TRIAL STATISTICAL ANALYSIS PLAN

c36762184-01

BI Trial No.:	1405-0003
Title:	Safety, tolerability and pharmacokinetics of single rising oral doses and multiple oral doses of BI 1323495 versus placebo in healthy male Japanese subjects genotyped as poor and extensive metabolizers of UGT2B17 (single-blind, randomised, placebo-controlled [within dose groups] trial), including an investigation of drug-drug interaction with itraconazole in healthy male subjects genotyped as poor metabolizers of UGT2B17 (an open-label, two-period, fixed sequence trial)
Investigational Product:	BI 1323495
Responsible trial statistician:	[redacted] Phone: [redacted]
Date of statistical analysis plan:	27 Aug 2021 SIGNED
Version:	1

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2. LIST OF ABBREVIATIONS

Term	Definition / description
AE	Adverse Event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC_{0-12}	Area under the concentration-time curve of the analyte in plasma over a uniform dosing interval of 12 h after administration of the first dose
$AUC_{0-\infty}$	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity
AUC_{0-tz}	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 to the last quantifiable data point
$AUC_{\tau,ss}$	Area under the concentration-time curve of the analyte in plasma at steady state over a uniform dosing interval τ
BI	Boehringer Ingelheim
BP	Blood pressure
C_{max}	Maximum measured concentration of the analyte in plasma
$C_{max,ss}$	maximum measured concentration of the analyte in plasma at steady state over a uniform dosing interval τ
COVID	Coronavirus disease
CRF	Case Report Form
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
CV	Arithmetic coefficient of variation
DDI	Drug-drug interaction
ECG	Electrocardiogram
EM	Extensive metabolizer
gCV	geometric coefficient of variation
gMean	Geometric mean
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IPD	Important protocol deviations
IQRMP	Integrated quality and risk management plan

Term	Definition / description
MD	Multiple doses
MedDRA	Medical Dictionary For Regulatory Activities
NE	Neutrophil Elastase
PD	pharmacodynamic
PK	Pharmacokinetics
PKS	Pharmacokinetic parameter analysis set
PM	Poor metabolizer
PR	Pulse rate
RAGe	Report appendix generator
RPM	Report Planning Meeting
RR interval	ECG interval from the peak of the R wave to the peak of the subsequent R wave
SAE	Serious adverse event
SD	Standard Deviation
SOC	System Organ Class
SRD	Single rising dose
TS	Treated set
TSAP	Trial Statistical Analysis Plan
ULN	Upper limit of normal range

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 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 will be stored in a trial database within Medidata Rave system.

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

PK parameters will be calculated using Phoenix WinNonlin™ software (version Phoenix 6.3 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.

5. ENDPOINTS

5.1 PRIMARY ENDPOINTS

Section 2.1.2 of the CTP:

SRD and MD part; The primary endpoint for assessment of safety and tolerability of BI 1323495 is the percentage of subjects with drug-related adverse events.

DDI part; The following pharmacokinetic parameters will be determined for BI 1323495:

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

5.2 SECONDARY 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

Section 2.1.3 of the CTP:

SRD part; The following pharmacokinetic parameters will be determined if feasible:

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

DDI part; The following pharmacokinetic parameters will be determined for BI 1323495 if feasible:

- *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)*

MD part; The following pharmacokinetic parameters will be determined if feasible:

