TRIAL STATISTICAL ANALYSIS PLAN

Document No.:	c43187873-01
BI Trial No.:	1346-0036
Title:	The effect of multiple doses of BI 425809 on the pharmacokinetics of multiple doses of a combination of ethinylestradiol and levonorgestrel following oral administration in healthy premenopausal female subjects (an open-label, two-period, fixed sequence design trial with run-in period) (Revised protocol including Amendment 1 [c38699243-02])
Investigational Product:	BI 425809/iclepertin
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Date of statistical analysis plan:	27 OCT 2023
Version:	1.0

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2. LIST OF ABBREVIATIONS

See Medicine Glossary:
http://glossary

Term	Definition/description
AE	Adverse event
AESI	AE of special interest
ADS	Analysis data set
ALT	Alanine transaminase
ANOVA	Analysis of variance
AST	Aspartate transaminase
AUC	Area under the curve
$AUC_{\tau,ss}$	Area under the concentration-time curve of the analyte in plasma at steady state over a uniform dosing interval τ
BMI	Body mass index
BP	Blood pressure
C-SSRS	Columbia Suicide Severity Rating Scale
CARE	Clinical data Analysis and Reporting Environment
CI	Confidence interval
CL/F	Apparent clearance of the analyte in plasma after extravascular administration
CL/F_{ss}	Apparent clearance of the analyte in the plasma at steady state following extravascular multiple dose administration
C_{max}	Maximum plasma concentration
$C_{max,ss}$	Maximum measured concentration of the analyte in plasma at steady state over a uniform dosing interval τ
C_{min}	Minimum plasma concentration
$C_{min,ss}$	Minimum measured concentration of the analyte in plasma at steady state over a uniform dosing interval τ
CRF	Case report form
CTP	Clinical trial protocol
CTR	Clinical trial report
CV	Arithmetic coefficient of variation
DILI	Drug Induced Liver Injury

Term	Definition/description
ECG	Electrocardiogram
EDMS	Electronic documentation management system
EE	Ethinylestradiol
EOS	End of Study
ES	Entered set
EudraCT	European Union Drug Regulating Authorities Clinical Trials Database
gCV	Geometric coefficient of variation
gMean	Geometric mean
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
iPD	Important protocol deviation
λ_z	Terminal rate constant of the analyte in plasma
$\lambda_{z,ss}$	Terminal rate constant in plasma at steady state
LNG	Levonorgestrel
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
$MRT_{po,ss}$	Mean residence time of the analyte in the body at steady state after oral administration
N	Number of non-missing observations
OC	Oral contraceptive
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PKS	PK parameter analysis set
PR	Pulse rate
PT	Preferred term
PTM	Planned Time
q.d.	*Quaque die* (once daily)
R	Reference treatment
RAGe	Report Appendix Generator system
REP	Residual effect period
RPM	Report Planning Meeting

Term	Definition/description
SAS	Statistical analysis system
SD	Standard deviation
SOC	System organ class
τ (tau)	Uniform dosing interval
T	Test treatment
$t_{1/2}$	Terminal half-life of the analyte in plasma
$t_{1/2,ss}$	Terminal half-life of the analyte in plasma at steady state
t_{max}	Time point of maximum plasma concentration
$t_{max, ss}$	Time from last dosing to maximum concentration of the analyte in plasma at steady state
TMF	Trial master file
TS	Treated set
TSAP	Trial statistical analysis plan
ULN	Upper limit of normal
V_z/F	Apparent volume of distribution during the terminal phase after extravascular administration
V_z/F_{ss}	Apparent volume of distribution during the terminal phase λ_z at steady state following extravascular administration
WHO-DD	World Health Organization Drug Dictionary

3. INTRODUCTION

As per International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (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 revised 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, planning of sample size, or randomisation.

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

Pharmacokinetic (PK) parameters will be calculated using Phoenix WinNonlin™ software (version 8.1. or higher, [redacted] or Statistical Analysis System (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 adverse event [AE] data or laboratory data; Report Appendix Generator system (RAGe) for compilation/formatting of the clinical trial report [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. The following changes as compared to the CTP will be made:

The treated set (TS) will be re-defined in order to only include all subjects who were treated with at least one dose of trial drug during the trial treatment periods. This means, subjects only treated during the run-in period but not in the trial treatment periods will be excluded from the TS. An additional "entered set" (ES) will be defined that also comprises these subjects. For details, please see Section 6.4.

