TRIAL STATISTICAL ANALYSIS PLAN

Document No.:	**c42321766-01**
BI Trial No.:	**1479-0004**
Title:	The effect of multiple doses of itraconazole on the pharmacokinetics of a single oral dose of BI 1810631 in healthy male subjects (an open-label, two-period, fixed-sequence trial) (Revised Protocol #2 including Protocol Amendment No.1 [c40240667-02])
Investigational Product(s):	BI 1810631
Responsible trial statistician(s):	[redacted] On behalf of: [redacted]
Date of statistical analysis plan:	13 JUL 2023
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2. LIST OF ABBREVIATIONS

See Medicine Glossary.

Term	Definition / description
ADS	Analysis dataset
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine transaminase
ANOVA	Analysis of variance
AST	Aspartate transaminase
$AUC_{0\text{-}tz}$	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 to the last quantifiable data point
$AUC_{0\text{-}\infty}$	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity
BMI	Body mass index
BP	Blood Pressure
CDR	Clinical Data Repository
CI	Confidence interval
CL	Confidence interval limit
C_{max}	Maximum measured concentration of the analyte in plasma
CRF	Case Report Form
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
CV	Arithmetic coefficient of variation
DBLM	Database Lock Meeting
DILI	Drug induced liver injury
DLT	Dose-limiting toxicity
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EDMS	Electronic Document Management System
FU	Follow-up
gCV	Geometric coefficient of variation

Term	Definition / description
gMean	Geometric mean
ICH	International Council for Harmonisation
iPD	Important Protocol Deviation
ITZ	Itraconazole
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
PK	Pharmacokinetic
PKS	PK parameter analysis set
PR	Pulse Rate
PT	Preferred Term
Q1	1^{st} quartile
Q3	3^{rd} 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
TS	Treated set
TSAP	Trial Statistical Analysis Plan
t_z	Time of last measurable concentration of the analyte in plasma
ULN	Upper Limit of Normal
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 trial statistical analysis plan (TSAP) assumes familiarity with the Clinical Trial Protocol (CTP), including Protocol Amendments. In particular, the TSAP is based on the planned analysis specification as written in CTP Section 7 “Statistical Methods and Determination of Sample Size”. Therefore, TSAP readers may consult the CTP for more background information on the study, e.g., on study objectives, study design and population, treatments, definition of measurements and variables, planning of sample size, randomization.

Study data 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® 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(S)

5.1 PRIMARY ENDPOINT(S)

Section 2.1.2 of the CTP:

The following pharmacokinetic parameters will be determined for BI 1810631:

- *$AUC_{0-\infty}$ (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 ENDPOINT(S)