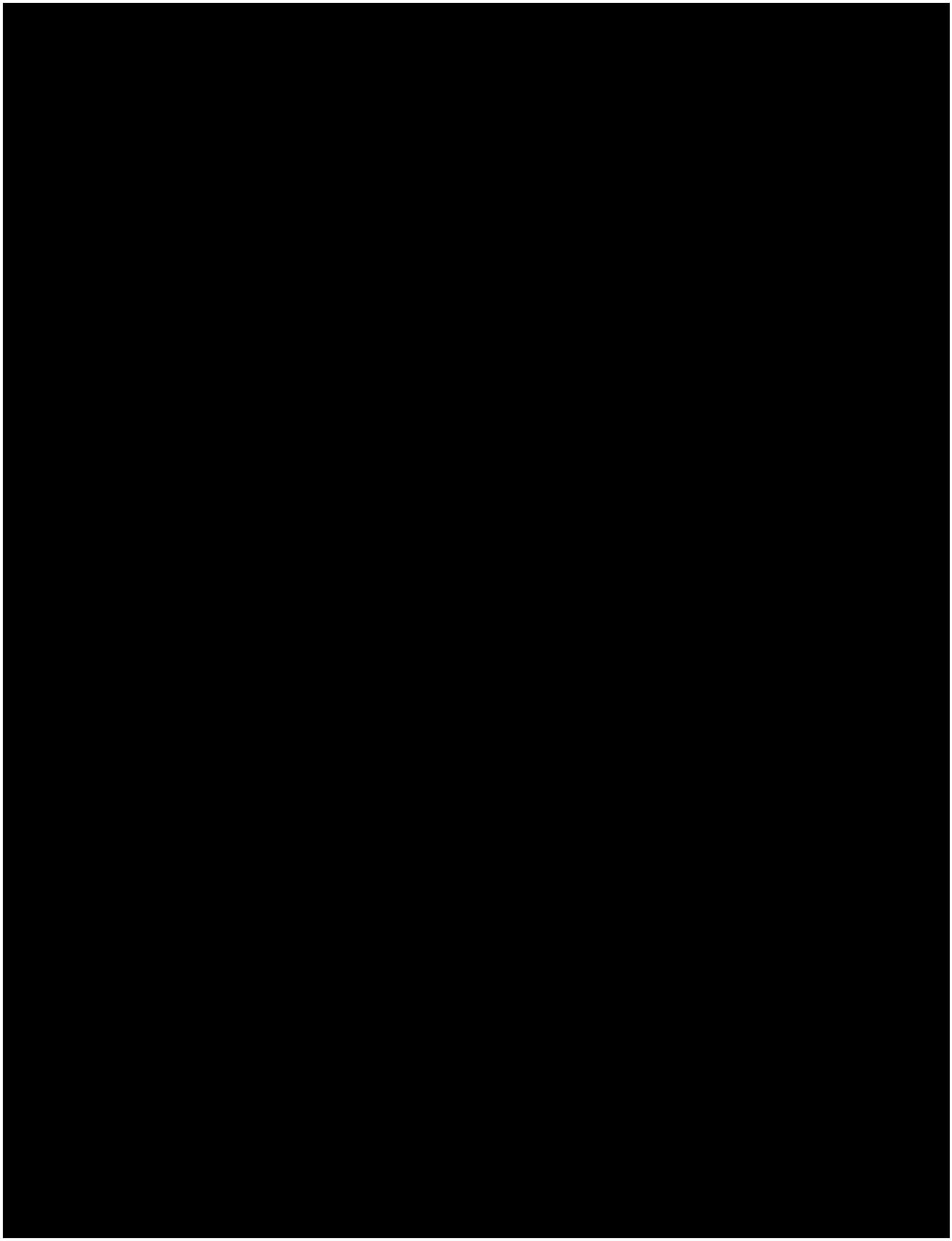
After the first dose of BI 1323495:

- *AUC_{0-12} (area under the concentration-time curve of the analyte in plasma over a uniform dosing interval of 12 h after administration of the first dose)*
- *C_{max} (maximum measured concentration of the analyte in plasma after the first dose)*

After the last dose of BI 1323495:

- *$AUC_{\tau,ss}$ (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)*



6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENTS

For basic study information on treatments to be administered, assignment of treatment groups, and selection of doses, cf. Section 4 of the CTP.

SRD part, PM: 24 subjects were planned to be treated with

- doses of 10 mg (1 x 10 mg tablet), 30 mg (3 x 10 mg tablets), or 100 mg (2 x 50 mg tablets) of BI 1323495 on Day 1 (test treatment)
- or matching placebo (reference treatment).

SRD part, EM: 12 subjects were planned to be treated with

- doses of 30 mg (3 x 10 mg tablets), 70 mg (2 x 10 mg tablets and 1 x 50 mg tablet) or 150 mg (3 x 50 mg tablets) of BI 1323495 on Day 1 (test treatments)
- or matching placebo (reference treatment).

MD part, PM: 24 subjects were planned to be treated with

- doses of 30 mg (3 x 10 mg tablets twice daily for 10 days and single dose on Day 11) or 60 mg (1 x 10 mg tablet and 1 x 50 mg tablet once daily for 11 days) of BI 1323495 (test treatment)
- or matching placebo (reference treatment).

