Boehringer Ingelheim

# TRIAL STATISTICAL ANALYSIS PLAN

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|---|---|
| **Document No.:** | **c43225188-01** |
| **BI Trial No.:** | **1509-0001** |
| **Title:** | A randomised, single-blind, placebo-controlled trial to investigate safety, tolerability, and pharmacokinetics of single rising doses of BI 3000202 administered as tablet to healthy male subjects, and a randomised, open-label, single-dose, two-way cross-over relative bioavailability comparison of BI 3000202 as tablet with and without food in healthy male subjects<br>Including Protocol Amendment 1 [c40535128-02] |
| **Investigational Product(s):** | BI 3000202 |
| **Responsible trial statistician(s):** | [redacted]<br>Phone: [redacted]<br>Fax: [redacted] |
| **Date of statistical analysis plan:** | 15 DEC 2023 |
| **Version:** | 1.0 |

# 1. TABLE OF CONTENTS

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# 2. LIST OF ABBREVIATIONS

| Term | Definition / description |
|---|---|
| ADS | Analysis data set |
| AE | Adverse Event |
| AESI | Adverse event of special interest |
| ALT | Alanine aminotransferase |
| ANOVA | Analysis of Variance |
| AST | Aspartate aminotransferase |
| $AUC_{0-\infty}$ | Area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity |
| $AUC_{0-24}$ | Area under the concentration-time curve of the analyte in plasma over the dosing interval 0 to 24 hours |
| BI | Boehringer Ingelheim |
| BLQ | Below Limit of Quantification |
| BMI | Body mass index |
| BP | Blood pressure |
| CARE | Clinical data analysis and reporting environment |
| CDR | Clinical Data Repository |
| CI | Confidence Interval |
| $C_{max}$ | Maximum measured concentration of the analyte in plasma |
| COVID | Coronavirus disease |
| CRF | Case Report Form, paper or electronic (sometimes referred to as ‘eCRF’) |
| CSD | Company Standard Displays |
| CTP | Clinical Trial Protocol |
| CTR | Clinical Trial Report |
| CV | Arithmetic coefficient of variation |
| DILI | Drug induced liver injury |
| ECG | Electrocardiogram |
| [redacted] | [redacted] |
| EDC | Electronic data capture |
| EDMS | Electronic Document Management System |
| EudraCT | European union drug regulating authorities clinical trials |
| FE | Food Effect |

| Term | Definition / description |
|---|---|
| gCV | Geometric coefficient of variation |
| gMean | Geometric mean |
| HR | Heart rate |
| ICH | International Conference on Harmonisation |
| iPD | Important Protocol deviations |
| [redacted] | [redacted] |
| MedDRA | Medical Dictionary For Regulatory Activities |
| PDS | Pharmacodynamic parameter analysis set |
| PK | Pharmacokinetic(s) |
| PKS | Pharmacokinetic parameter analysis set |
| PR | Pulse rate |
| PT | Preferred Term |
| QRS complex | Combination of the Q, R, and S waves |
| QT interval | Time between start of the Q-wave and the end of the T-wave in an electrocardiogram |
| QTcB | QT interval, corrected for heart rate according to Bazett formula |
| QTcF | QT interval, corrected for heart rate according to Fridericia formula |
| RAGe | Report appendix generator |
| REP | Residual Effect Period |
| RPM | Report Planning Meeting |
| RR interval | ECG interval from the peak of the R wave to the peak of the subsequent R wave |
| SAE | Serious Adverse Event |
| sd | Single dose |
| SOC | System Organ Class |
| SOP | Standard operating procedure |
| SRD | Single rising dose |
| [redacted] | [redacted] |
| TMF | Trial Master File |
| TS | Treated set |
| TSAP | Trial Statistical Analysis Plan |
| ULN | Upper limit of normal range |

| Term | Definition / description |
|---|---|
| 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 clinical trial protocol (CTP), 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 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 as collected in the electronic case report form (eCRF) will be stored in a trial database within the RAVE electronic data capture (EDC) system. All study data (including external data) will then be uploaded to the Clinical Data Repository (CDR).