5.2.1 Key secondary endpoint(s)

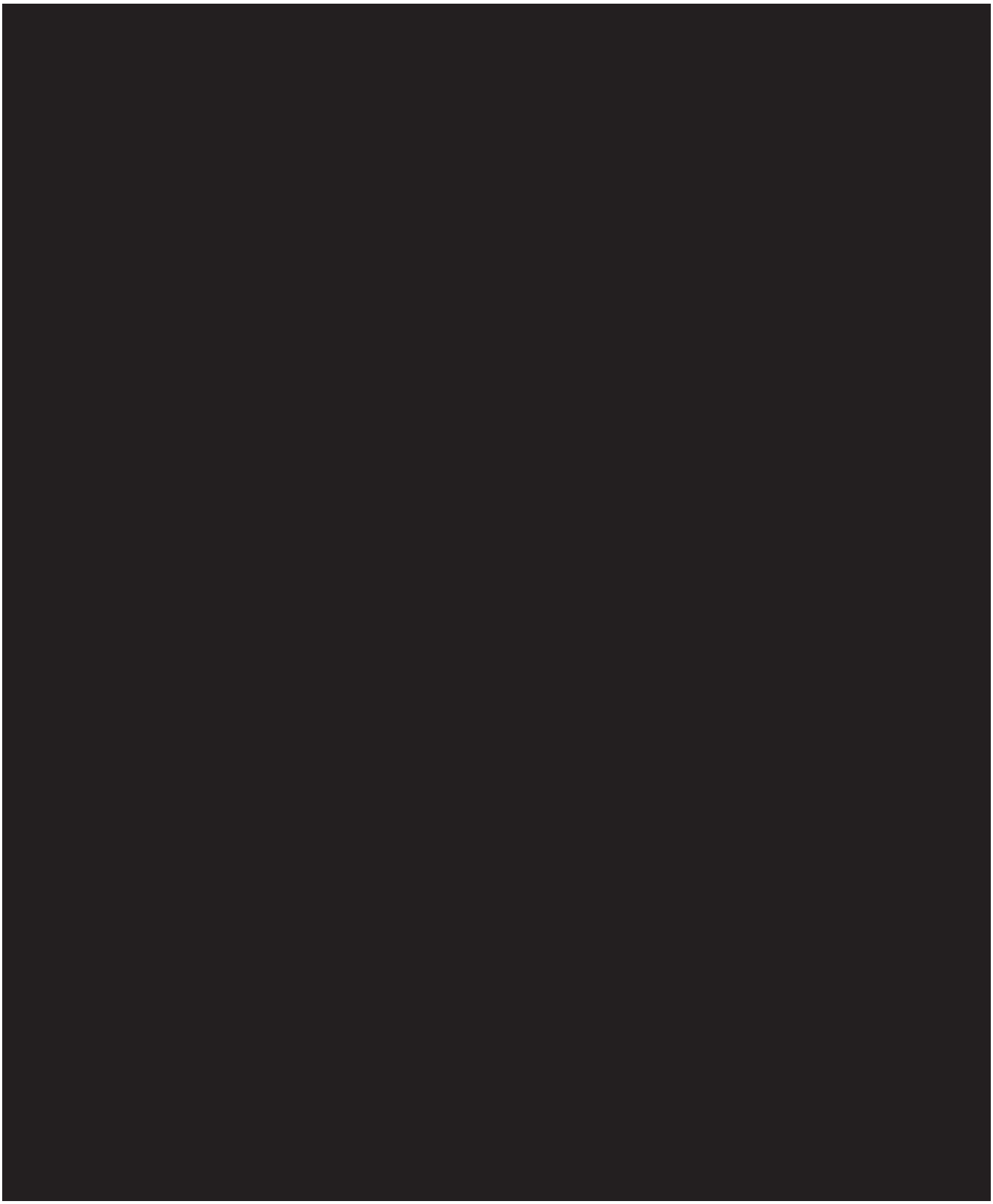
This section is not applicable as no key secondary endpoints have been defined in the CTP.

5.2.2 Secondary endpoint(s)

Section 2.1.3 of the CTP:

The following pharmacokinetic parameter will be determined for BI 1810631:

- *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)*



6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENT(S)

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

The study was performed as an open-label, fixed-sequence trial with 2 treatments: Test (T) and Reference (R). It was planned to assign 16 healthy male subjects (at least 12 completed).

Table 6.1: 1 Treatments and labels used in the analysis

Treatment	Label	Short label
R	BI 1810631, 1*[redacted] mg tablet, single dose	BI
T	BI 1810631, 1*[redacted] mg tablet, single dose + itraconazole, 200 mg oral solution, qd	BI+ITZ

There was only one treatment sequence (R-T) investigated in this trial, and each subject was allocated to the same treatment sequence (R-T).

Section 1.2.3 of the CTP:

The Residual Effect Period (REP) of single doses of BI 1810631 is conservatively estimated as [redacted] days. This is the period after the last dose during which measurable drug levels and/or pharmacodynamic effects are still likely to be present.

The REP of itraconazole is defined as 8 days.

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

- **Screening:** Ranging from 0:00 h on day of informed consent until first administration time of the study drug BI 1810631.
- **On-treatment**
  - **BI 1810631 (BI):** Ranging from the date/time of first administration of BI 1810631 until the first administration of itraconazole or [redacted] days thereafter, whichever comes first.
  - **Itraconazole (ITZ):** Ranging from the date/time of first administration of itraconazole until date/time of second administration of BI 1810631 or 8 days after the last dose of ITZ, whichever comes first.