DDI part, PM: Subjects were planned to be treated with

- a dose of 10 mg (1 tablet as single dose on Day 1 of period 1) of BI 1323495 (reference treatment)
- and – after a washout period of at least 11 days – doses of 10 mg (1 tablet as single dose on Day 1) of BI 1323495 and 200 mg of itraconazole once daily on Days -3 to 7 (test treatment).

In the SRD and MD parts, subjects are planned to be randomised within each dose group in a 3:1 ratio (test treatment to placebo). In the DDI part, randomisation is not applicable, because all subjects are planned to receive the same treatment in the same order.

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

Table 6.1: 1 Analysis phases and labels for statistical analyses in the SRD and MD parts

Study analysis phase	Label	Start	End
Screening[1]	**Screening**	Date of informed consent	Date/time of first administration of BI 1323495 or placebo
On treatment	**Placebo** **SRD PM 10 mg,** **SRD PM 30 mg,** **SRD PM 100 mg,** **SRD EM 30 mg,** **SRD EM 70 mg,** **SRD EM 150 mg,** **MD PM 30 mg BID,** **MD PM 60 mg QD,** respectively	Date/time of first administration of BI 1323495 or placebo	Date/time of last administration of BI 1323495 or placebo + REP (7 days, i.e., 7 * 24 h) or 12:00 a.m. on day after last contact date (whichever occurs first)
Follow-up	**Placebo** **F/U SRD PM 10 mg,** **F/U SRD PM 30 mg,** **F/U SRD PM 100 mg,** **F/U SRD EM 30 mg,** **F/U SRD EM 70 mg,** **F/U SRD EM 150 mg,** **F/U MD PM 30 mg BID,** **F/U MD PM 60 mg QD,** respectively	Date/time of last administration of BI 1323495 or placebo + REP (7 days, i.e., 7 * 24 h)	12:00 a.m. on day after last contact date

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

For the DDI part of this trial, the following separate phases will be defined for the analyses of AEs:

Table 6.1: 2 Analysis phases and labels for statistical analyses in DDI part

Study analysis phase	Label	Start	End
Screening[1]	**Screening**	Date of informed consent	Date/time of first administration of study drug
On treatment: BI Treatment	**DDI BI**	Date/time of first administration of BI 1323495 or placebo	Date/time of first administration of BI 1323495 + REP (7 days, i.e., 7 * 24 h)
On treatment: Itraconazole (ITZ)	**DDI ITZ**	Date/time of first administration of itraconazole	Date/time of BI 1323495 administration in treatment period 2 or alternatively, 0:00h on the day after trial termination date in case of no further treatment
On treatment-BI+ ITZ	**DDI BI+ITZ**	Date/time of BI 1323495 administration in treatment period 2	Date/time of last administration of itraconazole + REP (9 days, i.e., 9 * 24 h) or 12:00 a.m. on day after last contact date (whichever occurs first)
Follow-up BI	**F/U DDI BI**	End of DDI BI treatment phase (i.e. Date/time of first administration of BI 1323495 + REP (7 days, i.e., 7 * 24 h))	First drug administration of itraconazole or alternatively, 0:00h on the day after trial termination date in case of no further treatment
Follow-up BI	**F/U DDI BI+ITZ**	End of DDI BI+ITZ treatment phase (i.e. Date/time of last administration of itraconazole + REP (9 days, i.e., 9 * 24 h))	until 0:00h on the 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, ECG and vital signs.

Two types of AE displays will be provided in the report:

A. Section 15.3 and Appendix 16.1.13.1.8 (only for ClinicalTrials.gov and EudraCT) of the CTR displays:

In these displays, the on treatment phase will be analysed (labelled with the name of the study treatment (short label)). Screening and follow-up periods will not be included in this analysis. The following totals will be provided in addition (Section 15.3 only):

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

- a total over all on treatment phases included in this analysis ("**Total on-trt**")

B. Section 15.4 and Appendix 16.1.13.1.8 (except for ClinicalTrials.gov and EudraCT) of the CTR displays:

- Screening
- On treatment (labelled with the name of the study treatment (short label))
- Follow-up (labelled with the name of the study treatment (short label))

In Section 16.1.13.1.8 AE tables, the following totals will be provided in addition:

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

Tables of vital signs and laboratory values will present results by dose group and study period.