Pharmacokinetic (PK) parameters will be calculated using Phoenix WinNonlin™ software (version 8.1.1 or higher, [redacted] or SAS Version 9.4 (or later version).

The statistical analyses will be performed within the validated working environment CARE, including SAS™ (current Version 9.4, by [redacted]), and a number of SAS™-based tools (e.g., macros for the analyses of AE data or laboratory data; Report Appendix Generator system (RAGe) for compilation/formatting of the clinical trial report (CTR) appendices).

# 4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

All analyses described in this TSAP are in accordance with the statistical methods described in the revised CTP.

# 5. ENDPOINTS(S)

## 5.1 PRIMARY ENDPOINT(S)

**Section 2.1.2 of the CTP:**

*SRD part*

*The primary endpoint to assess safety and tolerability of BI 3000202 is the occurrence of any treatment-emergent adverse event assessed as drug-related by the investigator. This is expressed as the percentage of subjects treated with investigational drug who experience such an event.*

*FE part*

*The following pharmacokinetic parameters will be determined for BI 3000202:*

- *$AUC_{0-24}$ (area under the concentration-time curve of the analyte in plasma over the time interval from 0 to 24 hours)*
- *$C_{max}$ (maximum measured concentration of the analyte in plasma)*

## 5.2 SECONDARY ENDPOINT(S)

### 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 pharmacokinetic parameters will be determined for BI 3000202, if feasible:*

*SRD part*

- *$AUC_{0-24}$ (area under the concentration-time curve of the analyte in plasma over the time interval from 0 to 24 hours)*
- *$C_{max}$ (maximum measured concentration of the analyte in plasma)*

*FE part*

- *$AUC_{0-\infty}$ (area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity)*

## 5.3 FURTHER ENDPOINT(S)

### 5.3.1 Safety and tolerability endpoints

**Section 2.2.2.1 of the CTP:**

*Safety and tolerability of BI 3000202 will be assessed based on:*

- *AEs (including clinically relevant findings from the physical examination)*
- *Safety laboratory tests*
- *12-lead ECG*
- *Continuous ECG monitoring (SRD part only)*
- *Vital signs (blood pressure, pulse rate)*

**12-lead ECG endpoints (SRD part only):**

For the definition of baseline and a summary of time points scheduled for ECG recording and central evaluation please refer to Section 6.7.

Quantitative ECG endpoints

The following quantitative ECG endpoints will be determined for the ECG variables QTcF, HR, QT, PR, QRS, RR and QTcB, derived as described in Section 10.1:

- absolute values (per time point)
- changes from baseline (per time point)
- percent changes from baseline (per time point; for HR, PR, QRS)

Categorical ECG endpoints

The following categorical ECG endpoints will be determined based on the quantitative ECG endpoints:

- New onset (meaning that this or a higher category was not present any time at baseline) of maximum QTcF interval > 450 to 480 msec, > 480 to 500 msec, or > 500 msec on treatment. For assignment of a particular subject to one of the above categories, all time points on-treatment (refer to Table 6.7: 1) will be considered
- Maximum change from baseline in QT interval of ≤ 60 msec, or > 60 msec on treatment
- Maximum change from baseline in QTcF interval of ≤ 30 msec, > 30 to ≤ 60 msec, or > 60 msec on treatment

The occurrence of any of the following will be considered as “notable findings”:

- New onset (not present any time at baseline) of uncorrected QT interval > 500 msec at any time on treatment
- New onset of QTcF interval > 500 msec at any time on treatment

- Change from baseline of QTcF > 60 msec at any time on treatment
- Percent change from baseline of HR ≥ 25%, when corresponding on-treatment value of HR is > 100 beats/min, or percent change from baseline of HR ≤ - 25%, when corresponding on-treatment value of HR is < 50 beats/min, at any time on treatment
- Percent change from baseline of PR ≥ 25%, when corresponding on-treatment value of PR interval is > 200 msec, at any time on treatment
- Percent change from baseline of QRS ≥ 10%, when corresponding on-treatment value of QRS duration is > 110 msec, at any time on treatment

[redacted]

### 5.3.2 Pharmacokinetic (PK) endpoints

Other PK parameters of BI 3000202 are further study endpoints. For more details see CTP Section 2.2.2.2.

