TRIAL STATISTICAL ANALYSIS PLAN

c38312926-01

BI Trial No.:	1402-0020
Title:	Relative bioavailability of two different tablet formulations of BI 1358894 administered in healthy subjects in fasted and fed state (an open-label, randomised, single-dose, four-period, four-sequence crossover study)
Investigational Product(s):	BI 1358894
Responsible trial statistician(s):	[redacted] Phone: [redacted] Fax: [redacted]
Date of statistical analysis plan:	16 JUN 2022 SIGNED
Version:	1
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2. LIST OF ABBREVIATIONS

Term	Definition / description
AESI	Adverse event of special interest
ALT	Alanine transaminase
ANOVA	Analysis of variance
AST	Aspartate transaminase
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
$AUC_{0-\infty}$	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity
BMI	Body mass index
BP	Blood Pressure
CI	Confidence interval
CL	Confidence interval limit
C_{max}	Maximum measured concentration of the analyte in plasma
CSD	Company Standard Displays
C-SSRS	Columbia-Suicidal Severity Rating Scale
CV	Arithmetic coefficient of variation
EDMS	Electronic Document Management System
F/U	Follow Up
gCV	Geometric coefficient of variation
gMean	Geometric mean
iCF	Intended Commercial Formulation
iPD	Important Protocol Deviation
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
N	Number non-missing observations
P10	10^{th} percentile
P90	90^{th} percentile
PD	Protocol deviation
PKS	PK parameter analysis set
PR	Pulse Rate

Term	Definition / description
PT	Preferred Term
Q1	1st quartile
Q3	3rd quartile
qd	Quaque die
R	Reference treatment
RAGe	Report Appendix Generator system
REP	Residual Effect Period
RPM	Report Planning Meeting
SD	Standard deviation
SOC	System organ class
T	Test treatment
TFII	Trial Formulation 2
TS	Treated set
t_z	Time of last measurable concentration of the analyte in plasma
WHO-DD	World Health Organization Drug Dictionary

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 as collected in the eCRF will be stored in a trial database within the RAVE EDC system. All study data also including external data will then be uploaded to the CDR data warehouse.

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.

5. ENDPOINTS

5.1 PRIMARY ENDPOINTS

Section 2.1.2 of the CTP:

The following pharmacokinetic parameters will be determined for BI 1358894:

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

The following pharmacokinetic parameter will be determined for BI 1358894:

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

[redacted]