5. ENDPOINTS

5.1 PRIMARY ENDPOINTS

Section 2.1.2 of the CTP:

The following pharmacokinetic parameters will be determined for ethinylestradiol (EE) and levonorgestrel (LNG):

- *$AUC_{\tau,ss}$ (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)*
- *$C_{min,ss}$ (minimum 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 endpoints

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

6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENTS

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

This is a Phase I trial in healthy female subjects between 18 and 35 years of age. A total of 16 subjects will be entered to the trial.

Section 3.1 of the CTP:

The trial will be performed as a non-randomised, open-label, two-period, fixed sequence trial with run-in period in healthy female subjects in order to compare the test treatment (T) to the reference treatment (R).

Reference (R): *one tablet q.d. Microgynon® on Days 1-21 (R) in Period 1.*

Test (T): *one tablet q.d. Microgynon® and one tablet q.d. 10 mg of BI 425809 on Days 1-21 in Period 2.*

On Days 1, 18-21 in Period 1 and Days 1-21 in Period 2, the treatments will be given under fasting conditions. On Days 2-17 in Period 1 fasting will be not mandatory. The Reference Treatment will always be followed by the Test Treatment in a fixed sequence. There will be no wash-out period between the treatments.

All subjects will undergo a run-in period that starts between Day -56 and Day -28. In this period, the subjects will take one tablet of Microgynon® daily until Day -8.

In the last 7 days of each treatment period (i.e. Day 22 to Day 28) and the run-in period (i.e. Day -7 to Day -1) no treatment will be given in order to induce withdrawal bleeding.

For details of dosage and formulation, see Table 6.1: 1:

Table 6.1: 1 Treatments and labels used in the analysis

Treatment		Short label
R	Microgynon® tablet (30 µg EE/150 µg LNG), q.d.	OC
T	BI 425809, 10 mg tablet + Microgynon® (30 µg EE/150 µg LNG), q.d.	BI+OC

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 (PD) effects are still likely to be present.

The REP of ethinylestradiol is 5 days based on a minimum observation period of at least 5-fold estimated t½ (i.e. 5 x 20 h, or 4.2 days, rounded to 5 days). The REP of levonorgestrel is 6 days

based on a minimum observation period of at least 5-fold estimated t½ (i.e. 5 x 25 h, or 5.2 days, rounded to 6 days).

Overall, the REP of 11 days will be considered for evaluation of adverse events in the trial.

The following study phases will be defined for the analysis of AEs:

Table 6.1: 2 Analysis phases for statistical analyses of AEs

Study analysis phase	Label	Start (inclusive)	End (exclusive)
Screening	**Screening**	Date of informed consent	Date/time of first administration of OC in Run-in period
Run-in	**Run-in**	Date/time of first administration of OC in Run-in period	Date/time of first administration of OC in Period 1, or 0:00h on the day after end of study visit, whatever occurs first
On treatment	**OC**	Date/time of first administration of OC in Period 1	Date/time of last administration of OC in Period 1 plus 11 days (264 h) or date/time of first administration of BI+OC in Period 2, whatever occurs first
On treatment	**BI+OC**	Date/time of first administration of BI+OC in Period 2	Date/time of last administration of BI+OC in Period 2 plus 11 days (264 h)
Follow-up	**Follow-up**	Date/time of last administration of BI+OC in Period 2 plus 11 days (264 h)	0:00h on the day after end of study visit

The on treatment phase during OC treatment in Period 1 will generally be terminated by the first administration of BI+OC in Period 2 as there will be no wash-out period between the treatments. BI+OC treatment is scheduled to start one day after Day 28 of Period 1 (which is only 7 days after last OC administration).

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

The following AE displays will be provided in the report:

In Section 15.3 and Appendix 16.1.13.1.8 (for ClinicalTrials.gov and EudraCT) 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, the run-in period and the follow-up phase will additionally be included and no totals will be provided.

For detailed information on the handling of the treatments, refer to the Technical TSAP ADS (analysis data set) plan and the 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 (iPDs), 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. 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 the iPD specification file and in the decision log. Both documents will be stored within the TMF in EDMS.

The iPDs will be summarised and listed in the CTR.

6.3 INTERCURRENT EVENTS

This section is not applicable for this Phase I trial.