### 5.3.3 Exploratory biomarker endpoints

**Section 2.2.2.3 of the CTP:**

*SRD part*

*Percent change of INFα from ex vivo stimulated whole-blood will be used for the exploratory evaluation of the pharmacodynamics of BI 3000202.*

*Further pharmacodynamic parameters might be determined as appropriate.*

*FE part*

*No sampling of biomarkers will be done.*

[redacted]

# 6. GENERAL ANALYSIS DEFINITIONS

## 6.1 TREATMENT(S)

For basic study information on treatments to be administered, assignment of treatment groups, selection of doses, refer to CTP Section 3 and 4.

This trial consists of two parts, an SRD part and a FE part. It is planned to include a total of 68 healthy male subjects in the trial (SRD part: 56 subjects, FE part: 12 subjects).

The SRD part is designed as blinded to subjects (blinded to treatment but not to dose level), randomised, and placebo-controlled within parallel dose groups. Subjects in the SRD part will be assigned to 7 dose groups consisting of 8 subjects per group. Within each dose group, 6 subjects will receive BI 3000202 and 2 subjects will receive placebo.

The FE part is designed as randomised, open-label, two-way crossover. Subjects in the FE part are randomly allocated to one of the two treatment sequences (R-T or T-R). All subjects in this part will receive a single dose of [redacted] BI 3000202 administered as tablet in fasted state (reference treatment, R) and after a standardised high-fat, high-calorie meal (test treatment, T). There will be a washout period of at least 3 days between the treatments.

For details of dosage and formulation see Tables 6.1: 1 and 6.1: 2 below.

Table 6.1: 1 Treatments and labels used in the analysis – SRD part

| Treatment | | Short label |
|---|---|---|
| P[1] | Placebo, film-coated tablets, sd | Placebo |
| A | BI 3000202, film-coated tablets, [redacted] mg, sd | BI [redacted] |
| B | BI 3000202, film-coated tablets, [redacted] mg, sd | BI [redacted] |
| C | BI 3000202, film-coated tablets, [redacted] mg, sd | BI [redacted] |
| D | BI 3000202, film-coated tablets, [redacted] mg, sd | BI [redacted] |
| E | BI 3000202, film-coated tablets, [redacted] mg, sd | BI [redacted] |
| F | BI 3000202, film-coated tablets, [redacted] mg + [redacted] mg, sd | BI [redacted] |
| G | BI 3000202, film-coated tablets, [redacted] mg, sd | BI [redacted] |

[1] All subjects treated with placebo will be included and analysed in the placebo control group regardless of the dose group which they belonged to

Table 6.1: 2 Treatments and labels used in the analysis – FE part

| Treatment | | Short label |
|---|---|---|
| R | BI 3000202, film-coated tablets, [redacted] mg, sd, fasted | BI [redacted] fasted (R) |
| T | BI 3000202, film-coated tablets, [redacted] mg, sd, fed | BI [redacted] fed (T) |

**Section 1.2.2 of the CTP**

*The Residual Effect Period (REP) of BI 3000202, when measurable drug levels and/or pharmacodynamic effects are still likely to be present, is not known for this first-in-human trial.* [redacted]

Based on this, the following study phases will be defined for the analysis of AEs:

- **Screening**
  - Ranging from 0:00 h on day of informed consent until time of first drug administration (BI/Placebo)
- **On-treatment**
  - SRD part: Ranging from the time of drug administration until [redacted] after drug administration
  - FE part: Ranging from the time of drug administration until next drug administration OR until [redacted] after drug administration, whichever comes first
- **Follow-up (F/U)**
  - SRD part: Ranging from [redacted] after drug administration until 0:00 h on the day after trial termination date
  - FE part: Ranging from the end of REP until next drug administration OR until 0:00 h on the day after trial termination date, whichever comes first

**Section 7.2.5 of the CTP**

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

The following AE displays will be provided in the report:

AE displays in CTR Section 15.3 and Appendix 16.1.13.1.8 (for ClinicalTrials.gov and EudraCT) will present results for the on-treatment phase (as defined in Tables 6.1: 1 and 6.1: 2) only. Screening and follow-up phase will not be included in this analysis.