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

6.2 IMPORTANT PROTOCOL DEVIATIONS

Consistency check listings (for identification of deviations from time windows) and a list of protocol deviations (e.g. deviations in drug administration, in blood sampling times, etc.) will be provided to be discussed at the Report Planning Meeting (RPM). At this meeting, it will be decided whether a discrepant data value can be used in analyses or whether it must be corrected in the clinical database. Each protocol deviation must be assessed to determine whether it is an important PD (IPD). For definition of IPDs, and for the process of identification of these, refer to the BI reference document "Identify and Manage Important Protocol Deviations (IPD)" (2).

If any IPDs are identified, they are to be summarised into categories and will be captured in the decision log. Categories which are considered to be IPDs in this trial are defined in the integrated quality and risk management plan (IQRMP). If the data show other IPDs, the definition in the IQRMP 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.

6.3 SUBJECT SETS ANALYSED

Section 7.3 of the CTP:

[…]
Statistical analyses will be based on the following analysis sets:

- *Treated set (TS): The treated set includes all subjects who were randomised (SRD and MD part) / allocated (DDI part) and treated with at least one dose of trial drug. The treatment assignment will be determined based on the first treatment the subjects received. 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 primary or secondary PK endpoint that 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 subsection 'Pharmacokinetics'). Thus, a subject will be included in the PKS, even if he contributes only one primary or secondary PK parameter value for one period to the statistical assessment. Descriptive and model-based analyses of PK parameters will be based on the PKS.*

[…]

Plasma and urine 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.

Relevant 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 and urine 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),*

- *Missing samples/concentration data at important phases of PK disposition curve*

- *A predose concentration of BI 1323495 is >5% C_{max} value of that subject in the respective treatment period (only DDI part).*

The descriptive analysis of PK concentrations and endpoints will be based on the ADS ADPC and ADPP, respectively, as described at the beginning of Section 7.

Table 6.3: 1 Subject sets analysed

	Subject set	
Class of endpoint	TS	PKS
Analyses of PK endpoints		X
Analyses of PD endpoint	X	
Safety parameters	X	
Demographic/baseline parameters	X	
Important protocol deviations	X	
Disposition	X	
Treatment exposure	X	

[redacted]

6.5 POOLING OF CENTRES

This section is not applicable, because the study was performed in only one centre.

6.6 HANDLING OF MISSING DATA AND OUTLIERS

Section 3.3.4 of the CTP:

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, the data will be included in the CRF and will be reported in the CTR.

Section 7.5.1 of the CTP:

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 (3).

Missing data and outliers of PK data are handled according to BI standards (see (4) and (5)).

Section 7.5.2 of the CTP:

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 is defined as the last measurement before administration of BI 1323495 in each 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.*

Trial measurements and assessments scheduled to occur 'before' trial medication administration at Day 1 are to be performed and completed within a 3 h-period prior to the trial medication administration (including blank values for PK and biomarker). A blank urine sample for PK will be collected within 3 h before drug administration.

The acceptable deviation from the scheduled time for vital signs and ECG will be ± 10 min for the first 4 h after trial medication administration and ± 30 min thereafter (± 60 min for MD part). For laboratory test, the acceptable deviation is ± 30 min.

Adherence to time windows will be checked via the consistency check listings 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" (6) with the exception of those generated for PK concentrations and parameters following BI standards for PK/PD analysis (10).

PK evaluation will be performed by [redacted] and monitored by the department [redacted] at [redacted]. Descriptive statistics of PK endpoints and plasma concentrations will be presented in Section 15.6 of the CTR.

The individual values of all subjects will be listed. Listings will be sorted by treatment 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
P10	10^{th} percentile
Q1	1^{st} quartile
Q3	3^{rd} quartile
P90	90^{th} percentile

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

Tabulations of frequencies for categorical data will include all possible categories and will display the number of observations in a category as well as the percentage (%) relative to the respective treatment group. Percentages will be rounded to one decimal place. The category missing will be displayed if and only if there are actual missing values. Percentages will be

based on all subjects in the respective subject set whether they have non-missing values or not.

