# Trial Statistical Analysis Plan

**c28590228-01**

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|---|---|
| **BI Trial No.:** | 1402-0003 |
| **Title:** | A single dose, randomized, placebo controlled Phase I study on the effects of BI 1358894 on functional MRI measurements in an emotional processing paradigm in patients with Major Depressive Disorder<br>Including Protocol Amendment 2 [c17663416-03] |
| **Investigational Products:** | BI 1358894 |
| **Responsible trial statistician:** | Phone:<br>Fax: |
| **Date of statistical analysis plan:** | 22 OCT 2019 REVISED |
| **Version:** | Revised |

# 1. TABLE OF CONTENTS

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# 2. LIST OF ABBREVIATIONS

| Term | Definition / description |
|---|---|
| ADS | Analysis dataset |
| AE | Adverse event |
| AESI | Adverse event of special interest |
| ALT | Alanine transaminase |
| ANOVA | Analysis of variance |
| AST | Aspartate transaminase |
| $AUC_{0-tz}$ | Area under the concentration-time curve of the analyte in plasma over the time interval from 0 to the last quantifiable data point |
| $AUC_{t1-t2}$ | Area under the concentration-time curve of the analyte in plasma over the time interval $t_1$ to $t_2$ |
| BI | Boehringer Ingelheim |
| BMI | Body mass index |
| BP | Blood pressure |
| CI | Confidence interval |
| $C_{max}$ | Maximum measured concentration of the analyte in plasma |
| CRA | Clinical research associate |
| CRF | Case report form |
| CTP | Clinical Trial Protocol |
| CTR | Clinical Trial Report |
| CV | Arithmetic coefficient of variation |
| DBLM | Database lock meeting |
| DILI | Drug induced liver injury |
| ECG | Electrocardiogram |
| EDC | Electronic data capture |
| ES | Evaluable set |
| EudraCT | European Union Drug Regulating Authorities Clinical Trials |
| gCV | Geometric coefficient of variation |
| gMean | Geometric mean |
| HV | Healthy Volunteer |
| ICH | International Conference on Harmonisation |

| Term | Definition / description |
|---|---|
| iPD | Important Protocol Deviation |
| ISF | Investigator site file |
| $\lambda_z$ | Terminal rate constant 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 |
| PK | Pharmacokinetics |
| PKS | PK parameter analysis set |
| PR | Pulse rate |
| PT | Preferred term |
| Q1 | 1st quartile |
| Q3 | 3rd quartile |
| RAGe | Report Appendix Generator system |
| REP | Residual effect period |
| RPM | Report planning meeting |
| RS | Randomised set |
| SAS™ | Statistical Analysis System |
| SD | Standard deviation |
| SOC | System organ class |
| SOP | Standard operating procedure |
| $t_{max}$ | Time from dosing to maximum measured concentration of the analyte in plasma |
| TSAP | Trial statistical analysis plan |
| 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), 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).

The pre-processing of the functional images and the derivation of the primary and secondary PD endpoints will be performed by . Functional images will be pre-processed using MATLAB 2015a (The Mathworks, Natick, MA) and SPM12 (Statistical parametric mapping software, SPM; Wellcome Department of Imaging Neuroscience, London, UK).

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. No changes compared to the protocol were made.

# 5. ENDPOINTS

## 5.1 PRIMARY ENDPOINTS

**Section 5.1.1 of the CTP:** *The primary endpoint is mean BOLD signal % change in an emotional paradigm (emotional faces from WSEFEP) in the corticolimbic system, consisting of the following eight brain regions:*

- *Amygdala left*
- *Amygdala right*
- *Dorsolateral prefrontal cortex left*
- *Dorsolateral prefrontal cortex right*
- *Insula left*
- *Insula right*
- *Anterior cingulate cortex left*
- *Anterior cingulate cortex right*

## 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 5.1.2 of the CTP:** *The secondary endpoint is the mean BOLD signal % change in an emotional paradigm (affective picture set (OASIS task) in the corticolimbic system, consisting of the following eight brain regions:*

- *Amygdala left*
- *Amygdala right*
- *Dorsolateral prefrontal cortex left*
- *Dorsolateral prefrontal cortex right*
- *Insula left*
- *Insula right*
- *Anterior cingulate cortex left*
- *Anterior cingulate cortex right*

This endpoint will be derived in the same way as the primary endpoint. Please refer to

Section 5.1.