- **BI 1810631 + itraconazole (BI+ITZ):** Ranging from date/time of second administration of BI 1810631 until [redacted] days thereafter, or the REP of 8 days after the last administration of ITZ, whichever comes later.

- **Follow-up**

  - **Follow-up BI:** Ranging from end of BI treatment phase until next drug administration or alternatively, 0:00 h on the day after trial-termination date in case of no further treatment.

  - **Follow-up BI+ITZ:** Ranging from end of BI+ITZ phase until 0:00 h on the day after trial termination date.

Section 7.2.5 of the CTP:

Note that AEs occurring after the last per protocol contact but entered before unblinding the trial will be reported to Pharmacovigilance only and will not be captured in the trial database.

Displays of AEs will be presented separately for the following treatments during on-treatment phase:

- BI 1810631, 1*[redacted] mg tablet, single dose (labelled “BI“)
- Itraconazole, 200 mg oral solution, qd (labelled “ITZ”)
- BI 1810631, 1*[redacted] mg tablet, single dose + itraconazole, 200 mg oral solution, qd (labelled “BI+ITZ”)

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) of the CTR displays:

In these displays, the on-treatment phase will be analysed (labelled with the short labels of the study treatments as defined above). Screening, Follow-up BI and Follow-up BI+ITZ 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 on-treatment BI”)
- a total over all on-treatment phases included in this analysis ("Total on-treatment")

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 short labels of the study treatments as defined above)
- Follow-up BI (labelled “FU BI”)
- Follow-up BI+ITZ (labelled “FU BI+ITZ”)

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")

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 above.

Tables of vital signs and laboratory values will present results by study periods including baseline of the respective 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

Data discrepancies and deviations from the CTP will be identified for all entered subjects.

Listings of protocol deviations (e.g., deviations in drug administration, in blood sampling etc.) and of unresolved discrepancies will be provided to be discussed at the combined report planning meeting (RPM) and database lock meeting (DBLM). At this meeting, it will be decided whether the discrepant data values can be used in the analyses as they are or whether these data values have to be corrected in the clinical database.

Each protocol deviation must be assessed to determine whether it is an important protocol deviation (iPD). A protocol deviation (PD) is important if it affects the rights or safety of the study subjects or if it can potentially influence the primary outcome measure(s) for the respective subjects in a way that is neither negligible nor in accordance with the study objectives. 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). PDs that

do not influence the subject's rights and safety or the evaluability of the subjects for the main study objectives are called non-important PDs. These are only considered when checking the trial quality in general.

If any iPDs are identified, they are to be summarized into categories and will be captured in the decision log. Categories which are considered to be iPDs in this trial are defined in the DV domain template and stored within the TMF in EDMS. If the data show other iPDs, the definition in the DV domain template will be supplemented accordingly by the time of the RPM/DBLM.

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 RPM, after discussion of exceptional cases and implications for analyses.

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

6.3 SUBJECT SETS ANALYSED

The treated set (TS) and pharmacokinetic parameter analysis set (PKS) will be used as defined in the CTP, Section 7.2.1.1.

Section 7.2.1.1 of the CTP:

Statistical analyses will be based on the following analysis sets:

- *Treated set (TS): The treated set includes all subjects who were treated with at least one dose of trial drug. The treated set will be used for safety analyses.*

- *Pharmacokinetic parameter analysis set (PKS): This set includes all subjects in the treated set (TS) who provide at least one PK endpoint that was defined as primary or secondary and was not excluded due to a protocol deviation relevant to the evaluation of PK or due to PK non-evaluability (as specified in the following subsection 'Pharmacokinetics'). Thus, a subject will be included in the PKS, even if he 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.*

Table 6.3: 1 Subject sets analysed

	Subject set	
Class of analysis	TS	PKS
Primary PK endpoints		X
Secondary PK endpoint		X
Further PK endpoints		X
Safety parameters	X	
Demographic/baseline characteristics	X	
Important protocol deviations	X	
Disposition	X	
Treatment exposure	X	

Note that the number of subjects with available data for an endpoint may differ. For details, see section “Handling of missing data and outliers”.

