

TRIAL STATISTICAL ANALYSIS PLAN

c35064438-01

BI Trial No.:	1411-0010
Title:	Effect of itraconazole on the pharmacokinetics of a single oral dose of BI 474121 in healthy male subjects (an open-label, two-period fixed sequence design study) (Revised Protocol including Amendment 1 [c30888994-02])
Investigational Product(s):	BI 474121
Responsible trial statistician(s):	<div style="background-color: black; width: 360px; height: 75px; margin-bottom: 5px;"></div> Phone: <div style="background-color: black; width: 100px; height: 15px; display: inline-block;"></div> Fax: <div style="background-color: black; width: 80px; height: 15px; display: inline-block;"></div>
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2. LIST OF ABBREVIATIONS

See Medicine Glossary:
<http://glossary>

Term	Definition / description
ADPC	Analysis data pharmacokinetic concentrations
ADPP	Analysis data pharmacokinetic parameters
ADS	Analysis data set
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-∞}	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity
BMI	Body mass index
CI	Confidence interval
C _{max}	Maximum measured concentration of the analyte in plasma
CSD	Company Standard Displays
CV	Arithmetic coefficient of variation
DILI	Drug induced liver injury
F/U	Follow Up
gCV	Geometric coefficient of variation
gMean	Geometric mean
ITZ	Itraconazole
λ _z	Terminal rate constant of the analyte in plasma
LLT	Lower level term
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
N	Number non-missing observations
P10	10th percentile

Term	Definition / description
P90	90th percentile
PfoS	Powder for oral solution
PKS	PK parameter analysis set
Q1	1st quartile
Q3	3rd quartile
qd	Once daily
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
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, randomisation.

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

Pharmacokinetic (PK) parameters will be calculated using Phoenix WinNonlin™ software (version 8.1 or higher, [REDACTED]).

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.

In Section 7.3 of the CTP the following was defined: *Important protocol deviation (IPD) categories will be suggested in the IQRM plan, IPDs will be identified no later than in the Report Planning Meeting, and the IPD categories will be updated as needed.* Due to SOP changes, the IPD categories are no longer available in the IQRM plan but included in an IPD specification file (2). The IPD categories originally defined in the IQRM plan were transferred to this IPD specification file. Minor changes regarding the IPD categories were performed only.

The CTP refers to a central SOP of the sponsor (SOP 001-MCS-36-472 for PK and PD analysis) which is no longer applicable and was superseded by other procedural documents. These are outlined in the respective passages of this TSAP.

5. ENDPOINTS

5.1 PRIMARY ENDPOINTS

Section 2.1.2 of the CTP:

The following pharmacokinetic parameters will be determined for BI 474121:

- $AUC_{0-\infty}$ (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

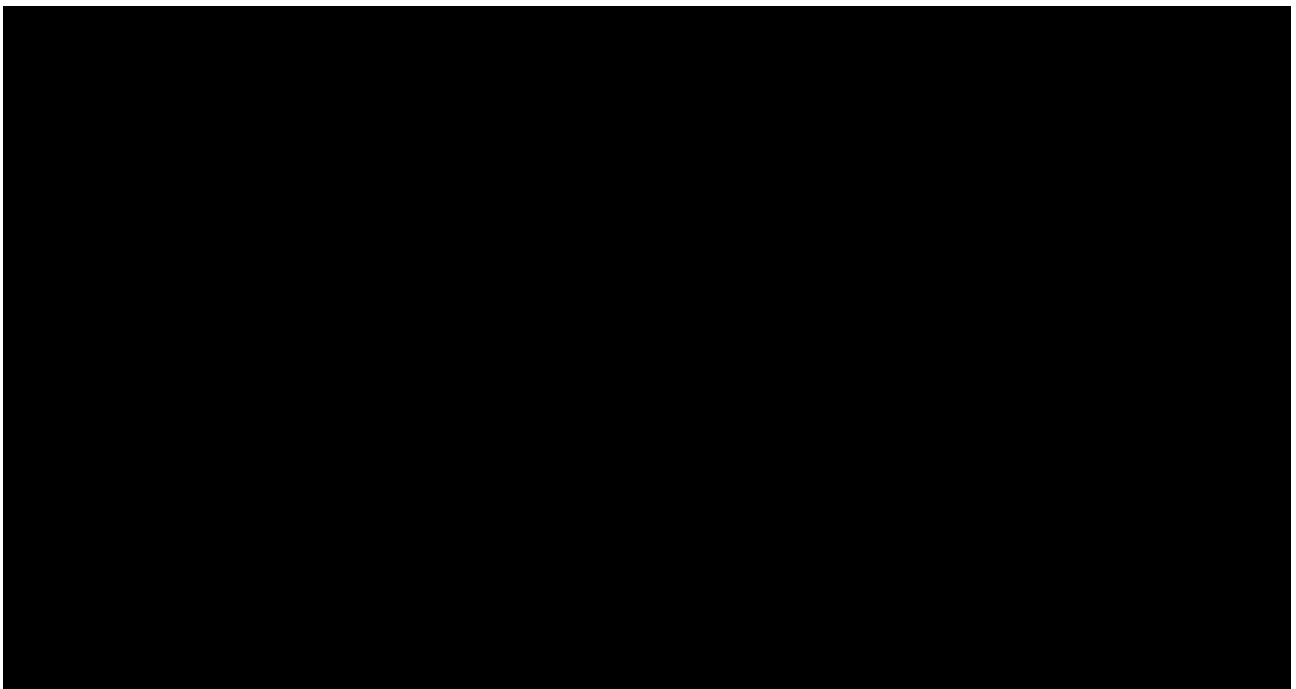
This section is not applicable as no key secondary endpoints have been defined in the CTP.

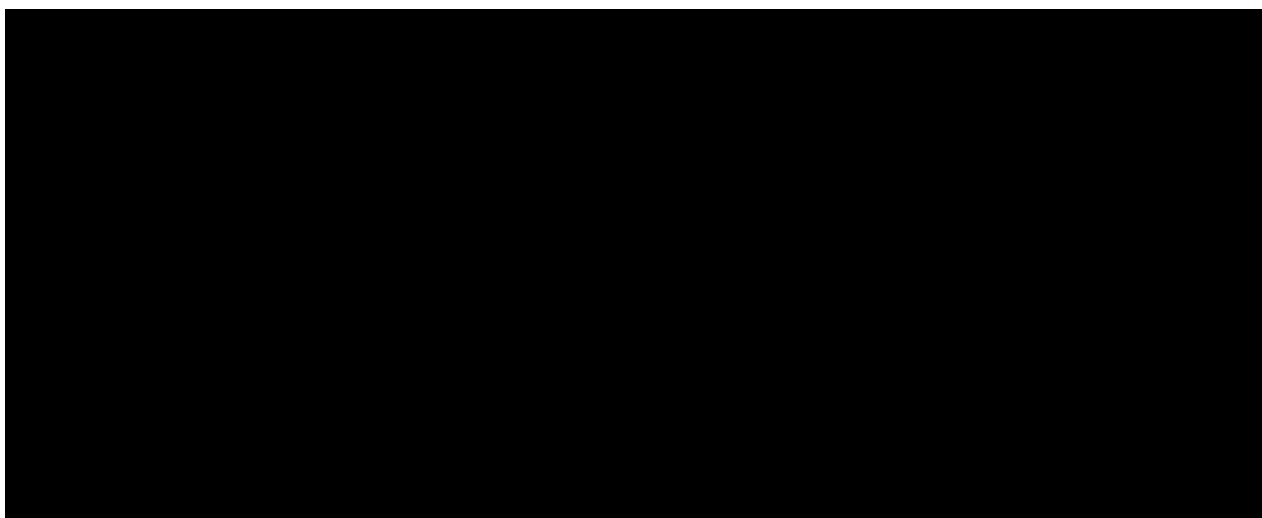
5.2.2 Secondary endpoint

Section 2.1.3 of the CTP:

The following pharmacokinetic parameter will be determined for BI 474121:

- AUC_{0-t_z} (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 TREATMENTS

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

The study will be performed as an open-label two-period trial with two treatments administered as oral solutions (T = Test treatment and R = Reference treatment). Healthy male subjects receive both treatments in a fixed sequence (period 1: R, period 2: T). There will be a washout period of at least 10 days between the administrations of BI 474121 in treatment period 1 and 2.

