TRIAL STATISTICAL ANALYSIS PLAN

Document No.:	**c42133572-01**
BI Trial No.:	**1346-0056**
Title:	The effect of multiple oral doses of bosentan on the steady state kinetics of BI 425809 after oral administration to healthy male subjects (an open-label, two-period fixed sequence trial) (revised protocol including Protocol Amendment No.1 [c40616508-02]).
Investigational Product:	BI 425809 (iclepertin), Tracleer® (bosentan)
Responsible trial statistician:	[redacted] Phone: [redacted] Fax: [redacted]
Date of statistical analysis plan:	10 JUL 2023 SIGNED
Version:	1

1. TABLE OF CONTENTS

LIST OF TABLES

2. LIST OF ABBREVIATIONS

See Medicine Glossary:
http://glossary

Term	Definition / description
ALT	Alanine Aminotransferase
ANOVA	Analysis of variance
AST	Aspartate Aminotransferase
$AUC_{\tau,ss}$	Area under the concentration-time curve of the analyte in plasma at steady state over a uniform dosing interval τ
bid	Twice a day
BMI	Body mass index
$C_{max,ss}$	Maximum measured concentration of the analyte in plasma in steady state
$C_{min,ss}$	Minimum measured concentration of the analyte in plasma in steady state
CTP	Clinical trial protocol
CTR	Clinical trial report
CV	Arithmetic Coefficient of Variation
DILI	Drug induced liver injury
gCV	Geometric Coefficient of Variation
gMean	Geometric Mean
Max	Maximum
Min	Minimum
N	Number non-missing observations
P10	10th percentile
P90	90th percentile
PKS	PK parameter analysis set
Q1	1st quartile
Q3	3rd quartile
qd	Once a day
R	Reference treatment
RPM	Report Planning Meeting
RAGe	Report Appendix Generator system
SD	Standard Deviation

Term	Definition / description
T	Test treatment
TS	Treated Set
TSAP	Trial Statistical Analysis Plan
ULN	Upper Limit of Normal

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 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, randomization.

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

Pharmacokinetic (PK) parameters will be calculated using Phoenix WinNonlin™ software (version 8.1.1 or higher, [redacted]) or SAS Version 9.4 (or later version).

The statistical analyses will be performed within the validated working environment CARE, including SAS™ (current Version 9.4, by [redacted]), and a number of SAS™-based tools (e.g., macros for the analyses of AE data or laboratory data; Report Appendix Generator system (RAGe) for compilation/formatting of the CTR appendices).

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

All analyses as planned in the CTP will be performed and are described in more detail in this TSAP.
Previous and concomitant therapies will be presented by treatment sequence instead of treatment group (Section 7.2). The definition in CTP Section 7.2.5 '*Previous and concomitant therapies will be presented per treatment group without consideration of time intervals and treatment periods.*' was changed to *'Previous and concomitant therapies will be presented per treatment* sequence *without consideration of time intervals and treatment periods.*'.

The baseline is defined as the last measurement before trial drug administration in first treatment period (Section 6.7). The definition in CTP Section 7.2.5 '*For laboratory data, ECG and vital signs, baseline is defined as the last measurement before first intake of BI 425809 in the respective trial period*.' was changed to '*For laboratory data and vital signs, baseline is defined as the last measurement before first intake of BI 425809 in first treatment period*.'

5. ENDPOINTS

5.1 PRIMARY ENDPOINTS

Section 2.1.2 of the CTP:

The following pharmacokinetic parameters will be determined for BI 425809:

- *$AUC_{\tau,ss}$ (area under the concentration-time curve of the analyte in plasma at steady state over a uniform dosing interval τ)*
- *$C_{max,ss}$ (maximum measured concentration of the analyte in plasma at steady state over a uniform dosing interval τ)*

5.2 SECONDARY ENDPOINTS

5.2.1 Key secondary endpoints

This section is not applicable as no key secondary endpoints have been defined in the CTP.

5.2.2 Secondary endpoint

Section 2.1.3 of the CTP:

The following pharmacokinetic parameter will be determined for BI 425809:

- *$C_{min,ss}$ (minimum measured concentration of the analyte in plasma at steady state over a uniform dosing interval τ)*

5.3 FURTHER ENDPOINTS

[redacted]

Safety and tolerability endpoints

Section 2.2.2.2 of the CTP:

Safety and tolerability of BI 425809 will be assessed based on:

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

[redacted]

6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENTS

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

This trial is designed as open-label, two period fixed sequence crossover trial in 14 healthy male subjects without wash-out phase between the two periods.

