# Boehringer Ingelheim

# TRIAL STATISTICAL ANALYSIS PLAN

**c35156017-01**

| | |
|---|---|
| **BI Trial No.:** | 1407-0039 |
| **Title:** | The effect of multiple doses of BI 730357 on the single dose pharmacokinetics of caffeine, warfarin, omeprazole and midazolam administered orally as a cocktail in healthy subjects (an open-label, two-period fixed sequence design trial) |
| | (Revised Protocol including Amendment 1 [c31764080-02]) |
| **Investigational Products:** | BI 730357 |
| **Responsible trial statistician:** | <br><br><br><br>Phone:<br>Fax: |
| **Date of statistical analysis plan:** | 12 APR 2021 SIGNED |
| **Version:** | 1 |
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# 1.      TABLE OF CONTENTS

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## 2.      LIST OF ABBREVIATIONS

See Medicine Glossary:
http://glossary

| Term | Definition / description |
| --- | --- |
| 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 |
| CI | Confidence interval |
| $C_{max}$ | Maximum measured concentration of the analyte in plasma |
| CSD | Company Standard Displays |
| C-SSRS | Columbia - Suicide Severity Rating Scale |
| CV | Arithmetic coefficient of variation |
| DILI | Drug induced liver injury |
| F/U | Follow Up |
| gCV | Geometric coefficient of variation |
| gMean | Geometric mean |
| $\lambda_z$ | 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 |
| P90 | 90th percentile |
| PKS | PK parameter analysis set |
| Q1 | 1st quartile |
| Q3 | 3rd quartile |

| Term | Definition / description |
| --- | --- |
| 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 trial objectives, trial 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 6.3 or higher, ███████████████████████████).

The statistical analyses will be performed within the validated working environment CARE, including SAS™ (current Version 9.4, by █████████████████████████), 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 1.2.3 of  the CTP the following REP of cocktail was defined:
*The Residual Effect Period (REP) of the cocktail is 9 days, referring to warfarin, the drug with the longest half-life among the cocktail components.* This has been modified, as after 7 days, exposure from a single dose of warfarin is negligible or a new onset of PD effects is very unlikely. Therefore, the REP has been adapted to 7 days for all study drugs (cocktail as well as BI 730357). AEs occurring 7 days after warfarin administration of the "cocktail alone" treatment are thus attributable to the multiple doses of BI 730357 administered from this time onward in the "BI alone" study phase.  AEs occurring 7 days after warfarin administration of treatment T ("BI+Cocktail") are thus to be assigned to the BI 730357 multiple doses of the "BI+Cocktail" phase.

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 (3). 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.

# 5. ENDPOINTS

## 5.1 PRIMARY ENDPOINTS

**Section 2.1.2 of the CTP:**

*The following primary endpoints will be determined for the probe drugs caffeine, warfarin (specifically S-warfarin), omeprazole, and midazolam when administered without BI 730357 and when co-administered with BI 730357 at BI 730357 steady-state:*

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

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

## 5.3 FURTHER ENDPOINTS

**Pharmacokinetic (PK) endpoints**

Other pharmacokinetic parameters of the probe drugs (and metabolites) are further study endpoints. In addition, PK endpoints will be calculated as appropriate for BI 730357 at steady state and, if feasible, for the metabolite CD 6975. For more details see CTP Section 2.2.2.1.

