Boehringer Ingelheim

TRIAL STATISTICAL ANALYSIS PLAN

Global ID_Version:	**228892_3453077_1.0**
BI Trial No.:	**1479-0020**
Title:	Pharmacokinetics, safety and tolerability of zongertinib following oral administration in male and female participants of non-childbearing potential with different degrees of hepatic impairment (Child-Pugh classification A and B) compared with matched male and female participants of non-childbearing potential with normal hepatic function (an open-label, non-randomised, single-dose, parallel, individual-matched design trial) (including Protocol Amendments No. 1-3 [228892_986299_4.0])
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Responsible trial statistician(s):	[redacted] Phone: [redacted] Fax: [redacted]
Date of statistical analysis plan:	21 JUL 2025
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2. LIST OF ABBREVIATIONS

Term	Definition / description
ADS	Analysis Data Set
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine Aminotransferase
ANOVA	Analysis of variance
AST	Aspartate Aminotransferase
$AUC_{0-\infty}$	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
BDS	Department of Biostatistics & Data Science
BI	Boehringer Ingelheim
BMI	Body mass index
BP	Blood pressure
CI	Confidence interval
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
CV	Arithmetic Coefficient of Variation
DILI	Drug induced liver injury
ECG	Electrocardiogram
EoT	End of Trial
eDMS	Electronic documentation management system
gCV	Geometric Coefficient of Variation
gMean	Geometric Mean
INR	International Normalization Ratio
iPD	Important protocol deviation
Max	Maximum

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Term	Definition / description
MedDRA	Medical Dictionary for Drug Regulatory Activities
Min	Minimum
N	Number non-missing observations
Nobs	Number of observations
P10	10^{th} percentile
P90	90^{th} percentile
PD	Pharmacodynamic
PK	Pharmacokinetic
PKS	PK parameter analysis set
PR	Pulse rate
PT	Preferred term
Q1	1^{st} quartile
Q3	3^{rd} quartile
QD	Quaque die, once daily
RAGe	Report Appendix Generator system
REP	Residual effect period
RPM	Report Planning Meeting
SAE	Serious adverse event
SD	Standard Deviation
SOC	System organ class
t_{max}	Time from (last) dosing to the maximum measured concentration of the analyte in plasma
TMCP	Department of Translational Medicine and Clinical Pharmacology
TMF	Trial master file
TS	Treated set
TSAP	Trial Statistical Analysis Plan
ULN	Upper Limit of Normal
WHO-DD	World Health Organization Drug Dictionary

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3. INTRODUCTION

As per ICH E9 (1), the purpose of this document is to provide a more technical and detailed elaboration of the principal features of the analysis described in the protocol, and to include detailed procedures for executing the statistical analysis of the primary and secondary variables and other data.

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

Study data (including data entered in the RAVE electronic data capture system and external data provided by suppliers) will be stored in a Data Repository.

The statistical analyses will be performed within the validated working environment CARE, including SAS™ (Version 9.4 or higher, 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).

Pharmacokinetic (PK) parameters will be calculated using Phoenix WinNonlin™ software (version Phoenix 8.1 or higher, [redacted]

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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.

In the CTP, the groups of hepatic impairment (normal, mild, moderate) are also referred to as ‘treatment groups’. In the TSAP, the term ‘hepatic impairment groups’ is preferably used, refer to TSAP Section 6.1 for further details.

For the vital signs and laboratory data, the tables also display measurements at Visit 3 (EoT), in addition to all on-treatment measurements.

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5. ENDPOINTS

5.1 PRIMARY ENDPOINTS

Primary endpoints are PK endpoints of zongertinib (BI 1810631), 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 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

The secondary endpoint is a PK endpoint of zongertinib (BI 1810631), 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)*



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6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENT

For basic study information on treatment to be administered and assignment of hepatic impairment groups, refer to **CTP Section 4**.

All participants will receive a single dose of 120 mg of zongertinib in fasting state.

Participants with hepatic impairment will be assigned to one of two groups based on their Child-Pugh classification (mild or moderate). Participants with normal hepatic function will be matched individually to participants with impaired hepatic function by sex, age (within ±10 years) and weight (within ±15%) and assigned to control groups as described in **CTP Sections 3.1 and 4.1.3**. One participant with normal hepatic function may be matched to a participant in one or both groups of participants with hepatic impairment.
If different matches are possible for one participant with hepatic impairment, the first match proposed by the site will be considered first.

The designations for the hepatic impairment groups will be used as indicated in Table 6.1: 1.

