prepared.

7.8.5.5 Body weight

Since body weight is only assessed at admission to trial and end of study, it will only be listed.

7.9 OTHER ANALYSIS

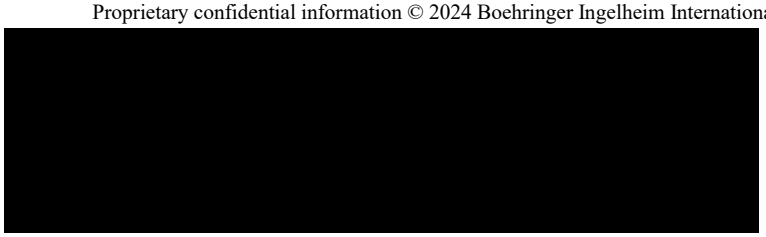
Not applicable.

8. TIMEPOINT OF RELEASE OF TREATMENT INFORMATION

The treatment information will be loaded into the trial database at trial initiation.

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	*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.
9.4	*BI-KMED-BDS-HTG-0035:* "Handling of missing and incomplete AE dates", current version; DMS for controlled documents.
9.5	*BI-KMED-TMCP-MAN -0014*: "Noncompartmental PK/PD Analyses of Clinical Studies", current version; DMS for controlled documents.
9.6	*BI-KMED-TMCP-MAN-0010:* "Description of Analytical Transfer Files, PK/PD Data Files and ADA files", current version; DMS for controlled documents.
9.7	*BI-KMED-BDS-HTG-0045:* "Standards for Reporting of Clinical Trials and Project Summaries", current version; DMS for controlled documents.
9.8	*BI-KMED-BDS-HTG-0066:* "Analysis and Presentation of Adverse Event Data from Clinical Trials", current version; DMS for controlled documents.
9.9	*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	**03-Jan-2024**	[redacted]	None	This is the final TSAP.