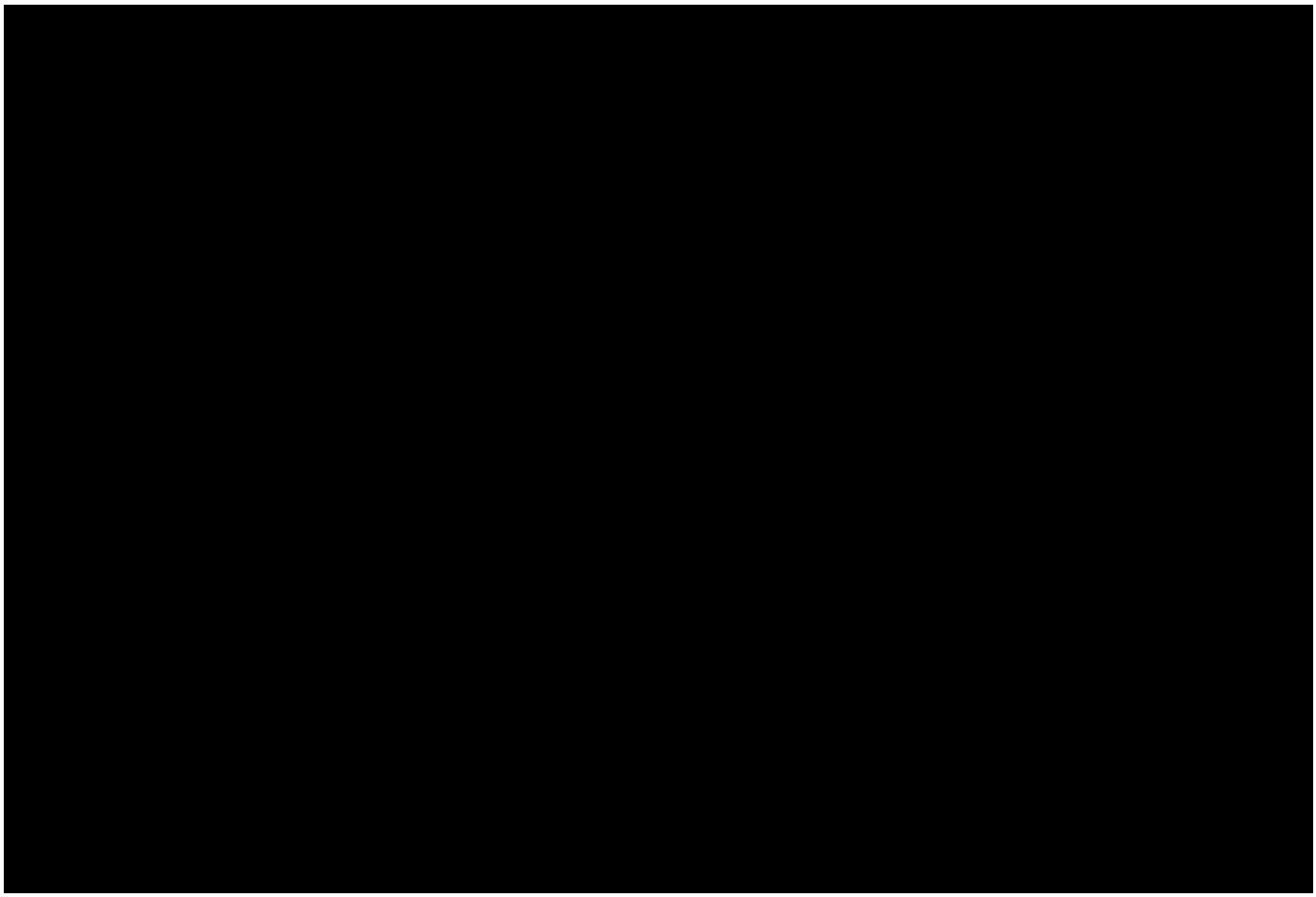
5.3.2 Safety parameters

Section 2.2.2.2 of the CTP:

Safety and tolerability of BI 1358894 will be assessed based on:

- *Adverse events (including clinically relevant findings from the physical examination)*
- *Safety laboratory tests*

- *12-lead ECG*
- *Vital signs (blood pressure, pulse rate)*
- *Prospective suicidality assessment (C-SSRS)*



6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENTS

For basic study information on investigational products and selection of doses, please see CTP Sections 3 and 4.

The treatments will be one 100 mg tablet (iCF) of BI 1358894 (test, T) administered to subjects in the fasting (T_{fasted}) and fed (T_{fed}) state and two 50 mg tablets (TFII) of BI 1358894 (reference, R) administered to subjects in the fasting (R_{fasted}) and fed (R_{fed}) state.

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_{fasted}	BI 1358894, 2 tablets à 50mg (TFII), fasted	Rfasted
R_{fed}	BI 1358894, 2 tablets à 50mg (TFII), fed	Rfed
T_{fasted}	BI 1358894, 1 tablet à 100mg (iCF), fasted	Tfasted
T_{fed}	BI 1358894, 1 tablet à 100mg (iCF), fed	Tfed

[redacted]

The following study phases will be defined for the analysis of adverse events (AEs):

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

Study analysis phase	**Label**	**Start**	**End**
Screening[1]	**Screening**	0:00h on date of informed consent	Date/time of administration of study drug in treatment period 1
On treatment	**Rfasted, Rfed, Tfasted or Tfed** respectively	Date/time of administration of study drug of respective treatment period	End of REP ([redacted]) Date/time of next administration of study drug in the next treatment period, if applicable OR Date/time of trial termination, whichever occurs first.
Follow-up	**Follow-up**	End of REP	Date/time of administration of study drug in the next treatment period, if applicable OR Date/time of trial termination, whichever occurs first

[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 each subject, the overall trial period lasts from signing informed consent until the last visit.

Section 7.2.5 of the CTP: *Note that AEs occurring after the last per protocol contact but entered before final 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:

A) Section 15.3 and Appendix 16.1.13.1.8 (for ClinicalTrials.gov and EudraCT only) 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 total will be provided in addition (Section 15.3 only):

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

B) Section 15.4 of the CTR displays:

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

C) Appendix 16.2 of CTR: all AEs will be listed.

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

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. 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 protocol deviation (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 DV domain template. If the data show other iPDs, the definition in the DV domain template will be supplemented accordingly by the time of the Report Planning Meeting.

iPDs will be summarized and listed in the CTR. 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 Report Planning Meeting, after discussion of exceptional cases and implications for analyses.