Exclusion of PK parameters

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

Exclusion of PK concentrations

The ADS "ADPC" (PK concentrations per time-point or per time-interval) contains column variables ACEXC and ACEXCO indicating inclusion/exclusion (ACEXC) of a concentration and an analysis flag comment (ACEXCO). Exclusion of a concentration depends on the analysis flag comment ACEXCO. For example, if ACEXCO is set to 'ALL CALC', the value will be excluded for all types of analyses based on concentrations. If ACEXCO is set to 'DESC STATS' the value will be excluded from descriptive evaluations per planned time point/time interval. If ACEXCO contains the addition 'TIME VIOLATION' or 'TIME DEVIATION' the value can be used for further analyses based on actual times. If ACEXCO is set to 'HALF LIFE', the value will be excluded from half-life calculation (and, as a consequence, any calculation that relies on λ_z) only; the value is included for all other analyses.

Further details are given in (5) and (11).

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

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

7.2 CONCOMITANT DISEASES AND MEDICATION

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

Concomitant diseases will be coded according to the most recent version of 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. Concomitant non-drug therapies will be coded according to the most recent version of MedDRA.

A medication will be considered concomitant to a dose group 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).

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 site under supervision of the investigating physician or a designee. The measured plasma concentrations and/or urinary excretion of trial medication will provide additional confirmation of compliance.

Subjects who are non-compliant (for instance, who do not appear for scheduled visits or violate trial restrictions) may be removed from the trial and the CRF will be completed accordingly (for further procedures, please see CTP *Section 3.3.4.1).*

Treatment compliance will not be analysed as a specific endpoint. Any deviations from complete intake will be addressed in the RPM (cf. Section 6.2) and described in the CTR.

7.4 PRIMARY ENDPOINTS

7.4.1 Primary analysis of the primary endpoints

For the SRD and MD parts of this trial, the primary endpoint for assessment of safety and tolerability of BI 1323495 is the percentage of subjects with drug-related AEs. The analysis will be based on the treated set (TS) and will be descriptive in nature. Refer to Section 7.8.1 for a description of the analysis of AEs, and in particular the analysis of the percentage of subjects with treatment-emergent drug-related AEs.

For the DDI part of this trial, relative bioavailability of BI 1323495 in plasma is to be determined based on the primary PK endpoints $AUC_{0-\infty}$ and C_{max} on the PKS (cf. Section 5.1).

Section 7.3.1 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 'subject' 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, ..., 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. The indices 'B' and 'W' correspond to 'between' and 'within' variability, respectively.

Point estimates for the ratios of the geometric means (test/reference) for the primary endpoints (see CTP *Section 2.1.2) 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 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;
```

7.4.2 Sensitivity analysis, subgroup analysis, exploratory analysis of the primary endpoints

Section 7.3.1 of the CTP:

The same statistical model as stated above will be repeated for the primary endpoints but with 'subjects' considered as fixed effect.

The following SAS code can be used to fit the model:

```
PROC GLM DATA=indata;
        CLASS subject treatment;
        MODEL logpk = treatment subject;
        LSMEANS treatment / PDIFF CL ALPHA=0.1;
        ESTIMATE 'T-R' treatment -1 1;
RUN;
```

Section 7.3.1 of the CTP:

In addition to the model-based approach, all parameters will be calculated and analysed descriptively. Furthermore, mean plasma concentration time curves as well as individual profiles will be provided.

7.5 SECONDARY ENDPOINTS

7.5.1 Key secondary endpoints

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

7.5.2 Secondary endpoints

Secondary PK endpoints in all trial parts will be assessed descriptively. The secondary endpoint in the DDI part will be assessed statistically using the same methods as described for the primary PK endpoints (cf. Section 7.4.1)

Section 7.3.2. of the CTP:

SRD part (both EM and PM)*:*

Dose proportionality will be explored via graphical checks and if applicable via the power model stated below. The analysis will be performed for the pharmacokinetic endpoints $AUC_{0-\infty}$ *and* C_{max} *specified in* CTP *Section 2.1.3.*

The power model describes the functional relationship between the dose level and PK endpoint on the log scale via

$$y_{km} = log\,(x_{km}) = \mu + \ b \cdot log\,(D_k) \ + \ e_{km}\,,$$

where

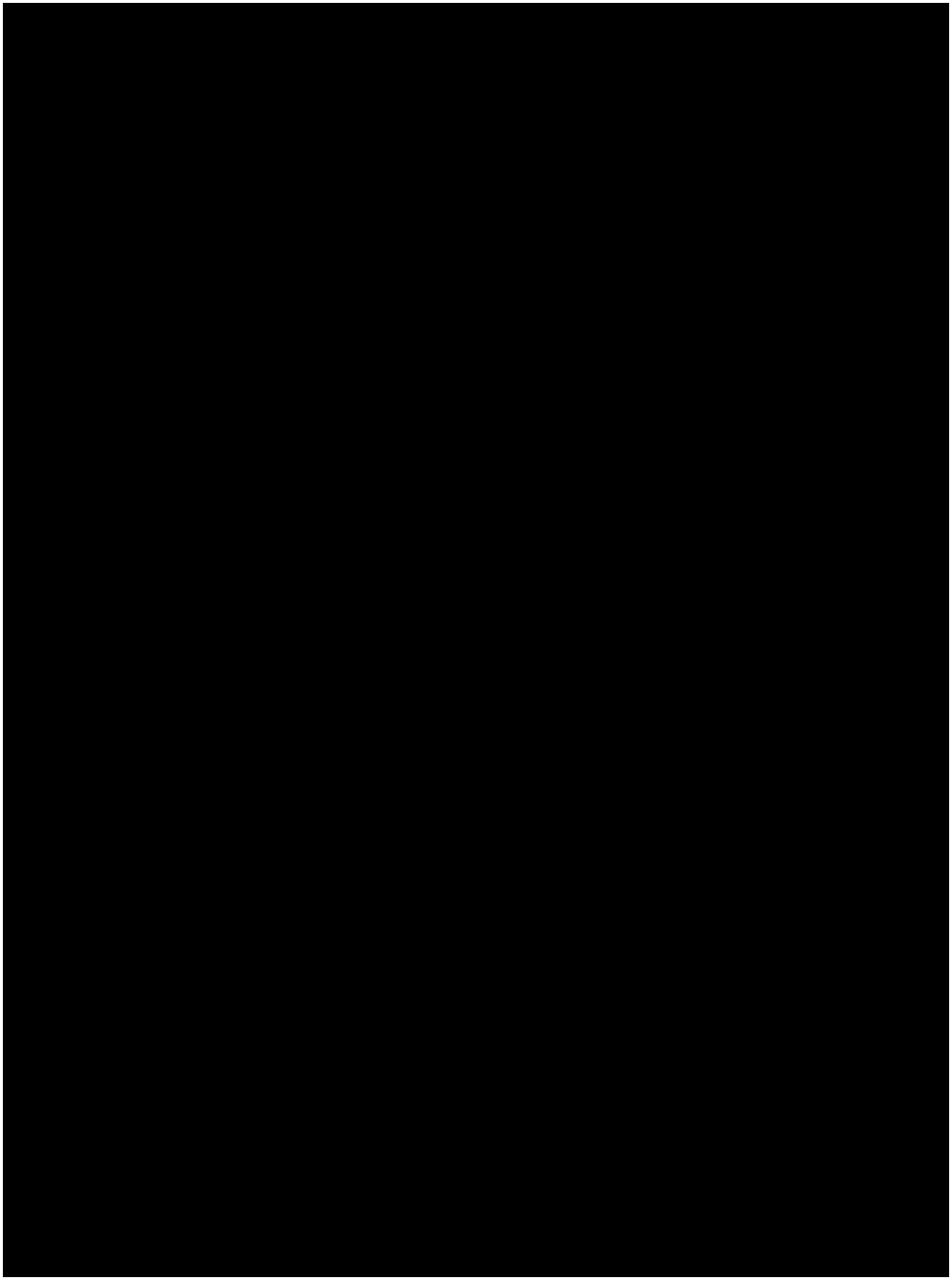
- y_{km} *logarithm of response (PK parameter) measured on subject m receiving dose k,*
- μ *the overall mean,*
- β *slope parameter of linear regression line,*
- D_k *level of dose k, k=1,…, 3,*
- e_{km} *the random error associated with the* m^{th} *subject who was administered dose level k where* ($e_{km} \sim N(0, \sigma^2)$ *iid).*

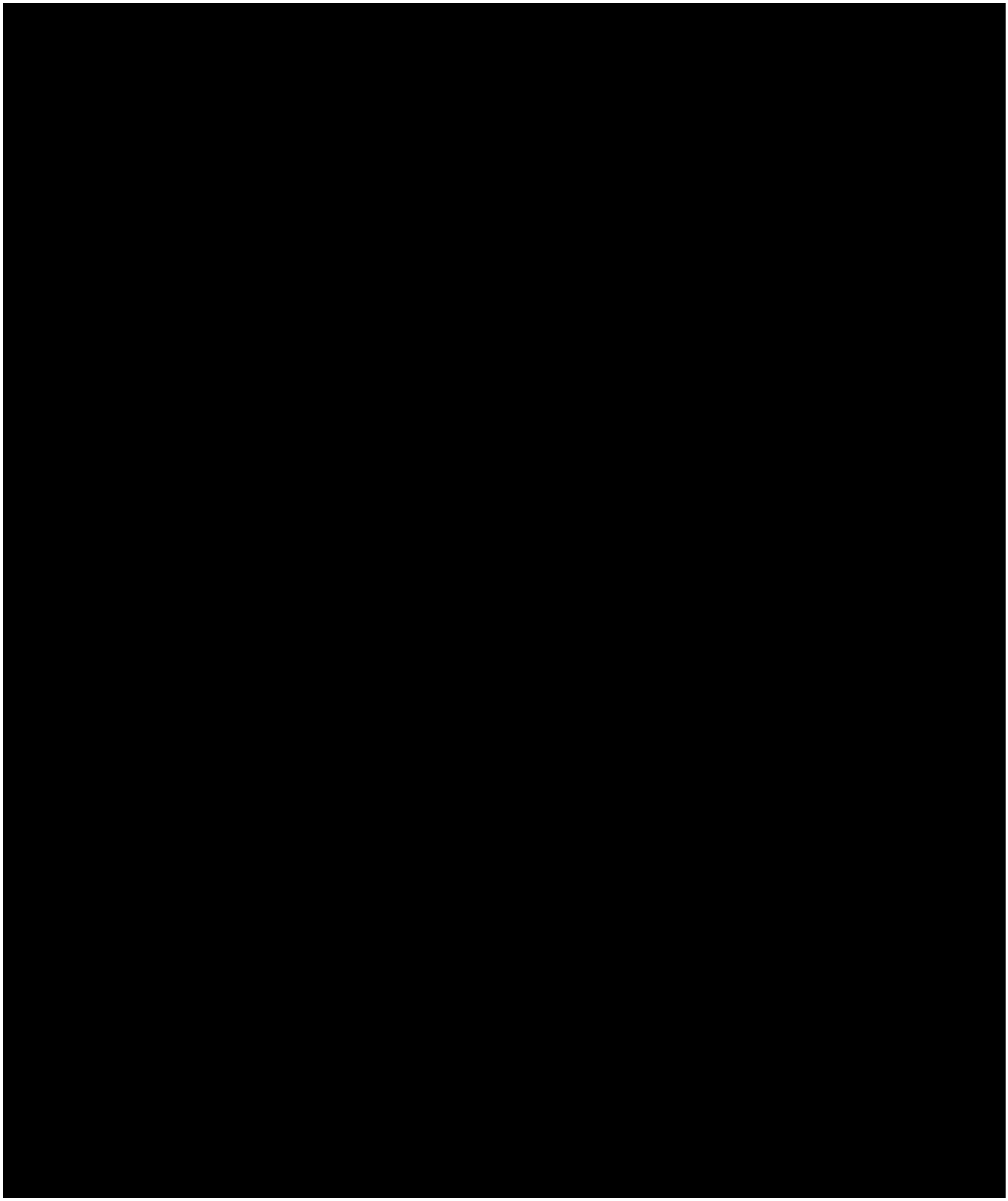
The slope parameter β together with its two-sided 90% confidence interval will be estimated. Additionally, the r-fold change $r^{\beta-1}$ *together with its 90% CI will be derived.*

DDI part (only PM)*:*

The secondary endpoints $AUC_{0\text{-}tz}$ *(refer to* CTP *Section 2.1.3) will be assessed statistically using the same methods as described for the primary PK endpoints in Section* CTP *7.3.1.*

In SRD part, the dose proportionality will be assessed and reported for EM and PM subjects separately.





7.7 EXTENT OF EXPOSURE

Descriptive statistics are planned for this section of the report based on the TS.

7.8 SAFETY ANALYSIS

All safety analyses will be performed on the TS.

7.8.1 Adverse Events