[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

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

It is not planned to impute missing values for safety parameters. 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.

Missing data and outliers of PK data will be handled according to the relevant BI internal procedures (3). PK parameters that cannot be reasonably calculated based on the available drug concentration-time data will not be imputed.

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

The baseline value for period 1 is defined as the last available measurement before first administration of BI 1810631 for both laboratory and vital signs. The baseline laboratory value for period 2 is defined as the last available measurement in period 1 (Visit 2, Day 2, 24:00 h) before first administration of itraconazole in period 2. For vital signs, the baseline

value for period 2 is defined as the last available measurement before administration of itraconazole at Day 1, -1:30 h.

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.

In treatment period T, a time window of ± 120 min around planned time applies to itraconazole dosings in the morning of Days -3 and -2. In the morning of Day -1, a time window of ± 60 min around planned time applies to itraconazole dosing.

If not stated otherwise in the Flow Chart, the acceptable deviation from the scheduled time for vital signs, ECG, and laboratory tests will be ± 60 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.

At visits 2 and 3, for PK samples, itraconazole administrations and safety laboratory tests at planned time +47 h and later, a time window of ± 120 min around planned time applies.

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

7. PLANNED ANALYSIS

Safety analysis (refer to Section 7.8) will be performed by [redacted] and will be presented in Sections 15.1 to 15.4 of the CTR and in Appendix 16.2 and 16.1.13.1.

Model-based inferential statistical analyses of PK endpoints (refer to Sections 7.5.2 and 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] at BI and will be presented in Section 15.6 of the CTR and in Appendix 16.1.13.5.

The format of the listings and tables will follow the BI standards (see "Standards for Reporting of Clinical Trials and Project Summaries" (4)) with the exception of those generated for PK-calculations following BI standards for PK/PD analysis (5).

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 16.1.13.5 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 (%) for each treatment group. Percentages will be rounded to one decimal place and 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.

Exclusion of PK concentrations and parameters

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*
- *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 predose concentration of BI 1810631 is >5% C_{max} value of that subject in the respective treatment period,*
- *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).

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

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

As all subjects were assigned to the same treatment sequence, the data will be summarized in total.

7.2 CONCOMITANT DISEASES AND MEDICATION

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

Concomitant diseases will be coded according to the most recent version of the coding system of the Medical Dictionary for Drug Regulatory Activities (MedDRA). Concomitant medications will be coded using 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.

The diagnoses and medications will be listed. Subjects without any concomitant diagnoses 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.

Section 7.2.5 of the CTP:

Previous and concomitant therapies will be presented per treatment group without consideration of time intervals and treatment periods.

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.

Treatment compliance will not be analyzed nor listed separately as a specific endpoint, but judged by observed analyte concentrations. Any deviation from complete intake will be addressed in the RPM (see TSAP Section 6.2) and described in the CTR.

7.4 PRIMARY OBJECTIVE ANALYSIS

The following pharmacokinetic parameters will be determined for BI 1810631:

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

7.4.1 Main analysis

Section 7.2.1.2 of the CTP:

The pharmacokinetic parameters listed in Section 2.1 and 2.2.2 for drug BI 1810631 will be calculated according to the relevant BI internal procedures.

Relative bioavailability is to be determined on the basis of the primary PK endpoints ($AUC_{0-\infty}$, C_{max}). Those parameters will be ln-transformed (natural logarithm) prior to fitting the ANOVA model (see below).

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 '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.*

Point estimates for the ratios of the geometric means (test/reference) for the primary endpoints (see Section 2.1) and their two-sided 90% confidence intervals (CIs) will be provided.

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

[redacted]

[redacted]

7.4.4 Supplementary analysis / Further exploratory analyses

Section 7.2.2 of the CTP:

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

In addition to the model based approach all parameters will be calculated and analysed descriptively.