Table 6.1: 1 Hepatic impairment group labels used in the analysis

Group	Details	Label
1	Participants with mild hepatic impairment (Child-Pugh A, Child-Pugh Score 5-6)	C-P A
2	Participants with moderate hepatic impairment (Child-Pugh B, Child-Pugh Score 7-9)	C-P B
3	Participants with normal hepatic function individually matched to participants of Group 1	Control C-P A
4	Participants with normal hepatic function individually matched to participants of Group 2	Control C-P B

Section 1.2.2 of the CTP:
The Residual Effect Period (REP) of single doses of zongertinib 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.

Based on this, the following phases for the analysis of Adverse Events (AEs) are defined for each participant in Table 6.1: 2.

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

Study analysis phase	Label	Start (inclusive)	End (exclusive)
Screening[1]	Screening	Date of informed consent	Date/time of administration of trial drug
On-treatment	Control C-P A, C-P A, Control C-P B or C-P B	Date/time of administration of trial drug	Date/time of administration of trial drug + residual effect period (14 days) OR 12:00 a.m. on day after participant's trial termination date, whichever occurs first
Follow-up	F/U Control C-P A, F/U C-P A, F/U Control C-P B or F/U C-P B	Date/time of administration of trial drug + residual effect period (14 days)	12:00 a.m. on day after participant's trial termination date

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

Section 7.2.5 of the CTP:
Note that AEs occurring after the last per protocol contact but entered before database lock of the trial will be reported to Pharmacovigilance only and will not be captured in the trial database.

In Section 15.3 and Appendix 16.1.13.1.8 (for ClinicalTrials.gov only) of the CTR displays, the on-treatment phase will be analysed (labelled with group labels as in Table 6.1: 1 and Table 6.1: 2). The screening and follow-up phase will not be included in this analysis.

The following totals will be provided in addition for Section 15.1 and 15.3:

- "**Total Impaired**", defined as the total over all hepatic impaired participants (Group 1 and Group 2)
- "**Total Control**", defined as the total over all participants with normal hepatic function (Group 3 and Group 4)
- "**Total**", defined as the total over all participants.

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 total will be provided.

For disclosure tables in Appendix 16.1.13.1 of the CTR displays, participants with normal hepatic function will be only reported combined as "Total Control" without displaying Group 3 and Group 4 separately.

Safety laboratory data and vital signs will be analysed based on hepatic impairment groups with clear differentiation between baseline (cf. Section 6.7) and on-treatment measurements

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including Visit 3/EoT Visit. Measurements will be considered on-treatment, if they were taken within the on-treatment phases as defined in Table 6.1: 2.

More details on the technical implementation of these analyses are provided in the Analysis Data Set (ADS) Plan of this TSAP.

6.2 IMPORTANT PROTOCOL DEVIATIONS

Data discrepancies and deviations from the CTP will be identified for all treated participants. Consistency check listings (for identification of deviations of time windows) and a list of protocol deviations (e.g. deviations in drug administration, in blood sampling times, etc.) will be provided to be discussed at the Report Planning Meeting (RPM). At this meeting, all manual deviations identified at the sites by the CRAs and deviations too complex to program will be reviewed by the trial team to decide which are considered important. For definition of important protocol deviations (iPD), and for the process of identification of these, refer to the Boehringer Ingelheim SOP "Identify and Manage Important Protocol Deviations (iPD)" (2). IPD categories will be suggested in the iPD specification document (3). IPDs will be identified no later than in the RPM, and the iPD categories will be updated as needed.
If any iPDs are identified, they are to be summarised into categories and will be captured in a protocol deviation log and in the decision log (4). Both documents will be stored within TMF in eDMS.

The iPDs will be summarised and listed in the CTR.

6.3 INTERCURRENT EVENTS

This section is not applicable.

6.4 SUBJECT SETS ANALYSED

Section 7.2.1.1 of the CTP:
Statistical analyses will be based on the following analysis sets:

- *Treated set (TS): The treated set includes all participants who were treated with one dose of trial drug. The treated set will be used for safety analyses.*
- *Pharmacokinetic parameter analysis set (PKS): This set includes all participants in the treated set (TS) who provide at least one PK endpoint that was defined as primary or secondary and were not excluded due to a protocol deviation relevant to the evaluation of PK or due to PK non-evaluability (as specified* [below]*). Thus, a subject will be included in the PKS, even if he/she contributes only one of the main PK parameter values to the statistical assessment. Descriptive and model-based analyses of PK parameters will be based on the PKS.*