**Safety:**

**Section 2.2.2 of the CTP:** *Further safety criteria of interest are:*

- *Adverse events (including clinically relevant findings from the physical and neurological examination)*
- *Safety laboratory tests*
- *12-lead ECG*
- *Vital signs (blood pressure, pulse rate)*

Age [years] will be determined as the difference between year of informed consent and year of birth.

BMI will be calculated as weight [kg] / (0.01 * height [cm])$^2$.

# 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 placebo-controlled, randomized, single dose, parallel group design with three treatment arms (BI 1358894, Citalopram, and placebo).

In total, it was planned to assign 24 patients with major depressive disorder aged 18 to 45 years and a Montgomery–Åsberg Depression Rating Scale (MADRS) total score ≥ 7 and < 26 at screening to each of the three treatment sequences in a 1:1:1 ratio.

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 | Short label for footnote |
|---|---|---|
| D 4 x 25 mg tablets of BI 1358894 | BI 1358894 | BI 1358894 100mg |
| E 1 x 20 mg tablets of Citalopram | Citalopram | Citalopram 20mg |
| P Placebo, tablet | Placebo | Placebo |

The following separate study phases will be defined for the analyses of AEs, safety laboratory data and vital signs:

- **Screening** (ranging from 0:00 h on day of informed consent until administration time of study drug)
- **On treatment (**ranging from the time of administration of BI 1358894 or BI-matching placebo (in the placebo and Citalopram arm) until time of administration of BI 1358894 or BI-matching placebo + REP (14*24 h) or 0:00 AM on day after subject's trial termination date, whatever occurs earlier),
- **Follow up (**ranging from time of administration of BI 1358894 or BI-matching placebo (in the placebo and Citalopram arm) + REP(14*24 h) until 0:00 AM on day after subject's trial termination date).

Displays of AEs will be presented separately for the treatments described in Table 6.1: 1 above. In the Citalopram arm, AE´s occurring between administration of placebo at 0:00 and administration of Citalopram at 3:00 (planned time) cannot be treatment related. If applicable, these AE´s will be checked individually in the listings and described in the CTR.

More details on the technical implementation of these analyses are provided in the ADS Plan of this TSAP.

## 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. 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 the RPM minutes via 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 RPM. Table 6.2: 1 specifies which kind of iPDs should be excluded from which analysis set. The decision on exclusion of subjects from analysis sets will be made at the latest at the RPM, after discussion of exceptional cases and implications for analyses.

Table 6.2: 1 iPDs and handling of iPDs

| Category / iPD Code | | Description | Excluded from which analysis set |
|---|---|---|---|
| **A** | | **Entrance criteria not met** | |
| | A1 | Inclusion criteria violated | None |
| | A2 | Exclusion criteria violated | None |
| **B** | | **Informed consent** | |
| | B1 | Informed consent not available/not done | All |
| | B2 | Informed consent date after start of study activities | None |
| **C** | | **Trial medication and randomisation** | |
| | C1 | Randomisation not followed (patients do not receive the treatment they were initially randomised to) | PKS, ES |
| | C2 | Non-compliance | PKS, ES |
| | C3 | Trial medication not taken according to protocol | PKS, ES |
| **D** | | **Concomitant medication** | |
| | D1 | Concomitant medication with the potential to affect the assessment of the trial medication | PKS |
| **E** | | **Missing data** | |
| | E1 | Certain violations of procedures used to measure primary or secondary data | None |
| **F** | | **Incorrect timing** | |
| | F1 | Certain violations of time schedule used to measure primary or secondary data | PKS |
| **G** | | **Other trial specific important deviation** | |
| | G1 | Incorrect intake of meal before administration of treatment | PKS |
| | G2 | Protocol deviations affecting safety and rights | None |

## 6.3 SUBJECT SETS ANALYSED

- Evaluable Set (ES)
  This subject set includes all randomised patients who performed the fMRI measurements and did not experience severe headaches directly before or during the fMRI measurements. In particular, patients that have to be replaced due to severe headaches will be excluded from the ES.

  Severe headaches are those with a severity of 7-10 assessed on the Numerical Ranking scale (NRS) scale.

- Randomised Set (RS)
  This subject set includes all patients who were randomised to receive BI 1358894, Citalopram or placebo. Patients without any post-randomization data will be excluded from the primary and secondary PD analyses.
  All analyses based on the randomised set will be done using the planned (i.e.randomised) treatment.

- Safety Set (SS)
  This subject set includes all randomised patients who received the study drugs (BI 1358894, Citalopram or placebo). In particular, patients that received treatment but have to be replaced will be included in the SS. It is used for safety analyses.
  All analyses based on the safety set will be done using the treatment actually received.