6.4 SUBJECT SETS ANALYSED

- **Entered set (ES):** The ES includes all subjects who were entered to the study. This also comprises subjects who were not treated or only treated in the run-in period. The ES will be used for disposition, if not stated otherwise, and for listings of adverse events and exposure.

Section 7.2.1.1 of the CTP:

- ***Treated set (TS):*** *The TS includes all subjects who were treated with at least one dose of trial drug* during the trial treatment periods (Period 1 and Period 2). *The TS will be used for safety analyses* (except for AE and exposure listings which are based on ES).
- ***Pharmacokinetic parameter analysis set (PKS):*** *This set includes all subjects in the TS who provide at least one PK endpoint that was defined as primary and was not excluded due to a protocol deviation relevant to the evaluation of PK or due to PK non-evaluability (as specified in the following* CTP *subsection* 7.2.1.2*). Thus, a subject will be included in the PKS, even if she contributes only one PK parameter value for one period to the statistical assessment. Descriptive and model-based analyses of PK parameters will be based on the PKS.*

Section 7.2.1.2 of the CTP:

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 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)*
- *The subject experiences emesis at any time during the labelled dosing interval*
- *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. Descriptive and inferential statistics of PK parameters will be based on the PKS.

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

Table 6.4: 1 Subject sets analysed

	Subject sets		
Class of endpoint	**ES**	**TS**	**PKS**
Analysis of safety endpoints		X	
Analysis of PK endpoints			X
Disposition/disclosure of enrolment	X	X	
Demographic/baseline parameter		X	
Important protocol deviations		X	
Exposure		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 BI-KMED-BDS-HTG-0035) (3).

Missing data and outliers of PK data are handled according to BI standards (see BI-KMED-TMCP-HTG-0025 (4) and BI-KMED-TMCP-MAN-0014 (5)).

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

The baseline value is defined as the last measurement before first administration of study drug (administered at any study phase, including run-in 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. (...)*

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 Flow Chart, the acceptable deviation from the scheduled time for vital signs, ECG, and laboratory tests will be ± 30 min. (...)

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.

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

Unscheduled measurements of laboratory data and vital signs data are generally assumed to be repeat measurements of the most recent scheduled measurement. Therefore, unscheduled measurements will be assigned to the planned time point of the previous scheduled measurement except for the case, that administration of the next treatment (in the next treatment period) has already started when the unscheduled measurement is taken. Then the measurement will be assigned to the closest scheduled time point of the respective treatment period.

7. PLANNED ANALYSIS

The 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.

Model-based statistical analyses of PK endpoints (refer to Section 7.4 and Section 7.6) 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] 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 BI-KMED-BDS-HTG-0045 (6)) with the exception of those generated for PK-calculations following BI standards for PK/PD analysis (7).

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:

CV	arithmetic coefficient of variation
gMean	geometric mean
gCV	geometric coefficient of variation

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 (%). Percentages will be rounded to integers in case the denominator is less than 100; otherwise percentages will be rounded to one decimal point and the percentages will be based on all

subjects in the respective subject set whether they have non-missing values or not. 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.
- ‘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. The 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” (5) and “Description of Analytical Transfer Files and PK/PD Data Files” (8).

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

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

7.2 CONCOMITANT DISEASES AND MEDICATION

Frequency tables are planned for this section of the report, based on the TS.

Concomitant diseases will be coded using the coding system of the Medical Dictionary for Drug Regulatory Activities (MedDRA). Medications will be coded using the World Health

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

The diagnoses and medications will be listed. Subjects without any concomitant diagnoses or concomitant therapies will be marked with a "No" in the respective column.

The relevance of 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.

It is not intended to list the compliance separately. Any deviations from complete intake will be addressed in the RPM (cf. TSAP Section 6.2) and described in the CTR.

7.4 PRIMARY OBJECTIVE ANALYSIS

The effect of multiple oral doses of BI 425809 on the steady state pharmacokinetics of EE and LNG is to be determined based on the primary endpoints $AUC_{\tau,ss}$, $C_{max,ss}$, and $C_{min,ss}$.

7.4.1 Main analysis

All primary PK endpoints will be analysed descriptively. Additionally, a model-based analysis of relative bioavailability will be performed:

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 effects accounting for the following sources of variation: subject and treatment*. The effect* 'subjects' *will be considered as random, whereas* treatment *will be considered as fixed. The model is described by the following equation:*

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

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, ..., 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 Section 5.1) and their two-sided 90% confidence intervals (CIs) will be provided.