In total, it was planned to assign 14 healthy male subjects.

For details of dosage and formulation see [Table 6.1: 1](#) below. Itraconazole will be administered for 14 days, starting 3 days prior to administration of BI 474121 in period 2 until Day 11 after BI administration.

Table 6.1: 1 Treatments and labels used in the analysis

Treatment		Short label
R	BI 474121, 0.5 mg PfoS, single dose	BI
T	BI 474121, 0.5 mg PfoS, single dose + Itraconazole 20ml, 10mg/ml, qd for 14 days	BI+ITZ

Section 1.2.3 of CTP:

The Residual Effect Period (REP, i.e., the period after the last dose with measurable drug levels and/or pharmacodynamic effects still likely to be present) of BI 474121 is conservatively assumed to be 7 days. [...]

For the use of itraconazole in Treatment T, the REP is defined as 3 days after last administration of itraconazole [...].

The following study phases will be defined for the safety analysis:

- **Screening**
 - Ranging from 0:00h on day of informed consent until first administration time of BI 474121 alone in treatment period 1.
 - **On treatment** (labelled “BI”, “ITZ”, “BI+ITZ”)
 - **BI alone (“BI”)**: Ranging from the time of first administration of BI 474121 alone in treatment period 1 until 7 days (168h) thereafter.
 - **Itraconazole alone (“ITZ”)**: Ranging from the time of first administration of itraconazole until time of BI 474121 administration in treatment period 2 OR until 3 days (72h) after last dose of itraconazole (if subject discontinues treatment prior to BI 474121 drug administration in period 2).
 - **BI + ITZ (“BI+ITZ”)**: Ranging from time of BI 474121 administration in treatment period 2 until 3 days (72h) after the last administration of itraconazole OR 7 days (168h) after the BI 474121 administration in treatment period 2, whatever occurs later.
 - **Follow-up** (labelled “F/U BI”, “F/U ITZ”, “F/U BI+ITZ”)
 - **F/U BI**: Ranging from the end of REP of BI 474121 in treatment period 1 until the first administration of itraconazole in period 2 or until trial termination, whatever occurs first.
 - **F/U ITZ**: (only applicable if subject discontinues treatment prior to BI 474121 drug administration in period 2) Ranging from the end of REP of itraconazole in treatment period 2 until trial termination.
 - **F/U BI+ITZ**: Ranging from the end of REP of BI 474121 or itraconazole (whatever occurs later) in treatment period 2 until trial termination.
- “Until trial termination” is defined as 0:00h on the day after trial termination.

Section 7.3.4 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 involving BI ("**BI Total on treatment**")
- 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 name of the study treatment (short label))
- Follow-up BI (labelled "**F/U BI**")
- Follow-up BI+ITZ (labelled "**F/U BI+ITZ**")
- Follow-up ITZ (labelled "**F/U ITZ**") – if applicable

In Section 16.1.13.1.8 (except for ClinicalTrials.gov and EudraCT), the following totals will be provided in addition:

- a total over all on treatment phases involving BI ("**BI Total**")
- a total over all study phases (screening, on treatment and follow-up) ("**Total**")

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 treated subjects.

Consistency check listings (for identification of deviations of time windows) and a list of protocol deviations (e.g. deviations in drug administration, in blood sampling times, etc.) will be provided to be discussed at the Report Planning Meeting (RPM). At this meeting, all manual deviations identified at the sites by the CRAs and deviations too complex to program will be reviewed by the trial team to decide which are considered important. For definition of important protocol deviations (iPD), and for the process of identification of these, refer to the Boehringer Ingelheim (BI) SOP "Identify and Manage Important Protocol Deviations (iPD)" (3).

Categories which are considered to be iPDs in this trial were defined in the integrated quality and risk management plan (IQRMP) prior to trial initiation. The iPD list was transferred into the iPD specification file (due to changes in the SOP) (2). Within this transfer some minor adaptations were done to comply with new naming conventions and categorisations. IPDs will be identified no later than in the Report Planning Meeting and the iPD categories in the iPD specification file will be updated as needed. If any iPDs are identified, they are to be summarised into categories and will be captured in the RPM minutes (the decision log) and in the iPD specification file. The decision on exclusion of subjects from analysis sets will be made after discussion of exceptional cases and implications for analyses.