**Safety and tolerability endpoints**

**Section 2.2.2.2 of the CTP:** *Safety and tolerability of BI 730357 and the probe drugs will be assessed based on:*

- *AEs (including clinically-relevant findings from the physical examination)*
- *Safety laboratory tests*
- *12-lead ECG*
- *Vital signs (blood pressure, pulse rate)*
- *Assessment of suicidal ideation and behaviour (SIB) based on C-SSRS*
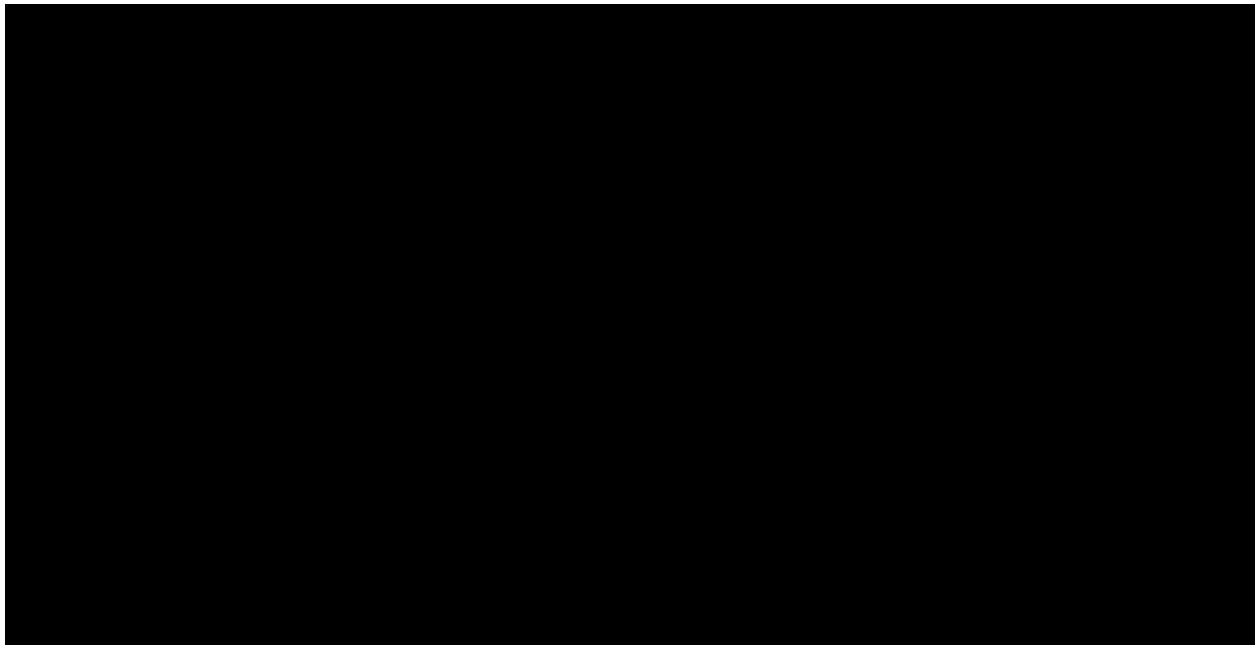
# 6.  GENERAL ANALYSIS DEFINITIONS

## 6.1  TREATMENTS

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

The study will be performed as an open-label, two-treatment, two-period fixed sequence design. A drug cocktail, including caffeine, warfarin, omeprazole and midazolam, will be administered alone (Reference treatment R) or with BI 730357 (Test treatment T). In total, it was planned to assign 16 healthy male and female subjects to the fixed sequence R-T.

There will be a washout period of at least 20 days between the cocktail administrations.

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 | Cocktail:<br>100 mg caffeine, 10 mg warfarin, 20 mg omeprazole, 2 mg midazolam (Day 1) | Cocktail |
| T | BI 730357 + Cocktail:<br>300 mg BI 730357 b.id. for 20 days (Day -14 to Day 6) combined with drug cocktail (Day 1, 1h after morning dose of BI 730357). | BI+Cocktail |

**Section 1.2.3 of CTP:**

*The Residual Effect Period (REP) of the cocktail is 9 days, referring to warfarin, the drug with the longest half-life among the cocktail components.* […].

*The Residual Effect Period (REP) of BI 730357 is 7 days.*

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

- **Screening**
  - Ranging from 0:00h on day of informed consent until administration time of drug cocktail in treatment period 1.

- **On treatment** (labelled "**Cocktail**", "**BI**", "**BI+Cocktail**")
  - **Cocktail alone** ("**Cocktail**"): Ranging from the time of administration of drug cocktail alone in treatment period 1 until 7 days (168 h) thereafter OR until first administration of BI 730357, whatever occurs first.
  - **BI alone** ("**BI**"): Ranging from the time of first administration of BI 730357 until time of administration of drug cocktail in treatment period 2 OR until 7 days (168h) after the last administration of BI 730357, if subject discontinues treatment prior to administration of drug cocktail.
  - **BI + Cocktail** ("**BI+ Cocktail**"): Ranging from time of administration of drug cocktail in treatment period 2 until 7 days (168h) after the last administration of BI 730357 OR until 7 days (168h) after administration of drug cocktail, whatever occurs later.