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

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;
        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 analyses are planned.

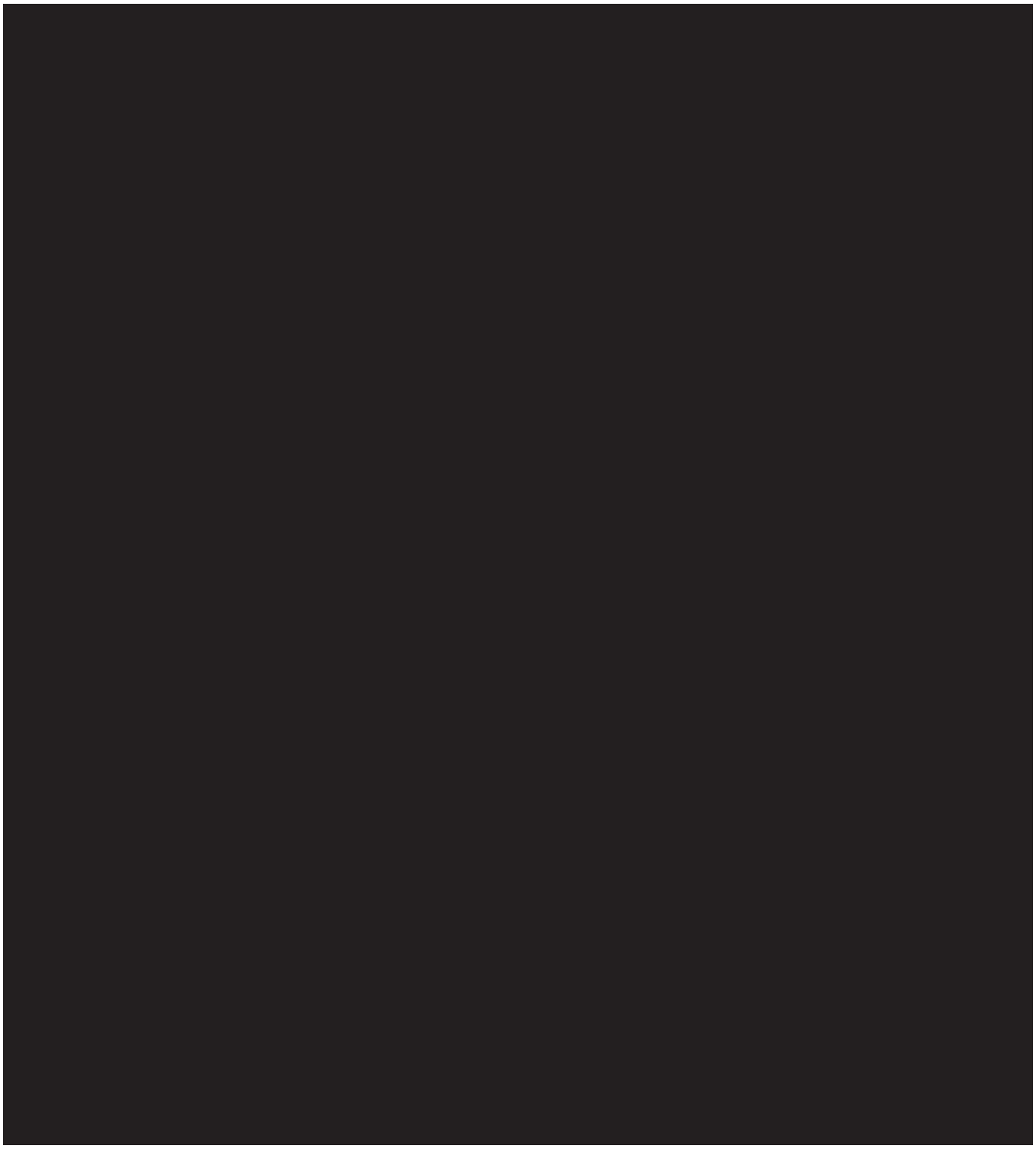
7.5 SECONDARY OBJECTIVE ANALYSIS

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.



7.7 EXTENT OF EXPOSURE

Descriptive statistics are planned for this section of the report based on the TS. The date and time of trial 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 usually be coded with the most recent version of MedDRA. The version to be used will be specified in the RPM. The coding version number will be displayed as a footnote in the respective outputs.