Non-important COVID-19 related PDs will only be listed.

6.3 SUBJECT SETS ANALYSED

Section 7.2.1.1 of the CTP:

- *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 the following subsection 'Pharmacokinetics'). Thus, a subject will be included in the PKS, even if he/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 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*
- *Incorrect intake of meal prior to drug administration in treatment periods under fed condition*
- *Use of restricted medications*

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

- *The subject experienced emesis that occurred at or before two times median t_{max} of the respective treatment (Median t_{max} is to be determined excluding the subjects experiencing emesis),*
- *A BI 1358894 predose concentration is >5% C_{max} value for a subject for a specific treatment period, that specific treatment period will be excluded*
- *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.

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

Table 6.3: 1 Subject sets used for analysis of endpoints

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

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

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

The only exceptions where imputation might be necessary for safety evaluation are AE dates. Missing or incomplete AE dates are imputed according to BI standards (see "Handling of Missing and Incomplete AE Dates") (3).

Missing data and outliers of PK data are handled according to BI standards (see "Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics" (4) and "Noncompartmental Pharmacokinetic / Pharmacodynamic Analyses of Clinical Studies" (5).

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

For each treatment period, the baseline value is defined as the last available off-treatment measurement before administration of BI 1358894 of the respective treatment period.

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

Up to 48 h after drug administration (planned time), the acceptable deviation from the scheduled time for adverse event/concomitant medication questioning, suicidality assessment,

vital signs, ECG, and laboratory tests will be ± 30 min, if not stated otherwise in the CTP *Flow Chart,*

Starting from planned time of 48 hours until 168 hours (not inclusive) *after drug administration (and beyond) a time window of +/- 120 minutes will be allowed for all procedures*

Starting from a planned time of 168 hours after drug administration (and beyond) a time window of +/- 26 hours will be allowed for all procedures

In addition the following time windows will be considered acceptable for PK sampling up to 48 hours after each study drug administration:

Starting from planned time of 0 hours until 2 hours (not inclusive) after drug administration a time window of +/- 5 minutes will be allowed. Starting from planned time of 2 hours until 48 hours (not inclusive) after drug administration a time window of +/- 10 minutes will be allowed.

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

Unscheduled measurements of laboratory data, vital signs data, for adverse event/concomitant medication questioning, suicidality assessment and ECG 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 the [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 and Section 7.5.2) will also be performed by the [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 16.1.13.3.

The format of the listings and tables will follow the BI standards (see "Standards for Reporting of Clinical Trials and Project Summaries" (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, except for listings regarding PK, which will be sorted by treatment, subject number and planned time. The listings will be included in Appendix 16.2 and for PK in Appendix 16.1.13 of the CTR.

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

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

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

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

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

P10	10^{th} percentile
Q1	1^{st} quartile
Q3	3^{rd} quartile
P90	90^{th} percentile

The descriptive statistics of concentrations will be displayed with three significant digits. 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 (unless otherwise specified, all subjects in the respective subject set whether they have non-missing values or not).

Percentages will be given in integer numbers due to the small sample size of <100. The category missing will be displayed only if there are actually missing values.

Main comparisons of interest

The main comparisons of interest in this trial to assess relative bioavailability are the following:

i) T_{fasted} versus R_{fasted}
ii) T_{fed} versus R_{fed}
iii) T_{fed} versus T_{fasted}
iv) R_{fed} versus R_{fasted}

In the remaining document treatment A represents the first, and treatment B the second treatment of each pairwise comparison stated above.

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 are based on PK parameter values which are not flagged for exclusion, i.e. with APEXC equal to "Included".

Exclusion of plasma concentrations

The ADS “ADPC” (PK concentrations per time-point or per time-interval) contains column variables ACEXC or 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.
- "DESC STATS" the value will be excluded from descriptive evaluations per planned time point/time interval.
- [redacted]

If ACEXCO contains the addition "TIME VIOLATION" or "TIME DEVIATION", the value can be used for further analyses based on actual times.

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 CTR.
The data will be summarised by treatment sequence and in total.

7.2 CONCOMITANT DISEASES AND MEDICATION

Descriptive statistics are planned for this section of the CTR.

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

In the remaining document 'therapy' will be used for non-drug therapies and concomitant medications.