Section 7.2.1.2 of the CTP:
The [PK] *parameters listed in* [CTP] *Section 2.1 and 2.2.2 for drug zongertinib (BI 1810631) will be calculated according to the relevant BI internal procedures.*

Plasma concentration data and parameters of a subject will be included in the statistical [PK] *analyses if they are not flagged for exclusion due to a protocol deviation relevant to the*

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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 t_{max} of the respective treatment (Median t_{max} is to be determined excluding the subjects experiencing emesis),*
- *A predose concentration is >5% C_{max} value of that subject*
- *Missing samples/concentration data at important phases of PK disposition curve*

Plasma concentration data and parameters of a subject which are flagged for exclusion will be reported with its individual values but will not be included in the statistical analyses. […]

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

Table 6.4: 1 shows the analysis sets used for the planned analyses.

Table 6.4: 1 Analysis sets

	Analysis set	
Class of endpoints/analysis	TS	PKS
Primary/secondary [redacted]		X
Safety assessments	X	
Disposition	X	
Demographic/baseline parameters	X	
iPDs	X	
Exposure	X	

[redacted]

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6.6 HANDLING OF MISSING DATA AND OUTLIERS

Handling of missing data and outliers will be performed as described in the **CTP Section 7.3**.

It is not planned to impute missing values for safety parameters. Nevertheless, missing or incomplete AE dates are imputed according to BI standards (see "Handling of Missing and Incomplete AE Dates" (5)).

Missing data and outliers of PK data are handled according to BI standards (see "Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics" (6) and "Noncompartmental Pharmacokinetic / Pharmacodynamic Analyses of Clinical Studies" (7)).

PK parameters that cannot be reasonably calculated based on the available drug concentration-time data will not be imputed.

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

The baseline value for laboratory and vital signs analysis is defined as the last measurement before zongertinib administration.

Section 6.1 of the CTP:
Study measurements and assessments scheduled to occur 'before' trial medication administration on Day 1 are to be performed and completed within a 3 h-period prior to the trial drug administration.

If not stated otherwise in the [CTP] *Flow Chart, the acceptable deviation from the scheduled time for vital signs, ECG, and laboratory tests will be ± 30 min for in-house visits and ± 2h for ambulatory visits.*

[...]

For planned blood sampling times refer to the [CTP] *Flow Chart. While these nominal times should be adhered to as closely as possible, the actual sampling times will be recorded and used for the determination of* [PK] *parameters.*

Adherence to time windows will be checked via the consistency check listings at the RPM.

Unscheduled measurements of laboratory data and vital signs data will be assumed to be repeat measurements of the most recent scheduled measurement (e.g. for follow-up or confirmation of a particular value). Therefore, unscheduled measurements will be assigned to the planned time point of the previous scheduled measurement.

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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.

Inferential statistical analyses 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 in Appendix 16.1.13.3.

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

The format of the listings and tables will follow the Boehringer Ingelheim standards (8) with the exception of those generated for PK-calculations following Boehringer Ingelheim standards for PK/PD analysis (9).

The individual values of all participants will be listed, sorted by hepatic impairment group, participant number, visit and time point. The listings will be included in Appendix 16.2 of the CTR.

For end-of-text tables, the set of summary statistics for non-PK parameters is:

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

For analyte concentrations and PK parameters, the following descriptive statistics will additionally be calculated:

Nobs	number of observations
CV	arithmetic coefficient of variation
gMean	geometric mean
gCV	geometric coefficient of variation
P10	10^{th} percentile
Q1	1^{st} quartile
Q3	3^{rd} quartile
P90	90^{th} percentile

The data format for descriptive statistics of concentrations will be identical to the data format of the respective concentrations. The descriptive statistics of PK parameters will be calculated using the individual values with the number of decimal places as provided by the evaluation program. Then the individual values as well as the descriptive statistics will be reported with three significant digits in the CTR. The estimated values of inferential statistical analysis will be rounded to 2 decimal places.

Descriptive statistics of PK parameters will be calculated if $N \geq 2$.

Tabulations of frequencies for categorical data will include all possible categories available in the CRF and will display the number of observations in a category, as well as the percentage (%). The precision for percentages should be one decimal point, unless the denominator is

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smaller than 100 (in all treatment columns), in which case percentages are given in integer numbers. The category 'missing' will be displayed only if there are actually missing values.

Units of variables should be given in the titles or column/row descriptors in brackets (e.g. (mg)).

