TRIAL STATISTICAL ANALYSIS PLAN

Document No.:	**c43607957-01**
BI Trial No.:	1305-0034
Title:	The effect of multiple oral doses of BI 1015550 on the pharmacokinetics of nintedanib and pirfenidone administered single dose to healthy male subjects (open-label, two-period, fixed-sequence crossover trial). Revised protocol #03 [c41830059-02]
Investigational Product(s):	BI 1015550
Responsible trial statistician(s):	[redacted] Phone: [redacted]
Date of statistical analysis plan:	15 Jan 2024
Version:	1.0
	Page 1 of 28

Proprietary confidential information

© 2024 Boehringer Ingelheim International GmbH or one or more of its affiliated companies. All rights reserved.

This document may not - in full or in part - be passed on, reproduced, published or otherwise used without prior written permission.

1. TABLE OF CONTENTS

TITLE PAGE 1
1. TABLE OF CONTENTS 2
LIST OF TABLES 4
2. LIST OF ABBREVIATIONS 5
3. INTRODUCTION 7
4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY 8
5. ENDPOINTS 9
5.1 PRIMARY ENDPOINTS 9
5.2 SECONDARY ENDPOINT 9
5.2.1 Key secondary endpoint 9
5.2.2 Secondary endpoint 9
[redacted]
5.3.2 Safety and tolerability 10
[redacted]
6. GENERAL ANALYSIS DEFINITIONS 12
6.1 TREATMENT(S) 12
6.2 IMPORTANT PROTOCOL DEVIATIONS 14
6.3 INTERCURRENT EVENTS 15
6.4 SUBJECT SETS ANALYSED 15
[redacted]
6.6 HANDLING OF MISSING DATA AND OUTLIERS 16
6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS 16
7. PLANNED ANALYSIS 17
7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS 18
7.2 CONCOMITANT DISEASES AND MEDICATION 18
7.3 TREATMENT COMPLIANCE 19
7.4 PRIMARY OBJECTIVE ANALYSIS 19
7.4.1 Main analysis 19
[redacted]
7.4.4 Supplementary analysis 20
7.5 SECONDARY OBJECTIVE ANALYSIS 20
7.5.1 Key secondary objective analysis 20
7.5.2 Secondary objective analysis 20
7.6 FURTHER OBJECTIVE ANALYSIS 20
[redacted]
7.6.2 Safety Parameters 21
7.7 EXTENT OF EXPOSURE 21

7.8 SAFETY ANALYSIS 21
7.8.1 Adverse Events 21
7.8.2 Laboratory data 23
7.8.3 Vital signs 23
7.8.4 ECG 24
7.8.5 Others 24
7.8.5.1 Suicidality assessment (C-SSRS) 24
7.8.5.2 Physical examination 24
7.9 OTHER ANALYSIS 24

8. TIMEPOINT OF RELEASE OF TREATMENT INFORMATION 25

9. REFERENCES 26

[redacted]

11. HISTORY TABLE 28

LIST OF TABLES

Table 6.1: 1 Analysis phases for statistical analysis of AEs. 13
Table 6.1: 2 Analysis phases for laboratory values and vital signs..................................... 14
Table 6.4: 1 Subject sets analysed 15
Table 11: 1 History table 28

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
[redacted]	[redacted]
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
BP	Blood pressure
CI	Confidence interval
[redacted]	[redacted]
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)
EUCT No.	European Clinical Trial Number
F/U	Follow-up
gCV	Geometric coefficient of variation
gMean	Geometric mean
iPD	Important protocol deviation
[redacted]	[redacted]
LC-MS/MS	Liquid chromatography with tandem mass spectrometry
MedDRA	Medical Dictionary for Regulatory Activities

Term	Definition / description
Min	Minimum
Max	Maximum
[redacted]	[redacted]
P10	10th percentile
P90	90th percentile
PK	Pharmacokinetic(s)
PKS	Pharmacokinetic set
PR	Pulse rate
Q1	1st quartile
Q3	3rd quartile
R	Reference treatment
REP	Residual effect period
RTK	Receptor tyrosine kinases
SAE	Serious adverse event
SD	Standard deviation
SOC	System organ class
SOP	Standard operating procedure
ss	(at) steady state
T	Test product or treatment
[redacted]	[redacted]
TS	Treated set
[redacted]	[redacted]
TSAP	Trial statistical analysis plan
ULN	Upper limit of normal
[redacted]	[redacted]
WOCBP	woman of child-bearing potential

3. INTRODUCTION

As per ICH E9, 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 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 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^{TM} (current Version 9.4, by [redacted]), and a number of SAS^{TM}-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^{TM} 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.