Section 7.2.5 CTP: *Previous and concomitant therapies will be presented per treatment sequence group.*

A therapy will be considered concomitant to a treatment, if it

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

The diagnoses and medications will be listed. Subjects without any concomitant disease or concomitant therapies should 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

Treatment compliance will not be analyzed or listed as a specific endpoint, but judged by observed analyte concentrations. Any deviation from complete food and medication intake will be addressed in the RPM (see Section 6.2) and described in the CTR.

7.4 PRIMARY ENDPOINTS

For BI 1358894, the relative bioavailability will be investigated on the basis of the primary PK endpoints $AUC_{0\text{-}tz}$ and C_{max} (see Section 5.1) and using the PKS.

7.4.1 Primary analysis of the primary endpoints

Section 7.2.1.2 of the CTP: *The pharmacokinetic parameters listed in Section 2.1 and 2.2.2 for drug BI 1358894 will be calculated according to the relevant BI internal procedures.*

Section 7.2.2 of the CTP:

Primary analyses

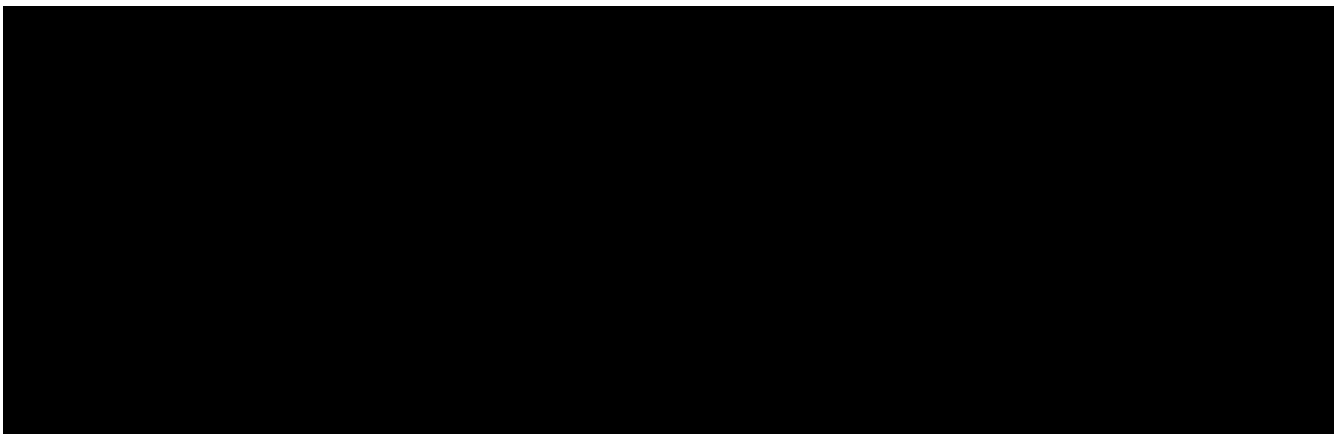
The statistical model used for the analysis of the primary endpoints will be an analysis of variance (ANOVA) model on the logarithmic scale. That is, the PK endpoints will be log-transformed (natural logarithm) prior to fitting the ANOVA model. This model will include effects accounting for the following sources of variation: sequence, subjects within sequences, period and treatment. The effect 'subjects within sequences' will be considered as random, whereas the other effects will be considered as fixed. The model is described by the following equation:

$y_{ijkm} = \mu + \zeta_i + s_{im} + \pi_j + \tau_k + e_{ijkm}$, *where*
y_{ijkm} = *logarithm of response measured on subject m in sequence i receiving treatment k in period j,*
μ = *the overall mean,*
ζ_i = *the* i^{th} *sequence effect, i = 1, 2, 3, 4*
s_{im} = *the effect associated with the* m^{th} *subject in the* i^{th} *sequence, m = 1, 2, ..., 6*
π_j = *the* j^{th} *period effect, j = 1, 2, 3, 4*
τ_k = *the* k^{th} *treatment effect, k = 1, 2, 3, 4*
e_{ijkm} = *the random error associated with the* m^{th} *subject in sequence i who received treatment k in period j.*

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

Point estimates for the ratios of the geometric means (treatment A / treatment B) for the comparisons as stated in Section 7 and the primary endpoints (see Section 5.1) with their two-sided 90% confidence intervals (CIs) will be provided.

For each endpoint, the difference between the expected means for log(A)-log(B) 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.