Exclusion of PK parameters

The ADS "ADPP" (PK parameters) contains column variables APEX and APEXCO indicating inclusion/exclusion (APEX) of a PK parameter and an analysis flag comment (APEXCO). All analyses based on the PKS will include parameters only if they are not flagged for exclusion, that is APEX is equal to "Included".

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 [RPM]*) 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 and 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 (and, as a consequence, any calculation that relies on λ_z) only; the value is included for all other analyses.

Further details are given in "Noncompartmental Pharmacokinetic / Pharmacodynamic Analyses of Clinical Studies" (7) and "Description of Analytical Transfer Files, PK/PD Data files and ADA files" (10).

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. Data will be summarised by hepatic impairment group.

In Appendix Table 16.1.13.1.4:1, demographics will be summarised by each patient group (C-P A, C-P B), Total Control, and Total (see Section 6.1 for a definition of labels and totals).

7.2 CONCOMITANT DISEASES AND MEDICATION

Frequency tables are planned for this section of the CTR. These will be based on the TS.

Concomitant diseases and non-drug therapies will be coded according to the most recent version of the coding system of the Medical Dictionary for Drug Regulatory Activities (MedDRA). Concomitant medications will be coded according to the most recent version of

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the World Health Organization Drug Dictionary (WHO-DD). The coding version number will be displayed as a footnote in the respective output.

Section 7.2.5 of the CTP:

Previous and concomitant therapies will be presented per [hepatic impairment] *group* […].

A medication or drug or non-drug therapy will be considered concomitant to a treatment, if it

- is ongoing at the time of trial drug administration, or
- starts within the analysis phase of the respective treatment (see Section 6.1 for a definition of treatment and analysis phases).

The diagnoses, procedures/non-drug therapies and medications will be listed. Subjects without any diagnoses, procedures or therapies will be marked with a "No" in the respective column.

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

7.3 TREATMENT COMPLIANCE

Section 4.3 of the CTP:

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

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

Section 7.2.2 of the CTP:
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 the effects 'degree of hepatic impairment' and 'matched pair' as fixed effects . 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 with degree of hepatic impairment k,*

μ = *the overall mean,*

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s_m = the effect of the m^{th} matched pair, m = 1, 2, ..., 8,

τ_k = the effect of k^{th} degree of hepatic impairment, k=1 for no impairment (healthy), k= 2 for either Child-Pugh class A or B,

e_{km} = the random error associated with the k^{th} degree of hepatic impairment for matched pair m,

where, $e_{km} \sim N(0, \sigma_W^2)$ i.i.d.[…].

The model described above will be fitted separately for the two hepatic impaired groups, i.e., one model for the participants with mild hepatic impairment and their matched controls, and one model for the participants with moderate hepatic impairment and their matched controls.

For evaluation of each primary endpoint, the difference between the expected means for log response of hepatic impaired group ($log(\tau_2)$) – log response of the respective control group ($log(\tau_2) - log(\tau_1)$) will be estimated by the difference in the corresponding adjusted means (Least Squares Means). Additionally, their two-sided 90% CIs 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.

In addition to the model-based approach, all parameters will be calculated and analysed descriptively.

The PK parameters (see Section 5.1) will be calculated according to the relevant Boehringer Ingelheim internal procedures (7).

These analyses will be based on the PKS.

[redacted]

7.5 SECONDARY OBJECTIVE ANALYSIS

7.5.1 Key secondary objective analysis

This section is not applicable as no key secondary endpoint has been specified in the protocol.

7.5.2 Secondary objective analysis

Section 7.2.3 of the CTP:
The secondary endpoints (refer to [CTP] *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* [Section 7.4 of the TSAP].

These analyses will be based on the PKS.

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7.7 EXTENT OF EXPOSURE

Since only a single dose will be administered, the date and time of administration will be sufficient to give account of treatment exposure and will therefore only be listed based on the TS.

7.8 SAFETY ANALYSIS

All safety analyses will be performed on the TS.

7.8.1 Adverse Events

AEs will be coded using MedDRA. The coding version number will be displayed as a footnote in the respective output.

Unless otherwise specified, the analyses of AEs will be descriptive in nature. All analyses of AEs will be based on the number of participants with AEs and not on the number of AEs. Safety analyses will be based on Boehringer Ingelheim standards as presented in "Analysis and Presentation of Adverse Event Data from Clinical Trials – Display Template" (11) and "Analysis and Presentation of Adverse Event data from clinical trials" (12).

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' and 'follow-up' phases as defined in Section 6.1. For details on the treatment definition, see Table 6.1: 2.

