# TRIAL STATISTICAL ANALYSIS PLAN

**c28521708-01**

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|---|---|
| **BI Trial No.:** | 1402-0007 |
| **Title:** | Relative bioavailability of a single oral dose of BI 1358894 when administered alone or in combination with multiple oral doses of itraconazole in healthy male subjects (an open-label, fixed sequence study)<br>(including Protocol Amendments No.1 [c25796375-02] and No. 2 [c25796375-03]) |
| **Investigational Product:** | BI 1358894 |
| **Responsible trial statisticians:** | Phone:<br>Fax: |
| **Date of statistical analysis plan:** | 12JUL2019 SIGNED |
| **Version:** | Final |

# 1. TABLE OF CONTENTS

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# 2. LIST OF ABBREVIATIONS

See Medicine Glossary:
website: glossary

| Term | Definition / description |
|---|---|
| AESI | Adverse event of special interest |
| ALT | Alanine transaminase |
| ANOVA | Analysis of variance |
| AST | Aspartate transaminase |
| $AUC_{0-tz}$ | Area under the concentration-time curve of the analyte in plasma over the time interval from 0 to the last quantifiable data point |
| $AUC_{0-\infty}$ | Area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity |
| BMI | Body mass index |
| BWU | Bioavailability/Bioequivalence, Within-Subject Design, uncontrolled |
| CI | Confidence interval |
| $C_{max}$ | Maximum measured concentration of the analyte in plasma |
| CV | Arithmetic coefficient of variation |
| DBLM | Database lock meeting |
| DILI | Drug induced liver injury |
| gCV | Geometric coefficient of variation |
| gMean | Geometric mean |
| ITZ | Itraconazole |
| 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 / Ref | Reference treatment |
| RAGe | Report Appendix Generator system |
| 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 |
| XPKISTAT | Library of SAS® Macros for PK analysis |

# 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). 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 6.3 or higher, Certara USA Inc., Princeton, NJ, USA).

The statistical analyses will be performed within the validated working environment CARE, including SAS™ (current Version 9.4, by SAS Institute Inc., Cary, NC, USA), 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. The following changes compared to the protocol will be made:

No 'Entered set' (ES) will be defined in the TSAP as data of subjects discontinued before first administration of trial medication will not be entered in the database. A correct display of the ES would not be possible.

To define the study phases for adverse events conservatively, the period 'BI + ITZ' will be defined as follows:

**Section 7.3.4 of the CTP:** […] Adverse events *occurring between treatment with BI 1358894 and itraconazole in period 2 and end of residual effect period of itraconazole (6 days) after last intake of itraconazole or end of residual effect period of BI 1358894 (14 days) after BI 1358894 intake, whatever occurs ~~first~~ last, are attributed to the treatment interval "BI 1358894 + itraconazole".*

# 5. ENDPOINTS

## 5.1 PRIMARY ENDPOINTS

**Section 2.1.2 of the CTP:** *The following PK parameters will be determined for BI 1358894:*

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

The pharmacokinetic parameters listed in Sections 2.1 and 2.2 of the protocol for drug BI 1358894 or will be calculated according to the BI Standard Operating Procedure (SOP) 'Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics' [001-MCS-36-472] (7).

## 5.2 SECONDARY ENDPOINTS

### 5.2.1 Key secondary endpoints

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

### 5.2.2 Secondary endpoints

**Section 2.1.3 of the CTP:** *The following PK parameter will be determined for BI 1358894:*

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

### 5.3.2 Safety endpoints

**Section 2.2.2.2 and 5.2.5 of the CTP:** *Safety and tolerability of BI 1358894 will be assessed based on:*

- *Adverse events (including clinically relevant findings from the physical examination)*
- *Safety laboratory tests*
- *12-lead ECG*
- *Vital signs (blood pressure, pulse rate)*
- Suicidality assessment (Columbia Suicide Severity Rating Scale (C-SSRS))

# 6. GENERAL ANALYSIS DEFINITIONS

## 6.1 TREATMENTS

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

The study will be performed as a randomised, open-label trial with two treatments (T and R) and one fixed sequence (R then T).

In total, it was planned to assign 16 healthy male subjects.