The following totals will be provided in addition for Section 15.3:

- a total over all on-treatment phases of the SRD part involving BI drug (**"BI SRD Total"**)
- a total over all on-treatment phases of the SRD part involving BI drug and placebo (**"Total"**)
- a total over all on-treatment phases of the FE part ("**BI FE Total**")

In Section 15.4 and Appendix 16.2 (Listings) of the CTR displays, the screening period, as well as the follow-up phases will additionally be included and no totals will be provided. The labelling of the actual treatment in listings corresponds to the labelling of study phases defined above. Single exception is the Follow-up phase where the actual treatment will be labelled "F/U".

More details on the handling of the treatments refer to Technical TSAP ADS (Analysis Data Set) 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, it will be decided whether a discrepant data value can be used in analyses or whether it must be corrected in the clinical database. Each protocol deviation must be assessed to determine whether it is an important protocol deviation (iPD).

For definition of important protocol deviations (iPD), and for the process of identification of these, refer to the Boehringer Ingelheim (BI) Standard Operating Procedure (SOP) "Identify and Manage Important Protocol Deviations (iPD)" (2).

IPD categories will be suggested in the DV domain sheet, iPDs will be identified no later than in the Report Planning Meeting, and the iPD categories will be updated as needed.

If any iPDs are identified, they are to be summarised into categories and will be captured in the iPD specification file (DV domain) (3) and in the decision log (4). Both documents will be stored within the trial master file (TMF) in electronic document management system (EDMS).

The iPDs will be summarized and listed in the CTR. Non-important COVID-19 related protocol deviations will only be listed.

## 6.3 INTERCURRENT EVENTS

This section is not applicable.

## 6.4 SUBJECT SETS ANALYSED

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

*Statistical analyses will be based on the following analysis sets:*

- *Treated set (TS): The treated set includes all subjects who were treated with at least one dose of trial drug. The treatment assignment will be determined based on the first treatment the subjects received. The treated set will be used for safety analyses.*

- *Pharmacokinetic parameter analysis set (PKS): This set includes all subjects in the treated set (TS) who provide at least one PK endpoint that was not excluded due to a protocol deviation relevant to the evaluation of PK or due to PK non-evaluability (as specified in the following* CTP *subsection 'Pharmacokinetics'). 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. Descriptive and model-based analyses of PK parameters will be based on the PKS.*

*For the SRD part, the following analysis set will be created in addition:*

- *Pharmacodynamic parameter analysis set (PDS): This set includes all subjects in the treated set (TS) who provide at least one PD endpoint (see* CTP *Section 2.2.2.3) that was not excluded due to a protocol deviation relevant to the evaluation of PD or due to PD non-evaluability (as specified in the* CTP *subsection 7.2.1.3 'Biomarkers'). Descriptive analyses of PD endpoints will be based on the PDS.*

All ECG analyses are performed on the TS, [redacted]

Table 6.4: 1 Subject sets analysed

| | Subject set | | | |
|---|---|---|---|---|
| Class of analysis | TS | PKS | PDS | [redacted] |
| Primary endpoint (SRD part) | X | | | |
| Primary and secondary PK endpoints | | X | | |
| Further PK endpoints | | X | | |
| Biomarker/PD endpoints | | | X | |
| [redacted] | | | | |
| Safety & treatment exposure | X | | | |
| iPDs | X | | | |
| Disposition | X | | | |
| Demographic & baseline | X | | | |

[redacted]

## 6.6 HANDLING OF MISSING DATA AND OUTLIERS

**Section 3.3.4 of the CTP:**

*If a subject is removed from or withdraws from the trial prior to the first administration of trial medication, the data of this subject will not be entered in the case report form (CRF) and will not be reported in the clinical trial report (CTR).*

*If a subject is removed from or withdraws from the trial after the first administration of trial medication, this will be documented and the reason for discontinuation must be recorded in the CRF; in addition, trial data will be included in the CRF and will be reported in the CTR.*

**Section 7.3.1 of the CTP:**

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

Missing or incomplete AE dates are imputed according to BI standards (5).