After CTP finalisation, it was found that BI 1015550 undergoes chiral inversion *in vivo* and a chiral bioanaltyical assay was developed to measure the pharmacologically active R-enantiomer. It was therefore decided that the characterization of R-BI 1015550 pharmacokinetic (PK) is more relevant for further drug developemnt and the PK samples from this trial were analyzed using chiral bioanalytical assay for the concentration of R-BI 1015550.

5. ENDPOINTS

5.1 PRIMARY ENDPOINTS

Primary endpoints are PK endpoints of nintedanib and pirfenidone, as defined in **Section 2.1.2 of the CTP**.

The following pharmacokinetic parameters will be determined for nintedanib:

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

- $AUC_{0\text{-}\infty}$ *(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)*

The following pharmacokinetic parameters will be determined for pirfenidone:

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

- $AUC_{0\text{-}\infty}$ *(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

Not applicable.

[redacted]

[redacted]

5.3.2 Safety and tolerability

Safety and tolerability of BI 1015550 will be assessed based on further safety parameters defined in **Section 2.2.2.2 of the CTP**:

- *Adverse events (including clinically relevant findings from the physical examination)*
- *Suicidality assessment (C-SSRS)*
- *Safety laboratory tests*
- *12-lead ECG*
- *Vital signs (blood pressure, pulse rate)*

[redacted]

[redacted]

6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENT(S)

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

This is a two-period trial with a fixed sequence R-T. In trial period 1 subjects will receive pirfenidone and nintedanib alone (Reference Treatment (R)) whereas in trial period 2 pirfenidone and nintedanib will be administered together with BI 1015550 at steady state (Test Treatment (T)).

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

- 267 mg pirfenidone (single dose) alone as film-coated tablet in the morning on Day 1 of Visit 2 (R1)
- 100 mg nintedanib (single dose) alone as soft capsule in the morning on Day 2 of Visit 2 (R2)

For treatment T period 2, each subject will receive:

- Multiple doses of 18 mg BI 1015550 administered twice daily for 10 days (Day -6 to Day 4 of Visit 3) as film-coated tablets.
- Together with 267 mg pirfenidone (single dose) as film-coated tablet in the morning on Day 1 of Visit 3 (T1)
- Together with 100 mg nintedanib (single dose) as soft capsule in the morning on Day 2 of Visit 3 (T2)

Pirfenidone and nintedanib will be administered after a standardised breakfast. During ambulatory dosing of BI 1015550 no specific restrictions regarding food intake have to be followed. The start of BI 1015550 dosing at Visit 3 should be separated by a wash-out phase of at least 72 hours after nintedanib dosing at Visit 2.

CTP Section 1.2.4: [redacted] *This is the period after the last dose during which measurable drug levels are still likely to be present.*

The REP of nintedanib for a single dose is 3 days.

The REP of pirfenidone is 12 hours.

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.

Study analysis phase	Label	Start (inclusive)	End (exclusive)
Screening	**Screening**	Date of informed consent	Date/time of administration of pirfenidone
On treatment	**pirfenidone**	Date/time of first administration of pirfenidone	Date/time of first administration of nintedanib or 12:00 a.m. on day after subject's trial termination date, whichever occurs earlier
On treatment	**nintedanib**	Date/time of first administration of nintedanib	Date/time of first administration of nintedanib + REP (3 days * 24 hours) or 12:00 a.m. on day after subject's trial termination date, whichever occurs earlier
Follow-up	**F/U nintedanib**	Date/time of first administration of nintedanib + REP (3 days * 24 hours)	Date/time of first administration of BI 1015550 or 12:00 a.m. on day after subject's trial termination date, whichever occurs earlier.
On treatment	**BI 1015550**	Date/time of first administration BI 1015550	Date/time of second administration of pirfenidone or 12:00 a.m. on day after subject's trial termination date, whichever occurs earlier.
On treatment	**BI 1015550 + pirfenidone**	Date/time of second administration of pirfenidone (Day 1, Visit 3)	Date/time of second administration of nintedanib or 12:00 a.m. on day after subject's trial termination date, whichever occurs earlier.
On treatment	**BI 1015550 + nintedanib**	Date/time of second administration of nintedanib	Date/time of second administration of nintedanib + REP (3 days * 24 hours) or 12:00 a.m. on day after subject's trial termination date, whichever occurs earlier.
On treatment	**BI 1015550**	Date/time of second administration of nintedanib + REP (3 days * 24 hours)	Date/time of last administration of BI 1015550 + [redacted] or 12:00 a.m. on day after subject's trial termination date, whichever occurs earlier.
Follow-up	**F/U BI 1015550**	Date/time of last administration of BI 1015550 + [redacted]	12:00 a.m. on day after trial termination date