According to ICH E3 (13), in addition to Deaths and serious AEs (SAEs), '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). Since in this trial only one single tablet is administered, no action taken with study drug due to an AE is possible and therefore no other significant AE can occur.

An overall summary of AEs will be presented.

According to the CTP, adverse events of special interest (AESI) will be analysed:

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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 that occur after drug administration:

  For participants with normal hepatic function and mildly impaired hepatic function:

  1.) AST or ALT elevation ≥ 3x ULN or ≥300 U/L or ≥ 3x screening value (if elevated at screening) or ≥ 3x baseline value (if elevated at baseline) (whichever is higher) and total bilirubin ≥ 2 x ULN or ≥ 2 x screening value (if elevated at screening) or ≥ 2 x baseline value (if elevated at baseline) (whichever is higher) measured at the same visit and confirmed by repeat sample, or

  2.) AST or ALT elevation ≥ 3x ULN or ≥300 U/L or ≥ 3x screening value (if elevated at screening) or ≥ 3x baseline value (if elevated at baseline) (whichever is higher) and INR ≥ 1.5 x ULN or ≥ 1.5 x screening value (if elevated at screening) or ≥ 1.5 x baseline value (if elevated at baseline) (whichever is higher) measured at the same visit and confirmed by repeat sample, or

  3.) AST or ALT elevation ≥ 3x ULN or ≥300 U/L or ≥ 3x screening value (if elevated at screening) or ≥ 3x baseline value (if elevated at baseline) (whichever is higher) with new onset, or worsening of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (>5%), or

  4.) AST and ALT elevation ≥ 5 ULN or ≥300 U/L or ≥ 5 screening value (if elevated at screening) or ≥ 5 baseline value (if elevated at baseline) (whichever is higher)

  These laboratory findings constitute a hepatic injury alert, and participants showing any of these abnormalities need to be followed up according to the DILI Checklist provided in the ISF.

  Additionally, with participants having a normal AST and ALT at baseline, the emergence of an isolated AST or ALT elevation between ≥ 3x and < 5x ULN requires repeat testing within 72h. DILI Checklist is not required unless repeat testing triggers alerts 1,2,3, or 4.

For participants with moderately hepatic impaired function:

1.) AST or ALT elevation ≥ 2x ULN or ≥ 2x screening value (if elevated at screening) or ≥ 2x baseline value (if elevated at baseline) (whichever is higher), and total bilirubin >2x or ≥ 2x screening value (if elevated at screening) or ≥ 2x baseline value (if elevated at baseline) (whichever is higher)

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2.) *AST or ALT elevation ≥ 2x ULN or ≥ 2x screening value (if elevated at screening) or ≥ 2x baseline value (if elevated at baseline) (whichever is higher) and INR >1.2x or >1.2x screening (if elevated at screening) or baseline value (if elevated at baseline) (whichever is higher)*

3.) *AST or ALT elevation ≥ 2x ULN or ≥ 2x screening value (if elevated at screening) or ≥ 2x baseline value (if elevated at baseline) (whichever is higher) and any new onset, or worsening of signs and/or symptoms of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (>5%), or*

4.) *AST or ALT ≥ 3x ULN or ≥ 3x screening value (if elevated at screening) or ≥ 3x baseline value (if elevated at baseline) (whichever is higher)*

These lab findings constitute a hepatic injury alert and the subjects showing these lab abnormalities need to be followed up according to the 'DILI checklist' provided in the ISF. In case of clinical symptoms of hepatic injury (icterus, unexplained encephalopathy, unexplained coagulopathy, right upper quadrant abdominal pain, etc.) without lab results (ALT, AST, total bilirubin) available, the Investigator should make sure that these parameters are analysed, if necessary in an unscheduled blood test. Should the results meet the criteria of hepatic injury alert, the procedures described in the DILI checklist should be followed.

The frequency of participants with AEs will be summarised by hepatic impairment group, primary System Organ Class (SOC) and Preferred Term (PT). Separate tables will be provided for participants with serious AEs, for participants with drug-related AEs, for participants with drug-related serious AEs, for participants with AESIs and for participants with AEs by maximum Common Terminology Criteria for Adverse Events (CTCAE) grade.

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

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 PT) will be summarised by hepatic impairment group, primary SOC and PT. The frequency of participants with SAEs will also be summarised.

7.8.2 Laboratory data

The analyses of laboratory data will be descriptive in nature and will be based on Boehringer Ingelheim standards (14).