- **Follow-up** (labelled "**F/U Cocktail**", "**F/U BI**", "**F/U BI+Cocktail**")
  - **F/U Cocktail**: Ranging from the end of REP of drug cocktail in treatment period 1 (7 days) until the first administration of BI 730357 in period 2 or until trial termination, whatever occurs first.
  - **F/U BI** - if applicable - Ranging from the end of REP of the last BI 730357 administration in treatment period 2 (7 days) until trial termination, if subject discontinues treatment prior to administration of drug cocktail.
  - **F/U BI+Cocktail**: Ranging from the end of REP of either BI 730357 or drug cocktail (whatever occurs later) in treatment period 2 until 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 totals 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 drug cocktail (labelled "**F/U Cocktail**")
- Follow-up BI+Cocktail (labelled "**F/U BI+Cocktail**")
- Follow-up BI (labelled "**F/U BI**") – only if applicable

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 ("**BI Total**")
- a total over all study phases ("**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)" (2).

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) (3). 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 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 entered and treated with at least one dose of study drug* (Cocktail or BI 730357)*. The treated set will be used for safety analyses.*

- *PK 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 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 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 probe drugs 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

|  | 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 |  |
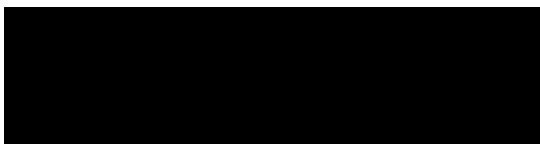


## 6.5      POOLING OF CENTRES

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 7.5.

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 drug cocktail in each treatment period.

**Section 6.1 of the CTP:** *Study measurements and assessments scheduled to occur 'before' trial medication administration on Day 1 of Visit 2 and Days -14, -8, -1, 1, and 3 of Visit 3 are to be performed and completed within a 2 hour-period prior to the next standardized breakfast or standardized breakfast planned at the same time, if not indicated otherwise in the CTP Flow Chart.*

*For ambulatory administration of BI 730357 prior to Day -1 of Visit 3 and after Day 5 of Visit 3, a time window of ± 70 minutes will be allowed.*

*Following cocktail administration in Visits 2 and 3, the acceptable deviation from the scheduled time for vital signs, ECG, and laboratory tests will be ± 30 min on Day 1, ± 45 minutes from 24 hours onwards, and ± 70 minutes from 119 hours onwards.*

*[…]*

*The acceptable deviation from the scheduled time for all meals on Day 2 in Period 1 is ± 1 hour, to allow that subjects may have their meal together.*

*[…]*

*For cocktail PK blood sampling on Days 6-7 of Visits 2 and 3, a time window of ± 60 minutes will be allowed.*

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 ███████████████████████ 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 ████████████████████ 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 █████████████████████████████████████████████████ at ██ 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 $\lambda_z$) 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 trial centre under supervision of the investigating physician or a designee. The measured plasma concentrations of trial medication will provide additional confirmation of compliance.*

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

## 7.4       PRIMARY ENDPOINTS

For each probe drug (caffeine, (S-)warfarin, omeprazole, midazolam), the effect of drug-drug interactions will be investigated on the basis of the primary PK 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 'subject' will be considered as random, whereas 'treatment' will be considered as fixed. The model is described by the following equation:*