7.5 SECONDARY ENDPOINTS

7.5.1 Key secondary endpoint

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

7.5.2 Other Secondary endpoint

Section 7.2.3 of the CTP: *The secondary endpoint* […] $AUC_{0-\infty}$ *will be calculated according to the relevant BI internal procedures and will be assessed statistically using the same methods as described for the primary endpoints.*

7.7 EXTENT OF EXPOSURE

Descriptive statistics of number of doses and calculated total dose are planned for this section of the CTR. Only aggregated exposure of BI 1358894 will be presented as all treatments have the same dose. The date and time of drug administrations 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 with the most recent version of MedDRA.

Unless otherwise specified, the analyses of AEs will be descriptive in nature. All analyses of AEs will be based on the number of subjects with AEs and NOT on the number of AEs. BI standards as presented in "Analysis and Presentation of Adverse Event Data from Clinical Trials – Display Template" (9) and "Analysis and Presentation of AE data from clinical trials" (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', '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.

An overall summary of AEs will be presented. This will comprise summary statistics for the class of AESIs.

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*

According to ICH E3 (11), in addition to deaths and serious adverse events, 'other significant' AEs need to be listed in the CTR. 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 (PT). Separate tables will be provided for subjects with serious AEs, for subjects with drug-related AEs, for subjects with drug-related serious adverse events and for subjects with AESIs. In addition, the frequency of subjects with AEs will be summarised by treatment, worst intensity, SOC and PT.

The SOCs and PTs within SOCs will be sorted by descending frequency over all treatment groups. The MedDRA version number will be displayed as a footnote in the respective output.

For disclosure of AE data on ClinicalTrials.gov, the frequency of subjects with non-serious AEs that had an incidence of > 5% (in preferred terms) for at least one treatment will be summarised by treatment, primary SOC and PT.

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

For support of lay summaries, the frequency of subjects with drug-related SAEs will be summarized 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 "Handling, Display and Analysis of Laboratory Data" (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 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 as well as values defined as possibly clinically significant will be flagged in the data listings.

Clinically relevant findings in laboratory data will be reported as baseline conditions (at screening) or as AEs (during the trial) if judged clinically relevant by the investigator, and will be analysed as such. It is the investigator's responsibility to decide whether a lab value is clinically significantly abnormal or not (at the RPM at the latest).

Descriptive statistics of laboratory data over time including change from baseline (see Section 6.7) 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

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.

7.8.4 ECG

ECG recordings will be checked by the investigator for pathological results. Clinically relevant abnormal findings for ECG will be listed under 'Relevant Medical History / Baseline Conditions' (when they occurred during screening) or will be reported as AEs (when they occurred during treatment), and will be analysed as such.
No separate ECG listing will be provided.

7.8.5 Others

7.8.5.1 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.

7.8.5.2 Body weight

Analysis of body weight at screening time point will be descriptive in nature.

7.8.5.3 C-SSRS

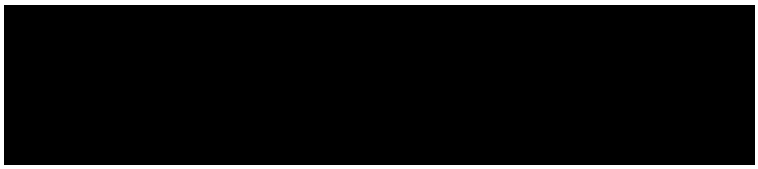
Section 7.2.5 of the CTP: *Reports of C-SSRS will be reported as AEs as described in Section 5.2.6.2.4 and will be summarized as such. Results of the C-SSRS will be provided as listing.*

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 Statistical Principles for Clinical Trials, current version.
2.	*001-MCS-40-413:* Identify and Manage Important Protocol Deviations (iPD)", current version, Group "Clinical Operations", IDEA for CON.
3.	*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.	*BI-KMED-BDS-HTG-0045*: "Standards for Reporting of Clinical Trials and Project Summaries", current version; KMED.
7.	*BI*-KMED-TMCP-OTH-0003: "Graphs and Tables for Clinical Pharmacokinetics and Pharmacodynamic Noncompartmental Analyses", current version, KMED.
8.	*001-MCS-36-472_RD-03*: "Description of Analytical Transfer Files and PK/PD Data Files", current version; KMED
9.	*BI-KMED-BDS-HTG-0041*: "Analysis and Presentation of Adverse Event Data from Clinical Trials – Display Template", current version; KMED.
10.	*BI-KMED-BDS-HTG-0066*: "Analysis and Presentation of AE data from clinical trials", current version, 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; KMED.



11. HISTORY TABLE

Table 11: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
1	**16-JUN-22**	[redacted]	None	This is the final TSAP