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" [BI-KMED-BDS-HTG-0041] (9) and "Analysis and Presentation of AE data from clinical trials" [BI-KMED-BDS-HTG-0066] (10) 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', 'run-in', 'on treatment' and '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 CTP, adverse events of special interest (AESIs) 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 upper limit of normal (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*

According to ICH E3 (11), 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 the study drug (e.g. discontinuation or dose reduced or interrupted).

An overall summary of AEs will be presented. The frequency of subjects with AEs will be summarised by treatment (R and T), primary system organ class (SOC), and preferred term (PT). Separate tables will be provided for subjects with

- Serious AEs
- Drug-related AEs
- Drug-related serious AEs
- AESIs
- Other significant AEs
- AEs leading to treatment discontinuation

In addition, the frequency of subjects with AEs will be summarised by worst intensity, treatment, primary SOC, and PT.

The system organ classes will be sorted alphabetically, PTs will be sorted by 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:

- AEs per arm for disclosure on EudraCT
- Non-serious AEs for disclosure on EudraCT
- Serious AEs 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 [BI-KMED-BDS-HTG-0042] (12). 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 a 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.

It is the investigator's responsibility to decide whether a lab value is clinically significantly abnormal or not (at the RPM at the latest). Possibly clinically significant values will be flagged in the data listings. A separate listing and if appropriate a frequency table including the number of subjects with such values will be provided by laboratory parameter. The analysis of possibly clinically significant abnormal values will be based on converted/standardised values.

Clinically relevant findings in laboratory data will be reported as baseline conditions (at screening) or as AEs (during the trial, including run-in period and Periods 1 and 2) if judged clinically relevant by the investigator, and will be analysed as such.

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

For vital signs (blood pressure and pulse rate), descriptive statistics including change from baseline will be calculated by planned time point based on the first value of the subject at that planned time point (or assigned to that planned time point), except for the baseline values for which the last value before drug administration will be used. In the listing, the difference from baseline will also be displayed.

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.

7.9 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 study drug) or as AE and will be summarised as such.

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

Columbia Suicide Severity Rating Scale (C-SSRS)

Suicidality assessment with the C-SSRS will be assessed as additional safety parameter, measured at screening, at Days 1, 11, and 21 of the second treatment period, and at the end of study. The results will be listed only. If applicable, the following sentence will be sufficient: No subjects with suicidal ideation, suicidal behaviour, or self-injurious behaviour without suicidal intent.

8. TIMEPOINT OF RELEASE OF TREATMENT INFORMATION

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

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-HTG-0035*: “Handling of Missing and Incomplete AE Dates”, current version, Group “Biostatistics & Data Sciences”, KMED.
4.	*BI-KMED-TMCP-HTG-0025*: “Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics”, current version; KMED.
5.	*BI-KMED-TMCP-MAN-0014*: “Noncompartmental Pharmacokinetic / Pharmacodynamic Analyses of Clinical Studies”, current version, Group “Translational Medicine Clinical Pharmacology”, KMED.
6.	*BI-KMED-BDS-HTG-0045*: “Standards for Reporting of Clinical Trials and Project Summaries”, current version, Group “Biostatistics & Data Sciences”, KMED.
7.	*BI-KMED-TMCP-OTH-0003*: “Graphs and Tables for Clinical Pharmacokinetics and Pharmacodynamic Noncompartmental Analyses”, current version, Group “Translational Medicine Clinical Pharmacology”, KMED.
8.	*BI-KMED-TMCP-MAN-0010*: “Description of Analytical Transfer Files and PK/PD Data Files”, current version, Group “Translational Medicine Clinical Pharmacology”, KMED.
9.	*BI-KMED-BDS-HTG-0041*: “Analysis and Presentation of Adverse Event Data from Clinical Trials – Display Template”, current version, Group “Biostatistics & Data Sciences”, KMED.
10.	*BI-KMED-BDS-HTG-0066*: “Analysis and Presentation of AE data from clinical trials”, current version, Group “Biostatistics & Data Sciences”, KMED.
11.	*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.
12.	*BI-KMED-BDS-HTG-0042*: “Handling, Display and Analysis of Laboratory Data”, current version, Group “Biostatistics & Data Sciences”, KMED.

[redacted]

11. HISTORY TABLE

Table 11: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
1.0	**27-OCT-23**	[redacted]	None	This is the final TSAP.