**Section 7.3.2 and 7.3.3 of the CTP:**

*Handling of missing PK data will be performed according to the relevant BI internal procedure.*

*PK parameters that cannot be reasonably calculated based on the available drug concentration-time data will not be imputed.*

Missing data and outliers of PK and PD data are handled according to BI standards (6) and (7).

[redacted]

No imputation will be done for ECG endpoints. If replicate ECG recordings are missing, the arithmetic means per time point will be computed with the reduced (1 or 2) number of recordings. If single cardiac cycles (also denoted as beats or waveforms) are missing, the arithmetic mean per single ECG will be computed with the reduced (1, 2 or 3) number of cardiac cycles.

[redacted]

[redacted]

## 6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

For all analyses (except for analyses of ECG variables), the baseline value is defined as the last measurement prior to the drug administration (in each treatment period for FE part).

There will be a centralised evaluation of the 12-lead ECG recordings at the time points and for the ECG recordings specified in Table 6.7: 1 below. This will be performed for the SRD part only.

Three triplicate ECGs will be recorded as the baseline before the first drug administration, but only the first ECG of each of the 3 baseline triplicates will be transferred to the database. At all other time points, 1 triplicate ECG will be recorded, but only the first single ECG of the triplicate will be transferred to the database. The baseline value of an ECG variable is defined as the mean of the ECG variable values prior to drug administration.

[redacted]

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.

Table 6.7: 1 Time schedule of 12-lead ECG recordings

| **Visit** | **Day** | **Planned time (hh:mm) (relative to drug administration)** | **Study phase** | **Central evaluation** |
|---|---|---|---|---|
| 1 | -21 to -1 | | Screening | NA |
| 2 | 1 | -01:00 | Baseline | first ECG of each of the 3 triplicate baselines |
| | | -00:45 | | |
| | | -00:30 | | |
| | | 00:30 | On-treatment | first single ECG of the triplicate |
| | | 01:00 | | |
| | | 01:30 | | |
| | | 02:00 | | |
| | | 03:00 | | |
| | | 04:00 | | |
| | | 06:00 | | |
| | | 08:00 | | |
| | | 12:00 | | |
| | 2 | 24:00 | | |
| | 3 | 48:00 | | NA |
| 4 | 4 to 14 | | End-of-study examination | NA |

Time windows are defined in Section 6.1 of the CTP. Adherence to time windows will be checked at the RPM.

# 7. PLANNED ANALYSIS

If not stated otherwise, the SRD part and the FE part will be analysed separately.

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

Statistical model-based analysis of PK endpoints (refer to Section 7.4 and Section 7.5) will be performed by [redacted] and will be presented in Section 15.5 of the CTR and Appendix 16.1.13.3.

Descriptive data analysis of PK endpoints will be performed by [redacted]. The results will be presented in Section 15.6 of the CTR and Appendix 16.1.13.5.

[redacted]

The format of the listings and tables will follow the BI guideline "Reporting of clinical trials and project summaries" (8) with the exception of those generated for PK-calculations following BI standards for PK/PD analysis (9).

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

The following standard descriptive statistical parameters will be displayed in summary tables of continuous variables:

| | |
|---|---|
| N | number of non-missing observations |
| Mean | arithmetic mean |
| SD | standard deviation |
| Min | minimum |
| Median | median |
| Max | maximum |

For plasma 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 |

For PK parameters the following descriptive statistics will additionally be calculated:

| | |
|---|---|
| P10 | $10^{th}$ percentile |
| Q1 | $1^{st}$ quartile |

| | |
|---|---|
| Q3 | 3rd quartile |
| P90 | 90th percentile |

The data format for descriptive statistics of plasma 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 (%) relative to the respective treatment group. The precision for percentages should be one decimal point, unless the denominator is smaller than 100 (in all treatment columns), in which case percentages are given in integer numbers. The category missing will be displayed only if there are actually missing values.

Exclusion of PK parameters

The ADS "ADPP" (PK parameters) contain column variables APEX and APEXCO indicating inclusion/exclusion (APEX) of a PK/PD parameter and an analysis flag comment (APEXCO). All PD analyses and all analyses based on the PKS will include parameters only if they are not flagged for exclusion, that is APEX is equal to "Included".