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

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

$\mu$ = *the overall mean,*

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

$\tau_k$ = *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 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 / PDIFF CL ALPHA=0.1;
        ESTIMATE 'T-R' treatment -1 1;
RUN;
```
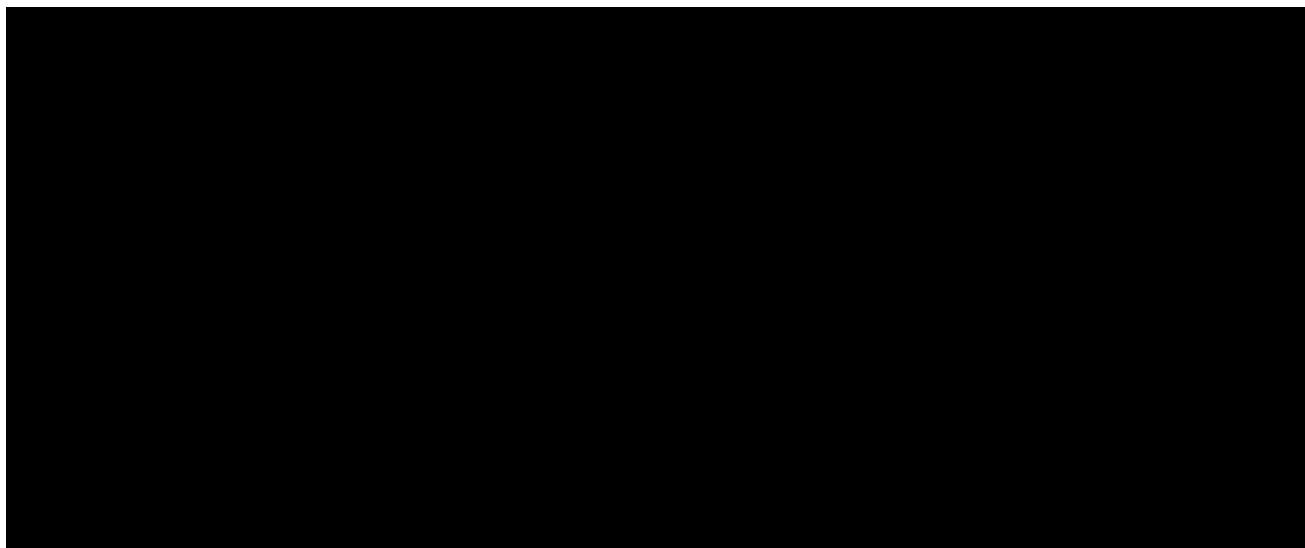
## 7.5      SECONDARY ENDPOINTS

### 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

This section is not applicable as no secondary endpoint has been specified in the protocol
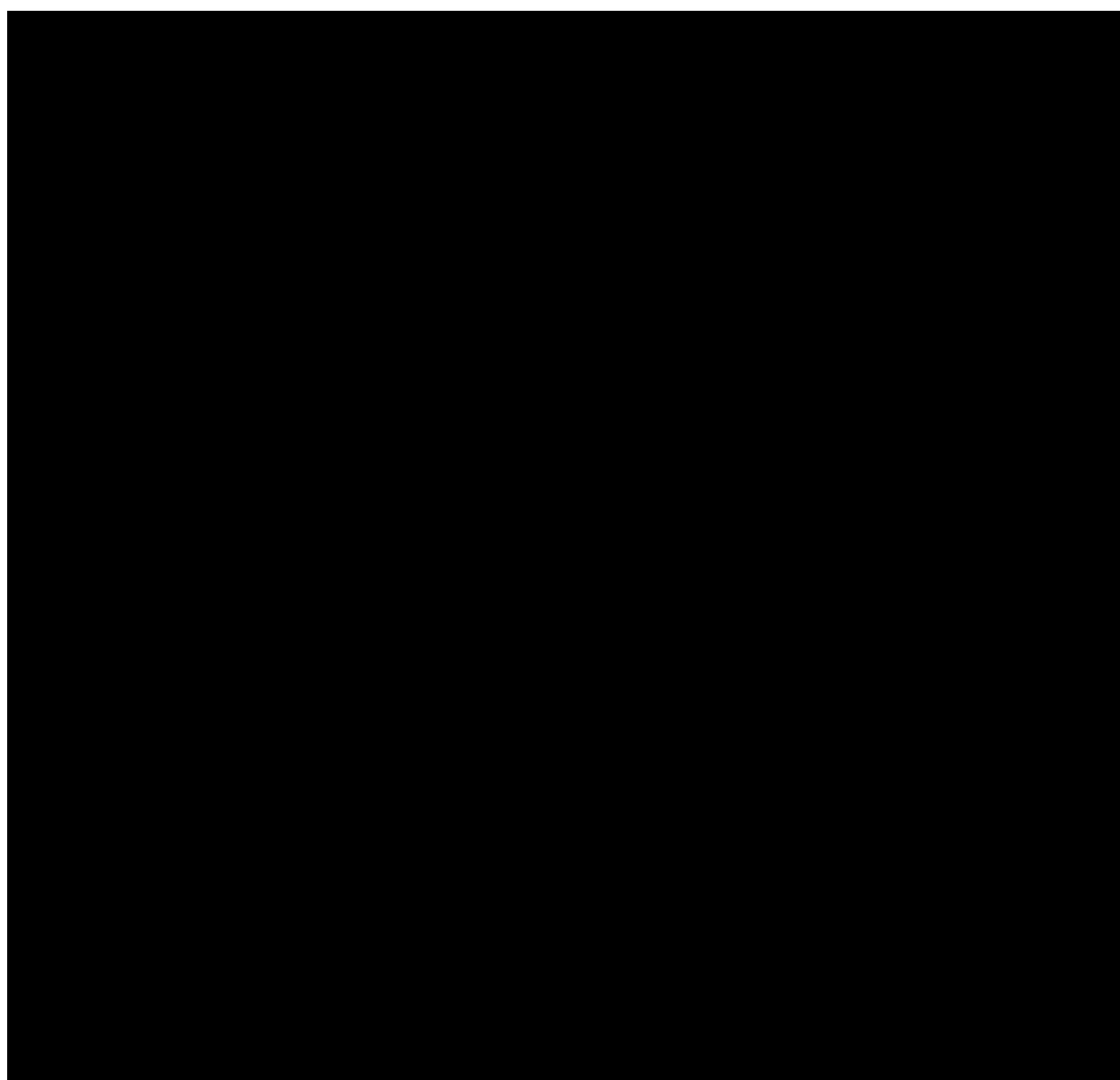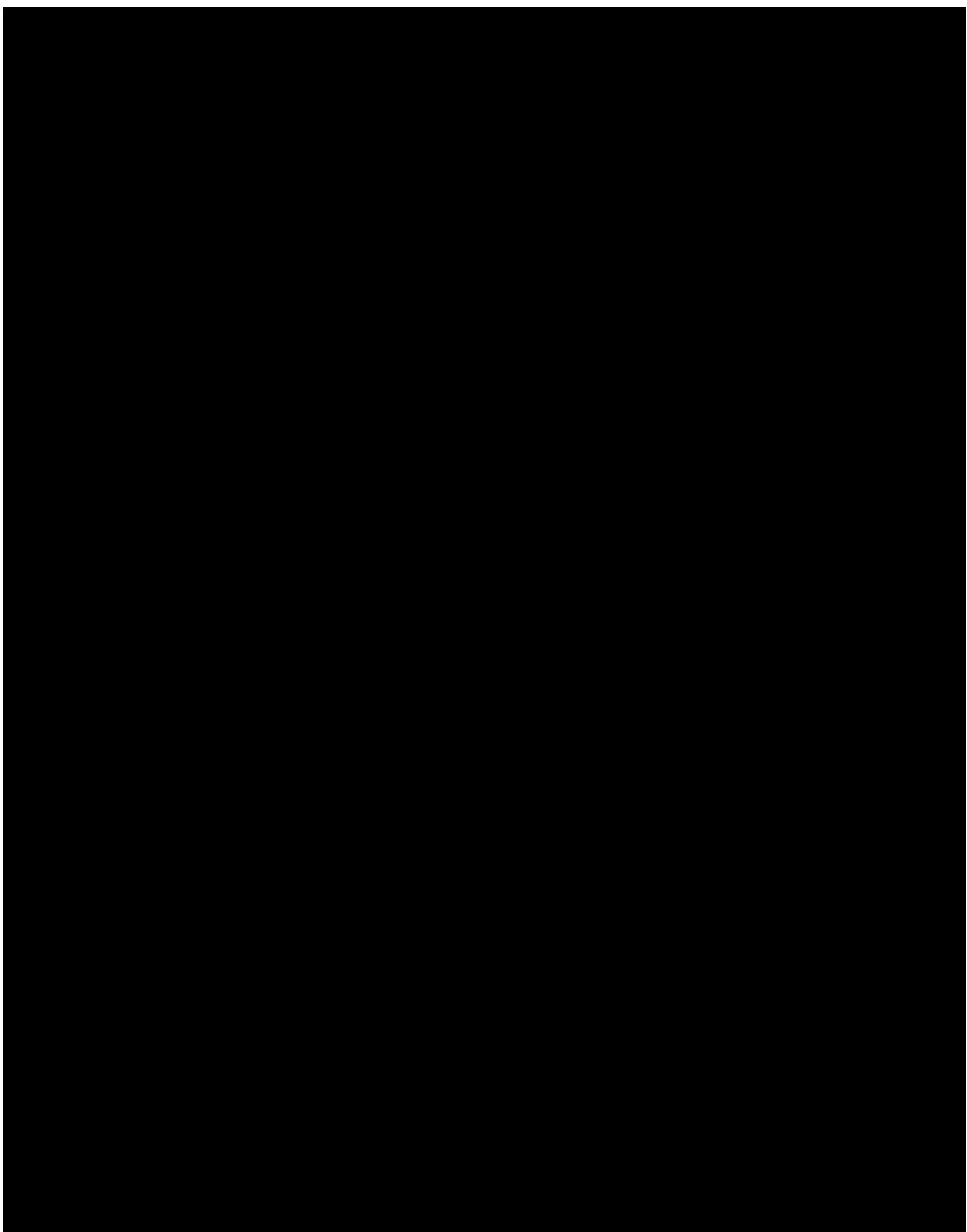
## 7.7 EXTENT OF EXPOSURE

Descriptive statistics  by substance (BI 730357, Caffeine, Warfarin, Omeprazole, Midazolam) are planned for this section of the report 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 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.

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

**Section 5.2.6.1.4 of the CTP:** *The following are considered as AESIs:*

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

[…]

- *Severe infections (grading according to Rheumatology Common Toxicity Criteria (RCTC) developed by OMERACT […])*

- *Opportunistic and mycobacterium tuberculosis infections*