- PK parameter analysis set (PKS)
  The PK parameter analysis set (PKS) includes all subjects in the SS who provide at least one PK parameter that was not excluded according to the description below. Thus, a subject will be included in the PKS, even if he/she contributes only one PK parameter value for one period to the statistical assessment.

**Section 7.3.5 of the CTP**: *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 Blinded 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 but are not restricted to:*
- *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 tmax of the respective treatment (median tmax is to be determined excluding the subjects experiencing emesis) or at least until completion of the fMRI procedures on day 1.*
- *The subject experiences emesis at any time during the labelled dosing interval.*
- *A pre-dose concentration is > 5% of the 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.

The following Table 6.3: 1 contains the information which subject is used for which class of endpoint:

Table 6.3: 1 Subject sets analysed

| | Subject set | | | |
|---|---|---|---|---|
| Class of endpoint | ES | RS | SS | PKS |
| Primary and secondary PD analyses | Primary analysis | Sensitivity analysis* | | |
| Safety endpoints | | | X | |
| Demographic/ baseline endpoints | X | X* | | |
| Important protocol deviations | | X | | |
| PK endpoints | | | | X |

* In case the ES and the RS differ by three or more patients (see section 7.1 and 7.4), analyses will be repeated for the RS.

## 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 exception where imputation might be necessary for safety evaluation is 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

For vital signs baseline is defined as the last measurement prior to administration of BI 1358894 or BI-matching placebo (in the placebo and Citalopram arm).

For laboratory parameters baseline is defined as the last measurement prior to administration of BI 1358894 or BI-matching placebo (in the placebo and Citalopram arm).

Exact times of measurements outside the permitted time windows will be documented. The acceptable time windows are provided in the Flow Chart of the CTP. Adherence to time windows will be checked via the consistency check listings at the RPM.

# 7. PLANNED ANALYSIS

Safety analysis (refer to Section 7.8) will be performed by Datamap GmbH 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 primary and secondary endpoints (refer to Section 7.4 and Section 7.5) will also be performed by Datamap GmbH and will be presented in Section 15.7 of the CTR and in Appendix 16.1.13.4.

Descriptive data analysis of PK parameters and concentrations will be performed by the department Translational Medicine and Clinical Pharmacology at BI and will be presented in Section 16.1.13.3 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, 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 as well as for all 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 with 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” (12).

## 7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

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

Treatment allocation and demographics will be summarised also for the RS.

The data will be summarised by treatment and in total.

In case the ES and the RS differ by three or more patients (e.g. at least three patients have been excluded from the RS due to severe headaches before or during the fMRI measurements), the descriptive statistics will also be provided for the RS.

## 7.2 CONCOMITANT DISEASES AND MEDICATION

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

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.

In case the ES and the RS differ by three or more patients, the frequency tables will also be provided for the RS.

## 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 (cf. TSAP Section 6.2) and described in the CTR.

## 7.4 PRIMARY ENDPOINTS

The primary endpoint analysis will be performed on the ES.

**Section 7.3.1. of the CTP:**

Primary Analysis:

*Each brain region of the primary endpoint will be analysed separately. Each brain region will be summarised descriptively.*
*An ANOVA model with treatment (BI 1358894 versus placebo) and severity of depression (MADRS ≥ 20 versus < 20) as fixed effects will be used. The model is described by the following equation:*

$$Y_{ikl} = \mu + \tau_k + \lambda_l + e_{ikl},$$

*where*

$Y_{kli}$ *= mean BOLD signal % change measured on patient i,*
$\mu$ *= the overall mean,*

*$\tau_k$ = the kth treatment effect, = 1 (placebo), 2 (BI 1358894),*
*$\lambda_l$ = the lth effect of depression=1 (MADRS ≥ 20) , 2 (MADRS < 20)*
*$e_{ikl}$ = the random error associated with patient i.*

*The absolute difference between BI 1358894 and placebo will be estimated by the difference of the arithmetic means. 90% CIs will be calculated based on the residual error from ANOVA.*

## 7.5 SECONDARY ENDPOINTS

The secondary endpoint will be derived and analysed in the same way as the primary endpoint.

**Safety:**

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

## 7.7 EXTENT OF EXPOSURE

Descriptive statistics are planned for this section of the report based on the ES. 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 SS.

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] (9).

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)

- 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 "Analysis and Presentation of Adverse Event Data from Clinical Trials" (9) and "Handling of missing and incomplete AE dates" (4).