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

The analyses of AEs will be descriptive in nature. All analyses of AEs will be based on the number of subjects with AEs and not on the number of AEs.

For further details on summarization of AE data, please refer to "Analysis and Presentation of Adverse Event Data from Clinical Trials" (7) and "Handling of missing and incomplete AE dates" (3).

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 and Table 6.1:2.

An overall summary of AEs will be presented. This overall summary will comprise summary statistics for the class of adverse events of special interest (AESIs).

Section 5.2.6.1.4 of the CTP:

The following are considered as AESIs:

Hepatic injury
A hepatic injury is defined by the following alterations of hepatic laboratory parameters:

- *an elevation of AST (aspartate transaminase) and/or ALT (alanine transaminase) ≥3 folds ULN combined with an elevation of total bilirubin ≥2 folds ULN measured in the same blood draw sample, or*
- *Aminotransferase (ALT, and/or AST) elevations ≥10 folds ULN.*

According to ICH E3 (8), 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).

The frequency of subjects with AEs will be summarised by treatment, primary System Organ Class (SOC) and preferred term. AEs which were considered by the investigator to be drug related will be summarised. Separate tables will also be provided for subjects with SAEs and subjects with AESIs. AEs will also be summarised by maximum intensity.

The SOCs and preferred terms within SOCs will be sorted by descending frequency over all treatment groups.

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 summarised.

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

7.8.2 Laboratory data

The analyses of laboratory data will be descriptive in nature and will be based on BI standards "Display and Analysis of Laboratory Data" (9).

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

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

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

Possibly clinically significant abnormal laboratory values are only those identified either in the Investigator's comments or at the Report Planning Meeting at the latest. It is the Investigator's responsibility to decide whether a lab value is clinically significant abnormal or not. Standard or project-specific rules for flagging clinically significant values in an automated manner will not be applied in this study.