The iPD specification file (e.g. the DV domain specifications) will be stored within the TMF in EDMS.

The iPDs will be summarised and listed.

6.3 SUBJECT SETS ANALYSED

Section 7.3 of the CTP:

- *Treated set (TS): The treated set includes all subjects who were treated with at least one dose of study 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.*

[...]

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.

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*

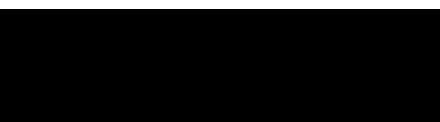
Plasma concentrations and/or parameters of a subject will be considered as non-evaluable, if for example

- *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 474121 is $>5\%$ C_{max} value of that subject in the respective treatment period*
- *Missing samples/concentration data at important phases of PK disposition curve*

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 analysed

Class of endpoint	Subject set	
	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 7.5.

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 BI-KMED-BDS-HTG-0035) (4).

Missing data and outliers of PK data are handled according to BI standards (see BI-KMED-TMCP-MAN-0012 (5) and BI-KMED-TMCP-MAN-0014 (6).

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

The baseline value is defined as the last measurement before administration of BI 474121 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.*

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 administration of 474121.

If not stated otherwise in the flow chart, the acceptable deviation from the scheduled time of safety assessments (e.g. vital signs, ECG, and laboratory tests) will be ± 60 min.

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

Unscheduled measurements of laboratory data and vital signs data will be assumed to be repeat measurements of the most recent scheduled measurement (e.g. for follow-up or confirmation of a particular value). Therefore, unscheduled measurements will be assigned to the planned time point of the previous scheduled measurement.

7. PLANNED ANALYSIS

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

Inferential statistical analyses of PK endpoints (refer to [Section 7.4](#) and [Section 7.5.2](#)) 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 department [REDACTED] at [REDACTED] and will be presented in Section 15.6 of the CTR.

The format of the listings and tables will follow the BI standards (see BI-KMED-BDS-HTG-0045 (7)) with the exception of those generated for PK-calculations following BI standards for PK/PD analysis (8).

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

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:

CV	arithmetic coefficient of variation
gMean	geometric mean
gCV	geometric coefficient of variation
P10	10th percentile
Q1	1st quartile
Q3	3rd quartile
P90	90th percentile

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

Tabulations of frequencies for categorical data will include all possible categories available in the eCRF and will display the number of observations in a category, as well as the percentage (%). 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 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 *BI-KMED-TMCP-MAN-0014* “Noncompartmental Pharmacokinetic / Pharmacodynamic Analyses of Clinical Studies” (6) and *BI-KMED-TMCP-MAN-0010*: “Description of Analytical Transfer Files and PK/PD Data Files” (9).

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

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

7.2 CONCOMITANT DISEASES AND MEDICATION

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

Concomitant diseases will be coded using the coding system of the Medical Dictionary for Drug Regulatory Activities (MedDRA). Medications will be coded using the World Health Organization Drug Dictionary (WHO-DD). The coding version number will be displayed as a footnote in the respective output.

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

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

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

7.4 PRIMARY ENDPOINTS

The effect of itraconazole on the exposure of BI 474121 in plasma is to be determined on the basis of the primary pharmacokinetic endpoints $AUC_{0-\infty}$ and C_{max} (see [Section 5.1](#)).

7.4.1 Primary analysis of the primary endpoints

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: subjects and treatment. The effect 'subjects' will be considered as random, whereas 'treatment' will be considered as fixed. The model is described by the following equation:

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

where

y_{km} = logarithm of response measured on subject m receiving treatment k ,

μ = the overall mean,

τ_k = the k^{th} treatment effect, $k = 1, 2$,

s_m = the effect associated with the m^{th} subject, $m = 1, 2, \dots, n$

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 CTP 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.