AE displays in CTR Section 15.3, Appendix 16.1.13.1.8. will present results for the on-treatment phase only as defined in Table 6.1: 1. Screening or follow-up 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 BI 1015550", defined as all AEs with an onset during on-treatment phases involving BI 1015550
- "Total pirfenidone", defined as all AEs with an onset during on-treatment phases involving pirfenidone
- "Total nintedanib", defined as all AEs with an onset during on-treatment phases involving nintedanib
- "Total on-trt", defined as all AEs with an onset during on-treatment phases involving BI 1015550, pirfenidone and nintedanib.

Table 6.1: 2 Analysis phases for laboratory values and vital signs

Study analysis phase	**Start (inclusive)**	**End (exclusive)**
Screening[1]	Date of informed consent	Date/time of first administration BI 1015550
On treatment	Date/time of first administration BI 1015550	Date/time of last administration of BI 1015550 [redacted] or 12:00 a.m. on day after subject's trial termination date, whichever occurs earlier.
Follow-up	Date/time of last administration of BI 1015550 + [redacted]	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.

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 or excluded from analyses. 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)" (9.3) 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) and the pharmacokinetic parameter analysis set (PKS) will be used as defined in the **CTP, Section 7.2.1.1**.

Table 6.4: 1 Subject sets analysed

	Subject set	
Class of analysis	Treated set	PKS
Disposition	X	
iPDs	X	
Primary endpoints		X
[redacted]		[redacted]
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 (9.5)

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 (9.6) and (9.7).

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

The last non-missing value of safety parameters determined prior to the first drug administration of BI 1015550 will be defined as baseline.

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

7. PLANNED ANALYSIS

The format of the listings and tables will follow the BI guideline "Reporting of clinical trials and project summaries" (9.8).

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	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 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 or not they have missing values.

The analysis of standard PK parameters is performed according to BI standards (9.6).

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.

Further details are given in "Noncompartmental Pharmacokinetic / Pharmacodynamic Analyses of Clinical Studies" (9.6) and "Description of Analytical Transfer Files and PK/PD Data Files" (9.7).

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

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

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 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 pirfenidone under steady state exposure of BI 1015550 (T1) compared with pirfenidone alone (R1) and nintedanib under steady state exposure of BI 1015550 (T2) compared with nintedanib alone (R2) will be evaluated as defined in the CTP for the primary endpoints specified in Section 5.1

The models for pirfenidone and nintedanib will be analysed separately.

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

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

y_{km} = *logarithm of response measured on subject m receiving treatment k,*
μ = *the overall mean,*
s_m = *the effect associated with the* m^{th} *subject,* $m = 1, 2, \ldots, n$,
τ_k = *the* k^{th} *treatment effect,* $k = 1, 2$,
e_{km} = *the random error associated with the* m^{th} *subject who received treatment k*

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

Point estimates for the ratios of the geometric means (test/reference) for the primary endpoints (see **[CTP]** *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[1]*)-log(*R[1]*)*) [or log(T[2])-log(R[2)] *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.*

[redacted]

7.4.4 Supplementary analysis

Not applicable since no supplementary analysis is planned in the CTP.

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

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

7.6 FURTHER OBJECTIVE ANALYSIS

[redacted]

[redacted]

7.6.2 Safety Parameters

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

7.7 EXTENT OF EXPOSURE

Descriptive statistics of exposure of BI 1015550, nintedanib and pirfenidone 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 summarisation of AE data, please refer to "Analysis and Presentation of Adverse Event Data from Clinical Trials" (9.9) and "Handling of missing and incomplete AE dates" (9.5).

The analysis of AEs will be based on the concept of treatment emergent AEs.

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.