  *These include pneumocystis jirovecii, BK virus disease including polyomavirus-associated nephropathy, cytomegalovirus, posttransplant lymphoproliferative disorder (Epstein-Barr virus), progressive multifocal leukoencephalopathy, bartonellosis (disseminated only), blastomycosis, toxoplasmosis, coccidioidomycosis, histoplasmosis, aspergillosis (invasive only), candidiasis (invasive or pharyngeal), cryptococcosis, other invasive fungi (mucormycosis (zygomycosis, rhizopus, mucor, lichtheimia), scedosporium/pseudallescheria boydii, fusarium), legionellosis, listeria monocytogenes (invasive only), tuberculosis, nocardiosis, non-tuberculous mycobacterium, salmonellosis (invasive only), hepatitis B virus reactivation, herpes simplex (invasive only), herpes zoster, strongyloides (hyperinfection syndrome and disseminated forms only), paracoccidioides, penicillium marneffei, sporothrix schenckii, cryptosporidium species (chronic only), microsporidiosis, leishmaniasis (visceral only), trypanosoma cruzi Infection (Chagas' disease) (disseminated only), campylobacteriosis (invasive only), shigellosis (invasive only), vibriosis (invasive due to vibrio vulnificus), hepatitis C virus progression.*

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. | *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, IDEA for CON. |