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.

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 time point based on the last value of the subject at that planned time point (or assigned to that planned time point).

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.

7.8.4 ECG

Abnormal findings will be reported as baseline conditions (prior to first study drug administration) or as AEs (from first study drug administration onwards) if judged clinically relevant by the investigator.

7.8.5 Others

Physical examination findings will be reported as relevant medical history/baseline condition (if a condition already exists before first administration of study treatment) or as AE (if condition emerges after first administration of study treatment) and will be summarized as such. No separate listing or analysis of physical examination findings will be prepared.

8. TIMEPOINT OF RELEASE OF TREATMENT INFORMATION

The treatment information will be loaded into the trial database after completion of enrolment, i.e. the randomization has been completed.

9. REFERENCES

1	*CPMP/ICH/363/96*: "Statistical Principles for Clinical Trials", ICH Guideline Topic E9; Note For Guidance on Design, Conduct, Analysis and Evaluation of Clinical Trials, current version
2	*001-MCS-40-413:* "Identify and Manage Important Protocol Deviations (iPD)", current version; IDEA for CON
3	*KM Asset BI-KMED-BDS-HTG-0035:* "Handling of missing and incomplete AE dates", current version; KMED
4	*BI-KMED-TMCP-MAN-0012*: "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; KMED.
6	*KM Asset BI-KMED-BDS-HTG-0045:* "Reporting of Clinical Trials and Project Summaries", current version; KMED
7	*KM Asset BI-KMED-BDS-HTG-0041:* "Analysis and Presentation of Adverse Event Data from Clinical Trials", current version; KMED
8	*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
9	*KM Asset BI-KMED-BDS-HTG-0042:* "Display and Analysis of Laboratory Data", current version; KMED
10	*BI*-KMED-TMCP-OTH-0003: "Graphs and Tables for Clinical Pharmacokinetics and Pharmacodynamic Noncompartmental Analyses", current version, KMED.
11	*BI-KMED-TMCP-MAN-0010*: "Description of Analytical Transfer Files and PK/PD Data Files", current version; KMED.

11. HISTORY TABLE

Table 11: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
1	**27-AUG-2021**	[redacted]	None	This is the final TSAP.