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

Table 6.1: 1 Treatments and labels used in the analysis

Treatment		Short label
R	BI 425809, 1*10mg tablet, qd	BI
T	BI 425809, 1*10 mg tablet, qd+Bosentan, 125 mg tablet, bid	BI + Bosentan

Section 1.2.3 of the CTP:
The Residual Effect Period (REP) of BI 425809 is 11 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 residual effect period of bosentan is about 1 day.

Based on this, the following study phases will be defined for the analysis of adverse events (AEs):

- **Screening**
  - Ranging from 0:00h on day of informed consent until time of first drug administration.
- **On treatment** (labelled with short label)
  "BI":
  - Ranging from first drug administration in treatment period 1 until first drug administration in treatment period 2 or (in case of treatment discontinuation) until 11 days (264 h) after last treatment administration in period 1.

  "BI + Bosentan":
  - Ranging from first drug administration in treatment period 2 until 11 days (264 h) after last treatment administration in period 2 OR until trial termination (0:00 h on the day after trial termination), whatever occurs first.
- **Follow-up** (labelled "F/U")
  - Ranging from the end of REP until trial termination (0:00 h on the day after trial termination).

Section 7.2.5 of the CTP:
Note that AEs occurring after the last per protocol contact will not be captured in the trial database.

The following AE displays will be provided in the report:

In Section 15.3 and Appendix 16.1.13.1.8 (for ClinicalTrials.gov and EudraCT only) of the CTR displays, the on treatment phase will be analysed (labelled with the short label of the study treatment). The screening and follow-up phases will not be included in this analysis.

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

- a total over all on treatment phases **("Total"**)

In Section 15.4 and Appendix 16.2 (Listings) of the CTR displays, the screening period, as well as the follow-up phases will additionally be included and no totals will be provided.

For detailed information on the handling of the treatments refer to Technical TSAP ADS (analysis data set) plan and Analysis Data Reviewers guide.

6.2 IMPORTANT PROTOCOL DEVIATIONS

Data discrepancies and deviations from the CTP will be identified for all treated subjects. 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 (BI) SOP "Identify and Manage Important Protocol Deviations (iPD)" (2).

Important protocol deviation (iPD) categories are pre-specified in the iPD specification file (DV domain) (3). IPDs will be identified no later than in the Report Planning Meeting, and the iPD categories will be updated as needed.

If any iPDs are identified, they are to be summarised into categories and will be captured in the iPD specification file (DV domain) (3) and in the decision log (4). Both documents will be stored within the TMF in EDMS.

The iPDs will be summarized 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 subjects who were treated with at least one dose of trial drug. The treated set will be used for safety analyses.*
- *Pharmacokinetic parameter analysis set (PKS): This set includes all subjects in the treated set (TS) who provide at least one PK endpoint that was defined as primary or secondary and was not excluded due to a protocol deviation relevant to the evaluation of PK or due to PK non-evaluability (as specified* in CTP Section 7.2.1.2 and below*). Thus, a subject will be included in the PKS, even if he/she contributes only one PK parameter value 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 pharmacokinetic parameters listed in CTP *Section 2.1 and 2.2.2 for drug BI 425809 will be calculated according to the relevant BI internal procedures.*

Plasma concentration data and parameters of a subject will be included in the statistical pharmacokinetic (PK) analyses if they are not flagged for exclusion due to a protocol deviation relevant to the evaluation of PK (to be decided no later than in the Report Planning Meeting) or due to PK non-evaluability (as revealed during data analysis, based on the criteria specified below). Exclusion of a subject's data will be documented in the CTR.

Important protocol deviations may be

- *Incorrect trial medication taken, i.e. the subject received at least one dose of trial medication the subject was not assigned to*
- *Incorrect dose of trial medication taken*
- *Use of restricted medications*

Plasma concentrations and/or parameters of a subject will be considered as non-evaluable, if for example

- *The subject experienced emesis that occurred at or before two times median t_{max} of the respective treatment (Median t_{max} is to be determined excluding the subjects experiencing emesis),*
- *If a subject experiences emesis at any time during ambulatory dosing of BI 425809 the potential impact on the attainment of steady state will be assessed at the report planning meeting*
- *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 pharmacokinetic parameters. Concentrations used in the

pharmacokinetic calculations will be in the same format provided in the bioanalytical report, (that is, to the same number of decimal places provided in the bioanalytical report).