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 | BI 1358894, 2*5 mg tablet, po, qd | BI |
| T | BI 1358894, 2*5 mg tablet + Itraconazole 20ml, 10mg/ml, qd | BI + ITZ |

**Section 1.2.3 of the CTP:** *The Residual Effect Period (REP) of BI 1358894 is approximately 14 days. This is the period after the last dose where measurable drug levels and/or pharmacodynamic effects are still likely to be present.*

*For the use of itraconazole in this trial, the REP is defined as 6 days.*

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

Table 6.1: 2 Flow chart of analysis phases for statistical analyses of AEs

| **Study analysis phase** | **Label** | **Start (inclusive)** | **End (exclusive)** |
|---|---|---|---|
| Screening | **Screening** | Date of informed consent | Date/time of first administration of BI 1358894 alone in treatment period 1 |
| On-treatment | **BI** | Date/time of first administration of BI 1358894 alone in treatment period 1 | Date/time of first administration of BI 1358894 alone in treatment period 1 + 14 days (336 h) thereafter |
| On-treatment | **ITZ** | Date/time of first administration of Itraconazole alone | Date/time of first administration of BI 1358894 administration in treatment period 2 |
| On-treatment | **BI+ITZ** | Date/time of first administration of BI 1358894 in treatment period 2 | Date/time of first administration of BI 1358894 in treatment period 2 + 6 days (144 h) after last administration of Itraconazole OR 14 days (336 h) after the BI 1358894 administration in treatment period 2, whatever occurs later |
| Follow-up | **F/U BI** | Date/time of first administration of BI 1358894 alone in treatment period 1 + 14 days (336 h) thereafter | Date/time of first administration of Itraconazole alone OR 0:00h on the day after trial-termination date in case of no further treatment |
| Follow-up | **F/U BI+ITZ** | Date/time of first administration of BI 1358894 in treatment period 2 + 6 days (144 h) after last administration of Itraconazole OR 14 days (336 h) after the BI 1358894 administration in treatment period 2, whatever occurs later | 0:00h on the day after trial termination date |

Two types of 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 "**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**")

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.

**Section 7.3 of the CTP:** *Important protocol deviation (IPD) categories will be suggested in the Integrated Quality and Risk Management Plan (IQRMP), IPDs will be identified no later than in the Report Planning Meeting, and the IPD categories will be updated as needed.*

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).

If any iPDs are identified, they are to be summarised into categories and will be captured in an accompanying Excel spreadsheet (3). Categories which are considered to be iPDs in this trial are defined in the integrated quality and risk management plan (IQRMP). If the data show other iPDs, the definition in the IQRMP will be supplemented accordingly by the time of the Report Planning Meeting.

The iPDs will be summarised and listed.

## 6.3 SUBJECT SETS ANALYSED

- 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.

**Section 7.3 of the CTP:**

- *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 pre-dose concentration is >5% Cmax value of that subject*
- *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 | |

## 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 001-MCG-156_RD-01 (4)).

Missing data and outliers of PK data are handled according to BI standards (see 001-MCS-36-472_RD-01) (5).

## 6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

The baseline value is defined as the last measurement before administration of BI 1358894 in each 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' BI 1358894 administration on Day 1 of Period 1 are to be performed and completed within a 2 h-period prior to BI 1358894 administration. Study measurements and assessments scheduled to occur 'before' itraconazole administration on Days -3 to -1 and 2 to 11 of Period 2 are to be performed and completed within a 2 h-period prior to itraconazole administration. Study measurements and assessments scheduled to occur 'before' BI 1358894 administration on Day 1 of Period 2 are to be performed and completed within a 1.0 h-period prior to itraconazole administration.*

*In visits 2 and 3, the acceptable deviation from the scheduled time for vital signs, ECG, and laboratory tests will be ± 45 min on Day 1, ± 60 min on Day 2, and ± 120 min from Day 3 onwards.*

[…]

*Starting from 48 hours after BI 1358894 administration (and beyond) a time window of ± 120 min will be allowed for pharmacokinetic blood sampling times.*

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, Section 7.5.2 and Section 7.6) 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 department Translational Medicine and Clinical Pharmacology (TMCP) at BI and will be presented in Section 15.6 of the CTR.

The format of the listings and tables will follow the standards defined in the BI corporate guideline "Reporting of Clinical Trials and Project Summaries" [001-MCG-159] (6) with the exception of those generated for PK-calculations (7).

The individual values of all subjects will be listed, sorted by treatment sequence, subject number, visit and actual treatment (if appropriate).
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 and will display the number of observations in a category, as well as the percentage (%) for each treatment sequence/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.

Units of variables should be given in the titles or column/row descriptors in square brackets (e.g. [mg]).

Exclusion of PK parameters

The ADS ADPP (PK parameters) contains column variables 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 APEXCO 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 001-MCS-36-472_RD-01 “Noncompartmental Pharmacokinetic / Pharmacodynamic Analyses of Clinical Studies” (5) and 001-MCS-36-472_RD-03 “Description of Analytical Transfer Files and PK/PD Data Files” (11).

## 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.

A medication will be considered concomitant, if it

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

The relevance of the concomitant therapies to the evaluation of PK will be decided no later than at the RPM.