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 / PDIF CL ALPHA=0.1;  
  ESTIMATE 'T-R' treatment -1 1;  
RUN;
```



[REDACTED]

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 endpoint

The secondary PK parameter AUC_{0-tz} will be assessed using the same methods as described for the primary endpoints.

[REDACTED]

7.7 EXTENT OF EXPOSURE

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

7.8 SAFETY ANALYSIS

All safety analyses will be performed on the TS.

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

7.8.1 Adverse Events

AEs will be coded 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” [BI-KMED-BDS-HTG-0041] (10) and [BI-KMED-BDS-HTG-0066] (11) will be applied.

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

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

Section 5.1.5.1.4 of the CTP: *The following are considered as AESIs:*

- Hepatic injury
A hepatic injury is defined by the following alterations of hepatic laboratory parameters:
 - o *An elevation of AST (aspartate transaminase) and/or ALT (alanine transaminase) ≥ 3 -fold ULN combined with an elevation of total bilirubin ≥ 2 -fold ULN measured in the same blood sample, or*
 - o *Aminotransferase (ALT, and/or AST) elevations ≥ 10 fold ULN*

According to ICH E3 (12), 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 AEs will be presented.

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

serious AEs, for subjects with 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, primary system organ class (SOC) and preferred term (PT).

The SOCs and PTs will be sorted by frequency (within SOC). The MedDRA version number will be displayed as a footnote in the respective output.

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

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

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

7.8.2 Laboratory data

The analyses of laboratory data will be descriptive in nature and will be based on BI standards [BI-KMED-BDS-HTG-0042] ([13](#)).

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

7.8.3 Vital signs

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

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 will be reported as AEs.

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

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.

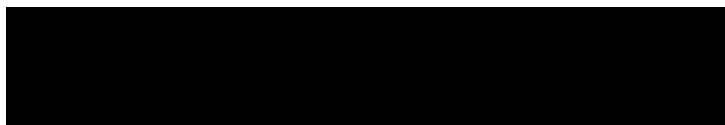
No separate listing or analysis of physical examination findings will be prepared.

8. TIMEPOINT OF RELEASE OF TREATMENT INFORMATION

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

9. REFERENCES

1.	<i>CPMP/ICH/363/96</i> : "Statistical Principles for Clinical Trials", ICH Guideline Topic E9, Note For Guidance on Statistical Principles for Clinical Trials, current version.
2.	<i>BI-KMED-BDS-TMP-0059</i> : "iPD specification document (sdm-dv-domain-specification)", template, current version, KMED.
3.	<i>001-MCS-40-413</i> : "Identify and Manage Important Protocol Deviations (iPD) ", current version, IDEA for CON.
4.	<i>BI-KMED-BDS-HTG-0035</i> : "Handling of Missing and Incomplete AE Dates", current version; KMED.
5.	<i>BI-KMED-TMCP-MAN-0012</i> : "Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics", current version; KMED.
6.	<i>BI-KMED-TMCP-MAN-0014</i> : "Noncompartmental Pharmacokinetic / Pharmacodynamic Analyses of Clinical Studies", current version; KMED.
7.	<i>BI-KMED-BDS-HTG-0045</i> : "Standards for Reporting of Clinical Trials and Project Summaries", current version; KMED.
8.	<i>BI-KMED-TMCP-OTH-0003</i> : "Graphs and Tables for Clinical Pharmacokinetics and Pharmacodynamic Noncompartmental Analyses", current version, KMED.
9.	<i>BI-KMED-TMCP-MAN-0010</i> : "Description of Analytical Transfer Files and PK/PD Data Files", current version; KMED.
10.	<i>BI-KMED-BDS-HTG-0041</i> : "Analysis and Presentation of Adverse Event Data from Clinical Trials – Display Template", current version; KMED.
11.	<i>BI-KMED-BDS-HTG-0066</i> : "Analysis and Presentation of AE data from clinical trials", current version, KMED.
12.	<i>CPMP/ICH/137/95</i> : "Structure and Content of Clinical Study Reports", ICH Guideline Topic E3; Note For Guidance on Structure and Content of Clinical Study Reports, current version.
13.	<i>BI-KMED-BDS-HTG-0042</i> : "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	12-MAY-21		None	This is the final TSAP