Table 6.4: 1 Subject sets analysed

	Subject set	
Class of analysis	TS	PKS
Primary/secondary [redacted] endpoints		X
Safety & treatment exposure & iPD analysis	X	
Demographics & baseline conditions	X	

[redacted]

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:

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.
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 analysis and vital signs is defined as the last measurement before trial drug administration in first treatment period.

Section 6.1 of the CTP:
Exact times of measurements outside the permitted time windows will be documented. The acceptable time windows for screening and the end of trial examination are provided in the CTP *Flow Chart.*

The tolerance time for drug dosing on Days 1-8 (period 1) and 1-12 (period 2) is ± 1 hour. If not stated otherwise in the Flow Chart, the acceptable deviation from the scheduled time for vital signs, ECG, and lab tests will be -60 min. The tolerance for suicidality assessment is ± 60 min.

If scheduled in the Flow Chart at the same time as a meal, blood sampling, ECG and vital signs have to be done first. Furthermore, if several measurements including venipuncture are scheduled for the same time, venipuncture should be the last of the measurements due to its inconvenience to the subject and possible influence on physiological parameters.

For planned blood sampling times, refer to the 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 pharmacokinetic parameters.

If a subject misses an appointment, it will be rescheduled if possible. The relevance of measurements outside the permitted time windows will be assessed no later than at the Report Planning Meeting.

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.

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 also 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 BI standards (see "Standards for Reporting of Clinical Trials and Project Summaries" (8)) with the exception of those generated for PK-calculations following BI standards for PK/PD analysis (9).

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

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

N	number 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.

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 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".

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.
- 'DESC STATS' the value will be excluded from descriptive evaluations per planned time point/time interval.
- 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.

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.

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

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Only descriptive statistics are planned for this section of the report, based on the TS.
The data will be summarised by treatment sequence.

7.2 CONCOMITANT DISEASES AND MEDICATION

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

Concomitant diseases and non-drug therapies will be coded according to the version defined in the decision log (4) 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 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 treatment sequence *without consideration of time intervals and treatment periods.*

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

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

7.3 TREATMENT COMPLIANCE

Section 4.3 of the CTP:
Compliance will be assured by administration of all trial medication in the trial centre under supervision of the investigating physician or a designee. The measured plasma concentrations of trial medication will provide additional confirmation of compliance.

It is not intended to list the compliance separately. Any deviations from complete intake will be addressed in the RPM and described in the CTR.

7.4 PRIMARY OBJECTIVE ANALYSIS

7.4.1 Main analysis

Section 7.2.2 of the CTP:
The statistical model used for the analysis of the primary and secondary *endpoints (refer to* Section 5.1 and Section 5.2.2*) 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:*

$y_{km} = \mu + s_m + \tau_k + e_{km}$, *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 and secondary *endpoints* […] *and their two-sided 90% confidence intervals (CIs) will be provided.*

For each endpoint, the difference between the expected means for log(T)-log(R) will be estimated by the difference in the corresponding adjusted means (Least Squares Means). Additionally their two-sided 90% confidence intervals will be calculated based on the residual error from the ANOVA and quantiles from the t distribution. These quantities will then be back-transformed to the original scale to provide the point estimate and 90% CIs for each endpoint.

The implementation for this analysis will be accomplished by using the CSD macros based on the PKS. The following SAS code can be used:

```
PROC MIXED DATA=indata METHOD=REML;
   CLASS subject treatment;
   MODEL logpk = treatment / DDFM=KR;
   RANDOM subject;
   LSMEANS treatment / PDIFF CL ALPHA=0.1;
   ESTIMATE 'T-R' treatment -1 1;
RUN;
```

7.4.4 Supplementary analysis

No supplementary analysis is planned.