**Section 7.3.4 of the CTP:** *Statistical analysis and reporting of AEs will concentrate on treatment-emergent AEs, i.e. all AEs occurring between start of treatment and end of the REP. AEs that start before first drug intake and deteriorate under treatment will also be considered as 'treatment-emergent'.*

All AEs will be assigned to screening, on-treatment or follow-up phases as defined in Section 6.1.

AEs will be analysed based on actual treatments, as defined in Table 6.1: 1.

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

**Section 5.2.6.1 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 and/or ALT > 3 fold ULN combined with an elevation of total bilirubin > 2 fold ULN measured in the same blood draw sample, and/or*

- *aminotransferase (ALT, and/or AST) elevations ≥ 10 fold ULN […]*

According to ICH E3 (10), AEs classified as 'other significant' need to be reported and will include those non-serious and non-significant adverse events with
(i) 'action taken with trial drug = discontinuation' or 'action taken with trial drug = reduced', or
(ii) marked haematological and other lab abnormalities or lead to significant concomitant therapy as identified by the Clinical Monitor/Investigator at a MQRM.

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

For disclosure of AE data on ClinicalTrials.gov, the frequency of subjects with non-serious AEs occurring with an incidence of greater than 5 % (in preferred terms) will be summarised by treatment, primary SOC and preferred term. The frequency of subjects with SAEs will also be summarised.

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

For support of lay summaries, the frequency of subjects with drug-related SAEs will be summarised by treatment, primary system organ class and preferred term.

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.

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))

- FU Phase

In Section 16.1.13.1.8 AE tables, the following totals will be provided in addition:

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

If the subject reports headaches during the treatment period further information about the duration of headache, headache severity (NRS), location, characteristics, and signs and symptoms were recorded. The information will be summarized with descriptive statistics.

### 7.8.2 Laboratory data

Descriptive statistics will be calculated by treatment including change from baseline.

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 possible clinically significant will be flagged in the data listings.

It is the investigator's responsibility to decide whether a lab value is clinically significantly abnormal or not (at the RPM at the latest).

The analyses of laboratory data will be based on BI standards "Display and Analysis of Laboratory Data" (11).

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.

### 7.8.3 Vital signs

Descriptive statistics including change from baseline will be performed for vital signs (blood pressure and pulse rate) by treatment.

Clinically relevant findings in vital signs 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.

### 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).

### 7.8.5 Others

#### 7.8.5.1 Physical examination

Physical examination findings will be reported as relevant medical history/baseline condition (i.e., a condition already existent before intake of study drug) or as AE and will be summarised as such. No separate listing or analysis of physical examination findings will be prepared.

#### 7.8.5.2 Neurological examination

Clinically relevant findings of the neurological examination will be reported as relevant medical history/baseline condition (if a condition already exists before first administration of study treatment) or as AE (if condition emerges after first administration of study treatment) and will be summarized as such. No separate listing or analysis of neurological examinations will be prepared.

#### 7.8.5.3 Suicidality assessment

Suicidality monitoring will be performed as described in Section 5.2.2 of the CTP, results will only be listed: No further analysis will be prepared.

# 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 | *KM Asset BI-KMED-BDS-HTG-0035:* "Handling of missing and incomplete AE dates", current version; KMED |
| 5 | *001-MCS-36-472_RD-01*: "Noncompartmental Pharmacokinetic/Pharmacodynamic Analyses of Clinical Studies", current version; IDEA for CON. |
| 6 | *KM Asset BI-KMED-BDS-HTG-0045:* "Reporting of Clinical Trials and Project Summaries", current version; KMED |
| 7 | *001-MCS-36-472*: "Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics", current version; IDEA for CON. |
| 8 | Neuenschwander B, Wandel S, Roychoudhury S, Bailey S. Robust exchangeability designs for early phase clinical trials with multiple strata. Pharm Stat 2015; 15:123-134 [R17-3435] |
| 9 | *KM Asset BI-KMED-BDS-HTG-0041:* "Analysis and Presentation of Adverse Event Data from Clinical Trials", current version; KMED |
| 10 | *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. |
| 11 | *KM Asset BI-KMED-BDS-HTG-0042:* "Display and Analysis of Laboratory Data", current version; KMED |
| 12 | *001-MCS-36-472_RD-03*: "Description of Analytical Transfer Files and PK/PD Data Files", current version; IDEA for CON. |

# 10. HISTORY TABLE

Table 10: 1 History table

| Version | Date (DD-MMM-YY) | Author | Sections changed | Brief description of change |
|---|---|---|---|---|
| Revision | **22-OCT-19** | | None | This is the final TSAP |