Exclusion of PK/PD concentrations

The ADS "ADPC" (PK concentrations per time-point or per time-interval) and ADS "ADYC" (PD concentrations per time-point or per time-interval) contain column variables ACEX and ACEXCO indicating inclusion/exclusion (ACEX) 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.
- 'DESC STATS' the value will be excluded from descriptive evaluations per planned time point/time interval.
- '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.

If ACEXCO contains the addition "TIME VIOLATION" or "TIME DEVIATION" the value can be used for further analyses based on actual times. Excluded concentration itself will be listed in the CTR associated with an appropriate flag.

Further details are given in "Noncompartmental Pharmacokinetic / Pharmacodynamic Analyses of Clinical Studies" (6) and "Description of Analytical Transfer Files and PK/PD Data Files" (7).

## 7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Only descriptive statistics are planned for this section of the report. This will be based on the TS. Data will be summarised by treatment group for SRD part and treatment sequence for FE part and in total.

## 7.2 CONCOMITANT DISEASES AND MEDICATION

Only descriptive statistics are planned for this section of the report. This will be based on the TS.

Concomitant diseases and non-drug therapies will be coded according to the most recent version of the coding system of the Medical Dictionary for Drug Regulatory Activities (MedDRA). Concomitant medication will be coded according to the most recent version of the World Health Organization - Drug Dictionary (WHO-DD). The coding version number will be displayed as a footnote in the respective output.

In the remaining document “therapy” will be used for non-drug therapies and concomitant medications.

**Section 7.2.5 of the CTP:**

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

The diagnoses and medications will be listed. Subjects without any concomitant diagnoses or concomitant therapies will be marked with a “No” in the respective column.

The relevance of concomitant therapies to the evaluation of PK data 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 and described in the CTR.

## 7.4 PRIMARY OBJECTIVE ANALYSIS

Independent of the main objectives stated in the CTP, this section describes further details of the primary endpoint analyses outlined in the CTP.

### 7.4.1 Main analysis

SRD part

For the description of the primary endpoint, the safety and tolerability of BI 3000202, please refer to Section 7.8.1.

FE part

**Section 7.2.2 of the CTP:**

*The statistical model used for the analysis of the primary endpoints as specified in Section 2.1.2 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: sequence, subjects within sequences, period and treatment. The effect 'subjects within sequences' will be considered as random, whereas the other effects will be considered as fixed. The model is described by the following equation:*

$y_{ijkm} = \mu + \zeta_i + s_{im} + \pi_j + \tau_k + e_{ijkm}$, *where*

$y_{ijkm}$ = *logarithm of response measured on subject m in sequence i receiving treatment k in period j,*

$\mu$ = *the overall mean,*

$\zeta_i$ = *the* $i^{th}$ *sequence effect, i = 1, 2,*

$s_{im}$ = *the effect associated with the* $m^{th}$ *subject in the* $i^{th}$ *sequence, m = 1, 2, ..., $n_i$*

$\pi_j$ = *the* $j^{th}$ *period effect, j = 1, 2,*

$\tau_k$ = *the* $k^{th}$ *treatment effect, k = 1, 2 (i.e. R, T)*

$e_{ijkm}$ = *the random error associated with the* $m^{th}$ *subject in sequence i who received treatment k in period j.*

*where* $s_{im} \sim N(0, \sigma_B^2)$ *i.i.d.,* $e_{ijkm} \sim N(0, \sigma_W^2)$ *i.i.d. and* $s_{im}$, $e_{ijkm}$ *are independent random variables.*

*Point estimates for the ratios of the geometric means (T/R) for the primary endpoints 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 Company Standard Displays (CSD) macros (10) based on the PKS.

[redacted]

## 7.5 SECONDARY OBJECTIVE ANALYSIS

Independent of the main objectives stated in the CTP, this section describes further details of the secondary endpoint analyses.

### 7.5.1 Key secondary objective analysis

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

### 7.5.2 Secondary objective analysis

**Section 7.2.3 of the CTP:**

*SRD part*

*Primary analyses:*

*The secondary endpoints (refer to Section 2.1.3) will be analysed descriptively. Analyses will be performed for the parent drug.*

[redacted]

*FE part*

*The secondary endpoint (refer to Section 2.1.3) will be calculated according to the relevant SOP of the Sponsor and will be assessed statistically using the same methods as described for the primary endpoints.*

[redacted]

## 7.7 EXTENT OF EXPOSURE

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

## 7.8 SAFETY ANALYSIS

All safety analyses will be performed on the treated set.