7.5 SECONDARY OBJECTIVE ANALYSIS

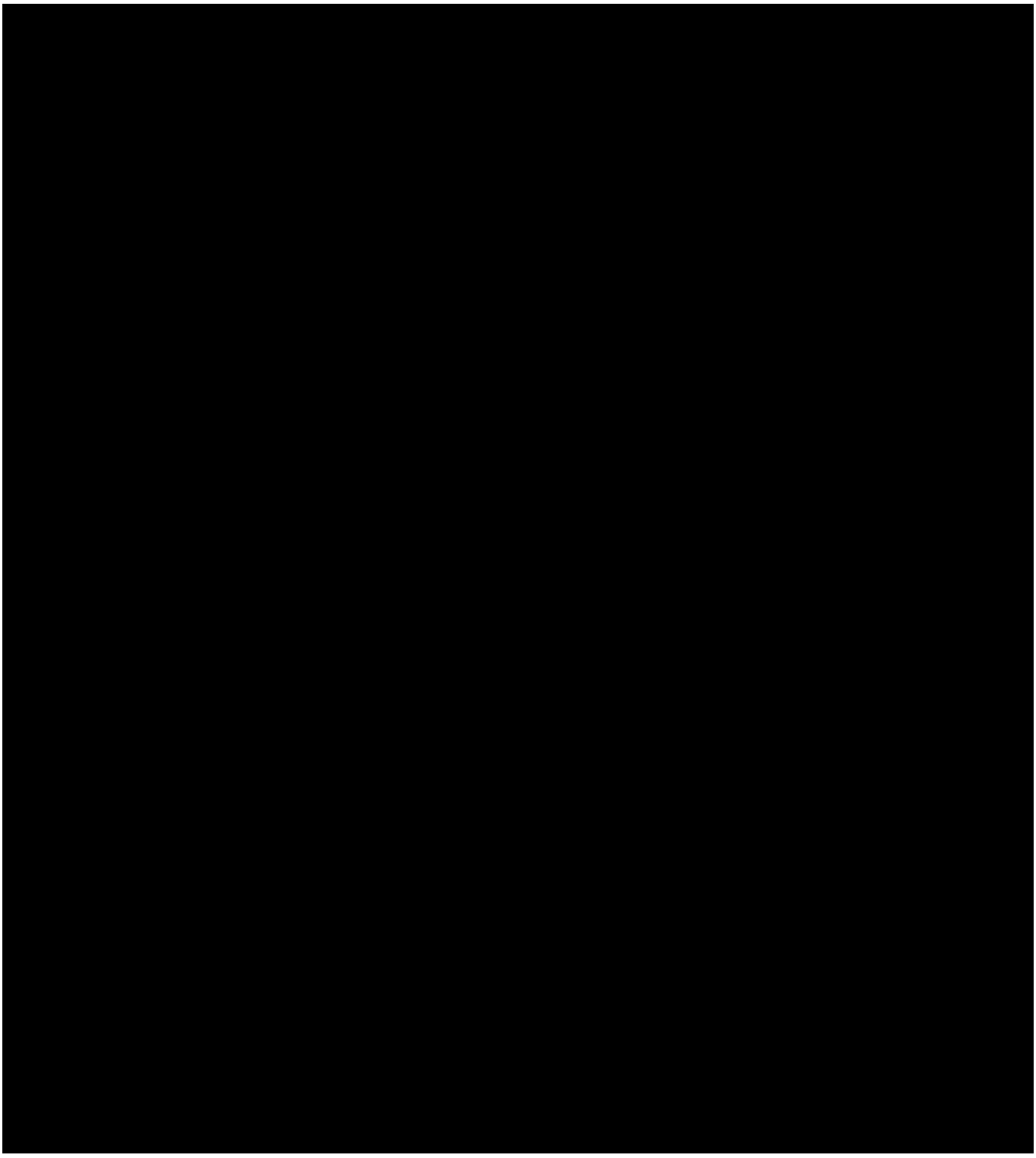
7.5.1 Key secondary objective analysis

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

7.5.2 Secondary objective analysis

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

7.6 FURTHER OBJECTIVE ANALYSIS



Safety endpoints

For a description of the analysis of safety and tolerability, please refer to Section 7.8.

7.7 EXTENT OF EXPOSURE

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

7.8 SAFETY ANALYSIS

All safety analyses will be performed on the TS.

The safety data for treated subjects who failed to complete the study (dropouts or withdrawals) will be reported as far as their data are available. All withdrawals will be documented and the reason for withdrawal recorded.

7.8.1 Adverse Events

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

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

The analysis of AEs will be based on the concept of treatment emergent AEs. That means that all AEs will be assigned to 'screening', 'on-treatment' or 'follow-up' phases as defined in Section 6.1. AEs will be analysed based on actual treatments, as defined in Table 6.1: 1.