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

Section 7.2.3 of the CTP:

The secondary endpoint (AUC_{0-tz}) 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.

7.6 FURTHER OBJECTIVE ANALYSIS

7.6.1 Pharmacokinetic endpoint(s)

Section 7.2.4.1 of the CTP:

Further PK endpoints will be analysed descriptively.

7.7 EXTENT OF EXPOSURE

Descriptive statistics of number of doses and calculated total dose are planned for this section of the CTR based on the TS. 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 treated set.

Section 7.2.5 of the CTP:

Safety will be analysed based on the assessments described in Section 2.2.2.2. All treated subjects (TS, refer to Section 7.2) will be included in the safety analysis. Safety analyses will be descriptive in nature and based on BI standards. No hypothesis testing is planned.

For all analyses, the treatment actually administered (= treatment at onset) to the subject will be used (any deviations from the assigned treatment will be discussed in the minutes of the Report Planning Meeting).

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" (6) and "Analysis and Presentation of AE data from clinical trials" (7) will be applied.

The analysis of AEs will be based on the concept of treatment emergent AEs. That means that all AEs occurring between first drug intake till end of REP after last drug intake will be assigned to the on-treatment. All AEs occurring before first drug intake will be assigned to 'screening' and all AEs occurring after last drug intake + REP will be assigned to 'follow-up'. For details on the treatment definition, see Section 6.1.

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*

[redacted]

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).

An overall summary of adverse events (including AESIs) will be presented.

The frequency of subjects with AEs will be summarised by treatment, primary system organ class (SOC) and preferred term (PT). Separate tables will be provided for subjects with SAEs, for subjects with drug-related AEs, for subjects with drug-related SAEs, for subjects with AESIs and for subjects with other significant AEs according to ICH E3 (8). In addition, the frequency of subjects with AEs will be summarised by treatment, maximum CTCAE grade, 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. AEs will be displayed by maximum CTCAE grade using the categorization "All grades", "Grade 1", "Grade 2", "Grade 3", "Grade 4" and "Grade 5".

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 and the frequency of subjects with SAEs will be summarised by treatment, primary SOC and PT. The frequency of all-cause mortality will be summarised by treatment.

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

(subjects and events) and the frequency of deaths (related or unrelated to SAEs) will be summarised by treatment, primary SOC and PT. The frequency of all-cause mortality will be summarised by treatment.

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

7.8.2 Laboratory data

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

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. In the listing the difference from baseline will also be displayed.

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.

7.8.6 Interim analysis

Section 7.2.6 in CTP:

No interim analysis is planned.

8. TIMEPOINT OF RELEASE OF TREATMENT INFORMATION

As this is a non-randomized trial, the treatment information will not be loaded into the trial database after completion of enrolment, but it will be populated during SDTM transformation in domain DM.

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”, KMED.
3.	*BI-KMED-TMCP-HTG-0025:* “Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics”, current version, Group “TMCP Data Analysis”, KMED.
4.	*BI-KMED-BDS-HTG-0045:* "Standards for Reporting of Clinical Trials and Project Summaries", current version, Group "Clinical Trial Data Analysis", KMed.
5.	*BI-KMED-TMCP-MAN-0014:* "Noncompartmental Pharmacokinetic/Pharmacodynamic Analyses of Clinical Studies", current version, Group "TMCP Data Analysis", KMed.
6.	*BI-KMED-BDS-HTG-0041:* "Analysis and Presentation of AE data from clinical trials - display template", current version, Group "Clinical Trial Data Analysis", KMed.
7.	*BI-KMED-BDS-HTG-0066:* "Analysis and Presentation of AE data from clinical trials", current version, Group "Clinical Trial Data Analysis", 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, EMA webpage.
9.	*BI-KMED-BDS-HTG-0042:* "Handling, Display and Analysis of Laboratory Data", current version, Group "Clinical Trial Data Analysis", KMed.

11. HISTORY TABLE

Table 11: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
1.0	**13-JUL-23**	[redacted]	None	This is the final TSAP.