| 3. | *BI-KMED-BDS-TMP-0059*: "iPD specification document (sdtm-dv-domain-specification)", template, current version, KMED. |
| 4. | *BI-KMED-BDS-HTG-0035*: "Handling of Missing and Incomplete AE Dates", current version; KMED. |
| 5. | *BI-KMED-TMCP-MAN-0012*: "Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics", current version; KMED. |
| 6. | *BI-KMED-TMCP-MAN-0014*: "Noncompartmental Pharmacokinetic / Pharmacodynamic Analyses of Clinical Studies", current version; KMED. |
| 7. | *BI-KMED-BDS-HTG-0045*: "Standards for Reporting of Clinical Trials and Project Summaries", current version; KMED. |
| 8. | *BI*-KMED-TMCP-OTH-0003: "Graphs and Tables for Clinical Pharmacokinetics and Pharmacodynamic Noncompartmental Analyses", current version, KMED. |
| 9. | *BI-KMED-TMCP-MAN-0010*: "Description of Analytical Transfer Files and PK/PD Data Files", current version; KMED. |
| 10. | *BI-KMED-BDS-HTG-0041*: "Analysis and Presentation of Adverse Event Data from Clinical Trials – Display Template", current version; KMED. |
| 11. | BI-KMED-BDS-HTG-0066: "Analysis and Presentation of AE data from clinical trials", current version, KMED. |
| 12. | *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. |
| 13. | *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 | **12-APR-21** | ██████████ | None | This is the final TSAP |