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 5.2.6.2.3: *Any suicidal ideation or behaviour will be reported to the sponsor. Suicidal ideation of type 1, 2 or 3 can be reported as AE, at the discretion of the investigator. All reports should be reviewed by the Investigator for clinical relevance and determination if an AE report is warranted.*

All reports of suicidal ideation type 4 and 5 and all reports of suicidal behaviour (based on C-SSRS questionnaire during the trial, see [**CTP**] *section 5.2.5.1), must be reported as separate SAEs by the investigator.*

CTP Section 5.2.6.1.4: *The following are considered as AESIs:*

- *Potential severe DILI*
  A potential severe Drug Induced Liver Injury (DILI) that requires follow-up is defined by the following alterations of hepatic laboratory parameters:
  - *An elevation of AST (aspartate aminotransferase) and/or ALT (alanine aminotransferase) ≥3-fold ULN combined with an elevation of total bilirubin ≥2-fold ULN measured in the same blood sample, or in samples drawn within 30 days of each other, or*
  - *Aminotransferase (ALT, and/or AST) elevations ≥10-fold ULN*
- *Serious infections, opportunistic or mycobacterium tuberculosis infections*

  [refer to **CTP Section 5.2.6.1.4** for the complete list of terms]

- Vasculitis

  Vasculitis is defined as any event term included in the MedDRA SMQ Vasculitis (broad).

The investigator had to classify on the eCRF whether an observed AE was an AESI.

According to ICH E3 (9.4), 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 subjects with AEs will be summarised by treatment, primary SOC and preferred term. Separate tables will be provided for subjects with

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

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

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

For disclosure of AE data in the EudraCT register, the frequency of AEs, the frequency of non-serious AEs with an incidence of greater than 5 % (in preferred terms) and the frequency of SAEs will be summarized.

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

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" (9.10).

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

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

Unscheduled measurements of laboratory data will be assumed to be repeat measurements of the most recent scheduled measurement (e.g. for follow-up or confirmation of a particular value). Therefore, unscheduled measurements will be assigned to the planned time point of the previous scheduled measurement. Descriptive statistics will be calculated by planned time point based on the worst value of the subject at that planned time point (or assigned to that planned time point).

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

Clinically relevant findings in laboratory data will be reported as baseline conditions (prior to first administration of study treatment) or as AEs (after first administration of study treatment) if judged clinically relevant by the investigator, and will be analysed as such.

7.8.3 Vital signs

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

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 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 Suicidality assessment (C-SSRS)

C-SSRS interview will be performed as described in **Section 5.2.5.1** of the **CTP**.
Results will be listed and findings will be reported as AEs as described in Section 7.8.1.

7.8.5.2 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 summarised as such. No separate listing or analysis of physical examination findings will be prepared.

7.9 OTHER ANALYSIS

Not applicable.

8. TIMEPOINT OF RELEASE OF TREATMENT INFORMATION

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

9. REFERENCES

9.1	*BI-VQD-23790-S-G_50-415_AD-02:* “Project Analysis Dataset (PADS) Template (template)”, current version, group / owning department “Med Biostatistics & Data Sciences”, DMS for controlled documents.
9.2	*CPMP/ICH/363/96:* "Statistical Principles for Clinical Trials", ICH Guideline Topic E9, Note For Guidance on Statistical Principles for Clinical Trials, current version.
9.3	*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.
9.4	*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.
9.5	*BI-KMED-BDS-HTG-0035:* "Handling of missing and incomplete AE dates", current version; DMS for controlled documents.
9.6	*BI-KMED-TMCP-MAN -0014*: "Noncompartmental PK/PD Analyses of Clinical Studies", current version; 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; DMS for controlled documents.
9.8	*BI-KMED-BDS-HTG-0045:* "Standards for Reporting of Clinical Trials and Project Summaries", current version; DMS for controlled documents.
9.9	*BI-KMED-BDS-HTG-0066:* "Analysis and Presentation of Adverse Event Data from Clinical Trials", current version; DMS for controlled documents.
9.10	*BI-KMED-BDS-HTG-0042:* "Handling, Display and Analysis of Laboratory Data", current version; DMS for controlled documents.

[redacted]

11. HISTORY TABLE

Table 11: 1 History table

Version	**Date (DD-MMM-YY)**	**Author**	**Sections changed**	**Brief description of change**
1.0	15-Jan-2024	[redacted]	None	This is the final TSAP.