Analyses will be based on normalised values, which means transforming to a standard unit and a standard reference range. The original values will be analysed if the transformation into standard unit is not possible for a parameter.

Descriptive statistics of laboratory data including change from baseline will be calculated by planned time point based on the first value of the participant at that planned time point (or assigned to that planned time point). For baseline value, see Section 6.7.

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Laboratory data will be analysed qualitatively via comparison of laboratory data to their reference ranges. Values outside the reference range will be flagged in the data listings.

Clinically relevant findings in laboratory data will be reported as baseline conditions (at screening) or as AEs (during the trial) if judged clinically relevant by the investigator, and will be analysed as such.

It is the investigator's responsibility to decide whether a lab value is clinically significantly abnormal or not (at the RPM at the latest).

7.8.3 Vital signs

Descriptive statistics of vital signs (blood pressure and pulse rate) including changes from baseline will be calculated by planned time point based on the first value of the participant at that planned time point (or assigned to that planned time point). For baseline value, see Section 6.7.

Clinically relevant findings will be reported as baseline conditions (at screening) or as AEs (during the trial) if judged clinically relevant by the investigator, and will be analysed as such.

7.8.4 ECG

Clinically relevant findings in ECG will be reported as baseline conditions (prior to administration of study treatment) or as AEs (after 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.

7.9 OTHER ANALYSIS

7.9.1 Physical examination

Physical examination findings will be reported as baseline conditions (prior to administration of study treatment) or as AEs (after administration of study treatment), and will be summarised as such.

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

7.9.2 Matching pairs

Matching pairs for participants included in the mild and moderate hepatic impairment group will be listed with their matching criteria.

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8. TIMEPOINT OF RELEASE OF TREATMENT INFORMATION

Not applicable due to open-label fashion of the trial as described in the CTP Section 4.1.5.

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

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9. REFERENCES

1.	*CPMP/ICH/363/96:* "Statistical Principles for Clinical Trials", ICH Guideline Topic E9, Note For Guidance on Statistical Principles for Clinical Trials, current version.
2.	*BI-VQD-12045_40-413:* "Identify and Manage Important Protocol Deviations (iPD)", current version, Group "Clinical Operations", KMED.
3.	*BI-VQD-189393-S-G_40-413_AD-01*: "iPD Specification Document (pdf of template)", template, current version, Group "Clinical Operations", KMED.
4.	*BI-VQD-12682-S-G_50-415_AD-03*: "Clinical Trial Analysis Decision Log (template with annotations)", current version, Group "Biostatistics & Data Sciences", KMED.
5.	*BI-KMED-BDS-HTG-0035*: "Handling of Missing and Incomplete AE Dates", current version, Group "Biostatistics & Data Sciences", KMED.
6.	*BI-KMED-TMCP-HTG-0025*: "Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics", current version, Group "Translational Medicine Clinical Pharmacology", KMED.
7.	*BI-KMED-TMCP-MAN-0014*: "Noncompartmental Pharmacokinetic / Pharmacodynamic Analyses of Clinical Studies", current version, Group "Translational Medicine Clinical Pharmacology", KMED.
8.	*BI-KMED-BDS-HTG-0045*: "Standards for Reporting of Clinical Trials and Project Summaries", current version, Group "Biostatistics & Data Sciences", KMED.
9.	*BI-KMED-TMCP-OTH-0003*: "Graphs and Tables for Clinical Pharmacokinetics and Pharmacodynamic Noncompartmental Analyses", current version, Group "Translational Medicine Clinical Pharmacology", KMED.
10.	*BI-KMED-TMCP-MAN-0010*: "Description of Analytical Transfer Files, PK/PD Data files and ADA files", current version, Group "Translational Medicine Clinical Pharmacology", KMED.
11.	*BI-KMED-BDS-HTG-0041*: "Analysis and Presentation of AE Data from clinical trials – display templates", current version, Group "Biostatistics & Data Sciences", KMED.
12.	*BI-KMED-BDS-HTG-0066*: "Analysis and Presentation of AE Data from clinical trials", current version, Group "Biostatistics & Data Sciences", KMED.
13.	*CPMP/ICH/137/95*: "Structure and Content of Clinical Study Reports", ICH Guideline Topic E3; Note For Guidance on Structure and Content of Clinical Study Reports, current version.

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14.	*BI-KMED-BDS-HTG-0042*: "Handling, Display and Analysis of Laboratory Data", current version, Group "Biostatistics & Data Sciences", 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	21-JUL-2025	[redacted]	None	This is the final TSAP.