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 using the most recent version of MedDRA. The coding version number will be displayed as a footnote in the respective output.

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" (11) and "Analysis and Presentation of AE data from clinical trials" (12) will be applied.

The analysis of AEs will be based on the concept of treatment emergent AEs. That means that all AEs will be assigned to "screening", "on-treatment" or "follow-up" phases as defined in Section 6.1. AEs will be analysed based on actual treatments, as defined in Tables 6.1: 1 and 6.1: 2.

An overall summary of AEs will be presented. This overall summary will comprise summary statistics for the class of adverse events of special interest (AESIs).

**Section 5.2.6.1.4 of the CTP**

*The following are considered as AESIs:*

- *Potential severe DILI*
  *A potential severe Drug Induced Liver Injury (DILI) that requires follow-up is defined by the following alterations of hepatic laboratory parameters:*
  - *An elevation of AST (aspartate aminotransferase) and/or ALT (alanine aminotransferase) ≥3-fold ULN combined with an elevation of total bilirubin ≥2-fold ULN measured in the same blood sample, or in samples drawn within 30 days of each other, or*
  - *Aminotransferase (ALT, and/or AST) elevations ≥10-fold ULN*

  *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 ISF. 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.*

According to ICH E3 (13), in addition to Deaths and serious AEs, "other significant" AEs need to be listed in the clinical trial report. These will be any non-serious AE that led to an action taken with study drug (e.g. discontinuation or dose reduced or interrupted).

The frequency of subjects with AEs will be summarised by treatment, primary system organ class (SOC) and preferred term (PT). Separate tables will be provided for subjects with SAEs, for subjects with drug-related AEs, for subjects with drug-related serious adverse events and for subjects with AESIs. In addition, the frequency of subjects with AEs will be summarised by treatment, worst intensity, primary SOC and PT.

The system organ classes will be sorted alphabetically, PTs will be sorted in descending order by frequency (within SOC).

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 PT. The frequency of subjects with SAEs will also be summarised.

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

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

### 7.8.2 Laboratory data

The analyses of laboratory data will be descriptive in nature and will be based on BI standards "Handling, Display and Analysis of Laboratory Data" (14). Analyses will be based on normalised values, which means transforming to a standard unit and a standard reference range. The original values will be analysed if the transformation into standard unit is not possible for a parameter.

Laboratory data will be analysed qualitatively via comparison of laboratory data to their reference ranges. Values outside the reference range 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 (checked 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

The analyses of vital signs (blood pressure, pulse rate) will be descriptive in nature. Descriptive statistics of vital signs over time and for the difference from baseline (see Section 6.7) will be provided. In addition, the time profiles of median and (min, max) will be displayed graphically by treatment.

Clinically relevant findings in vital signs data will be reported as baseline conditions (prior to first administration of study treatment) or as AEs (after first administration of study treatment) if judged clinically relevant by the investigator, and will be analysed as such.

### 7.8.4 ECG

SRD part

**Continuous safety ECG monitoring (by investigator)**

Clinically relevant abnormal findings will be reported as adverse events.

No separate listing or analysis of continuous ECG monitoring will be prepared.

**12-lead ECG**

Abnormal findings will be reported as baseline conditions (at screening) or as AEs (during the trial) if judged clinically relevant by the investigator.

All evaluations of ECG data will be based on the TS, [redacted].

Listing of individual data

For all quantitative endpoints, listings of individual data will be shown in Appendix 16.2. For QTcB and RR, only listings will be provided. Occurrences of notable findings will be flagged.