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

Section 5.2.6.1.4 of the CTP:

The following are considered as AESIs:

- *Potential severe DILI*

  A potential severe Drug Induced Liver Injury (DILI) that requires follow-up is defined by the following alterations of hepatic laboratory parameters:

  - *An elevation of AST (aspartate aminotransferase) and/or ALT (alanine aminotransferase) ≥3-fold ULN combined with an elevation of total bilirubin ≥2-fold ULN measured in the same blood sample, or in samples drawn within 30 days of each other, or*
  - *Aminotransferase (ALT, and/or AST) elevations ≥10-fold ULN*

  These lab findings constitute a hepatic injury alert and the subjects showing these lab abnormalities need to be followed up according to the 'DILI checklist' provided in the ISF. In case of clinical symptoms of hepatic injury (icterus, unexplained 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 that needs to be sent to central laboratory. Should the results meet the criteria of hepatic

injury alert, the procedures described in the DILI checklist should be followed.

According to ICH E3 (13), in addition to Deaths and serious adverse events, 'other significant' AEs need to be listed in the clinical trial report. These will be any non-serious adverse event that led to an action taken with study drug (e.g. discontinuation or dose reduced or interrupted).

An overall summary of adverse events will be presented.

The frequency of subjects with AEs will be summarised by treatment, primary system organ class (SOC) and preferred term (PT). Separate tables will be provided for subjects with serious AEs, for subjects with investigator-defined drug-related AEs, for subjects with investigator-defined drug-related serious adverse events, for subjects with AESIs and for subjects with AEs leading to discontinuation. In addition, the frequency of subjects with AEs will be summarised by treatment, worst intensity, primary system organ class (SOC) and preferred term (PT).

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

In addition, frequencies of subjects with non-serious AEs that had an incidence of > 5% for at least one treatment will be summarised by treatment, primary SOC and PT.

For disclosure of adverse events on EudraCT, additional information not included in a standard AE analysis will be performed. The following three entries will be created:

- Adverse Events per arm for disclosure on EudraCT
- Non-serious Adverse Events for disclosure on EudraCT
- Serious Adverse Events for disclosure on EudraCT

7.8.2 Laboratory data

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

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 (checked at the RPM at the latest).

Descriptive statistics of laboratory data including change from baseline will be calculated by planned time point based on the worst value of the subject at that planned time point (or assigned to that planned time point).

7.8.3 Vital signs

Descriptive statistics over time including change from baseline will be performed for vital signs (blood pressure and pulse rate). In the listing the change from baseline will also be displayed.

For post-dose measurements of vital signs, descriptive statistics will be calculated by planned time point based on the first value of the subject at that planned time point (or assigned to that planned time point). For baseline value, the last measurement before drug administration in each treatment period will be used.

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 abnormal findings will be reported as adverse events.
No separate listing or analysis of continuous ECG monitoring will be prepared.

7.9 OTHER ANALYSIS

Physical examination

Physical examination findings will be reported as relevant medical history/baseline condition (i.e., a condition already existent before intake of trial drug) or as AE and will be summarised as such.

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

C-SSRS – Suicidality assessment

The C-SSRS is a semi-structured, investigator-rated interview, assessing both suicidal behaviour and suicidal ideation. It will be administered at Screening, Visit 2 day 10, and Visit 3 day 14. Please refer to CTP Section 5.2.5.1 for more details.

Results of the C-SSRS will be listed only. If no suicidal ideation or behavior is assessed, the following sentence will be displayed only: 'No patients with suicidal ideation, suicidal behavior, or self-injurious behavior without suicidal intent.'

7.9.1 Biomarker analyses

No biomarker analysis is planned.

7.9.2 PK/PD analyses

No PK/PD analysis is planned.

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.

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-KMED-BDS-TMP-0059*: "iPD specification document (sdtm-dv-domain-specification)", template, current version, Group "Clinical Operations", KMED.
4.	*001-MCS-50-415_RD-03:* "Clinical Trial Analysis Decision Log (template)", 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 and PK/PD Data Files", current version, Group "Translational Medicine Clinical Pharmacology", KMED.
11.	*BI-KMED-BDS-HTG-0041*: "Analysis and Presentation of Adverse Event Data from Clinical Trials – Display Template", 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, EMA webpage.
14.	*BI-KMED-BDS-HTG-0042*: "Handling, Display and Analysis of Laboratory Data", current version, Group "Biostatistics & Data Sciences", KMED.

11. HISTORY TABLE

Table 11: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
1.0	**10-JUL-23**	[redacted]	None	This is the final TSAP.