## 7.3 TREATMENT COMPLIANCE

**Section 4.3 of the CTP:** *Compliance will be assured by administration of all trial medication in the study centre as medication will be administered by the investigator (or authorised 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 (cf. TSAP Section 6.2) and described in the CTR.

## 7.4 PRIMARY ENDPOINTS

Relative bioavailability of BI 1358894 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 'subject' and 'treatment'. The 'subject' effect will be considered as random, whereas the 'treatment' effect 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,*

$\mu$ = *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. The indices 'B' and 'W' correspond to 'between' and 'within' variability, respectively.*

*Point estimates for the ratios of the geometric means (T/R) for the primary endpoints (see* Section 5.1*) 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 XPKISTAT macro, based on PKS, and option BWU (Bioavailability/Bioequivalence, within-subject design, uncontrolled w.r.t. time).

## 7.5 SECONDARY ENDPOINTS

### 7.5.1 Key secondary endpoints

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

### 7.5.2 Secondary endpoints

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

### 7.6.2 Safety endpoints

Refer to TSAP Section 7.8 for a description of the analysis of safety and tolerability of BI 1358894.

## 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.

The analyses of AEs will be descriptive in nature and will be based on BI standards as presented in the corporate guideline: "Analysis and Presentation of Adverse Event Data from Clinical Trials" [001-MCG-156] (8).

The standard AE analyses will be based on the number of subjects with AEs (and not on the number of AEs).

For analysis, multiple AE occurrence data on the case report form (CRF) will be collapsed into one AE provided that all of the following applies:

- All AE attributes are identical (lower level term (LLT), intensity, action taken, therapy required, seriousness, reason for seriousness, relationship, outcome, AE of special interest (AESI))
- The occurrences were time-overlapping or time-adjacent (time-adjacency of two occurrences is given if the second occurrence started within one hour after end of the first occurrence).

For further details on summarization of AE data, please refer to [001-MCG-156] (8).

The analysis of AEs will be based on the concept of treatment-emergent AEs. That means that all AEs will be assigned to the screening, treatment or follow-up phases as defined in Section 6.1.

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

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

  *These lab findings constitute a hepatic injury alert and the subjects showing these lab abnormalities need to be followed up according to the 'DILI checklist' provided in the electronic data capture (eDC) system. In case of clinical symptoms of hepatic injury (icterus, unexplained encephalopathy, unexplained coagulopathy, right upper quadrant abdominal pain, etc.) without lab results (ALT, AST, total bilirubin) available, the investigator should make sure that these parameters are analysed, if necessary in an unscheduled blood test. Should the results meet the criteria of hepatic injury alert, the procedures described in the DILI checklist should be followed.*

**Section 7.3.4 of the CTP:** *Note that AEs occurring after the individual subject's end of trial but entered before final database lock will be reported to Pharmacovigilance only and will not be captured in the trial database.*

For more detail see the TSAP ADS plan.

According to ICH E3 (9), AEs classified as 'other significant' need to be reported and will include those non-serious and non-significant adverse events with
(i) 'action taken = discontinuation' or 'action taken = reduced', or
(ii) marked haematological and other lab abnormalities or lead to significant concomitant therapy as identified by the Clinical Monitor/Investigator at the Report Planning Meeting.

An overall summary of AEs (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 other significant AEs according to ICH E3 (9), for subjects with serious AEs, for subjects with drug-related AEs, for subjects with drug related serious adverse events and for subjects with AESIs.
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 [001-MCG-157] (10).

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/DBLM at the latest).

Descriptive statistics of laboratory data 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.

### 7.8.5 Others

Suicidality assessment (C-SSRS)

The C-SSRS will be done at

- Screening
- PTM 72:00 (in treatment period 1 and 2)
- end of trial examination

The results will be listed only.

# 8. 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-COPS-TMP-0001:* "iPD log", current version; IDEA for GEN. |
| 4. | *001-MCG-156_RD-01*: "Handling of Missing and Incomplete AE Dates", current version; IDEA for CON. |
| 5. | *001-MCS-36-472_RD-01*: "Noncompartmental Pharmacokinetic/Pharmacodynamic Analyses of Clinical Studies", current version; IDEA for CON. |
| 6. | *001-MCG-159*: "Reporting of Clinical Trials and Project Summaries", current version; IDEA for CON. |
| 7. | *001-MCS-36-472*: "Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics", current version; IDEA for CON. |
| 8. | *001-MCG-156*: "Analysis and Presentation of Adverse Event Data from Clinical Trials", current version; IDEA for CON. |
| 9. | *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. |
| 10. | *001-MCG-157*: "Handling, Display and Analysis of Laboratory Data", current version; IDEA for CON. |
| 11. | *001-MCS-36-472_RD-03*: "Description of Analytical Transfer Files and PK/PD Data Files", current version; IDEA for CON. |