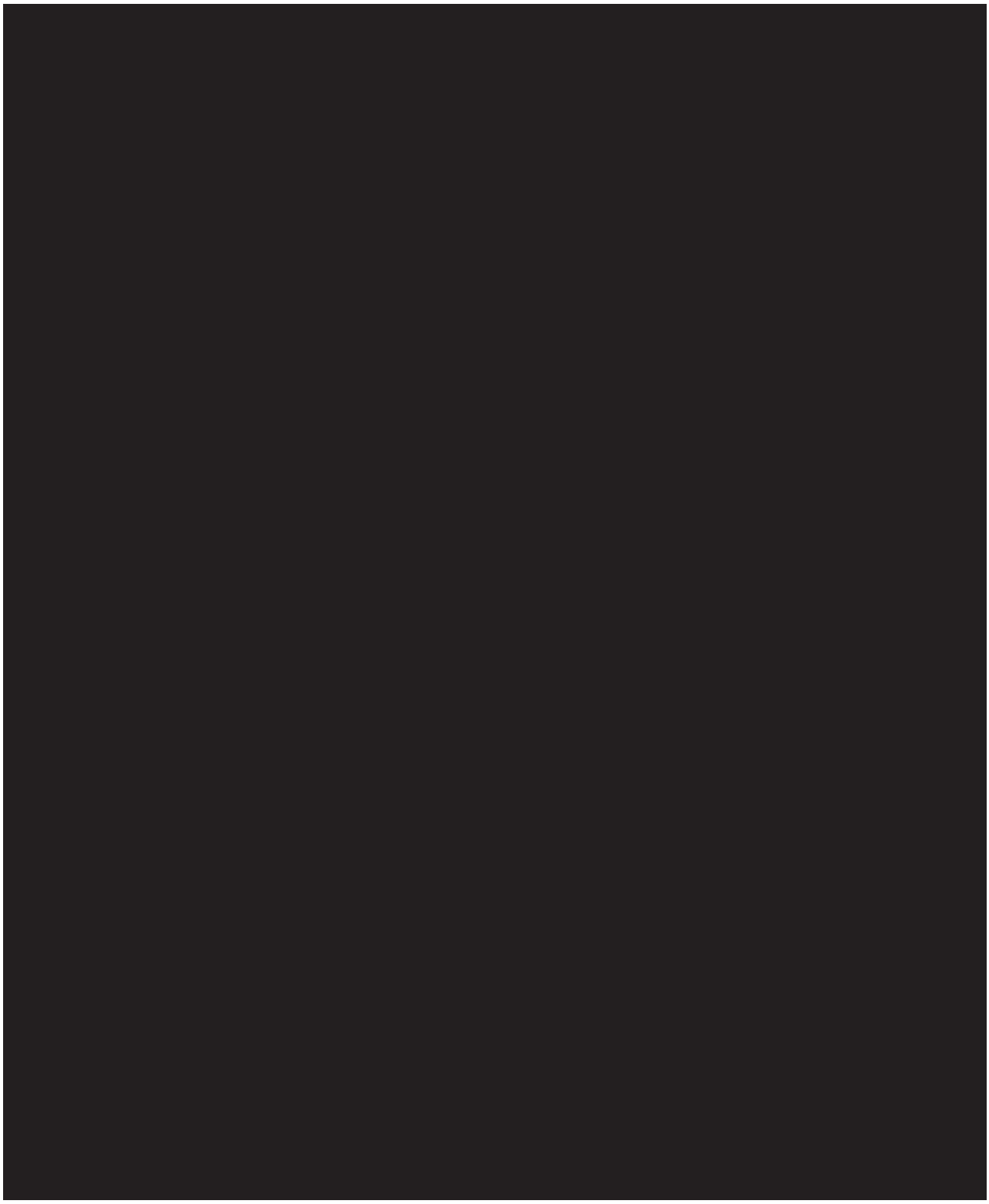
Categorical endpoints

For the categorical endpoints, frequency tables will be provided.

For all subjects with any notable finding in ECG intervals, a separate listing will be created as end-of-text display (based on the same display template as in Appendix 16.2), and the corresponding time profiles will be shown.

Quantitative endpoints

Descriptive statistics (N, mean, SD, min, median, max) will be provided for the absolute values and changes from baseline over time of QTcF, HR, QT, PR and QRS. The time profiles of mean and SD for the changes from baseline on treatment will be displayed graphically by treatment.



FE part

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.

## 7.9 OTHER ANALYSIS

### 7.9.3 Physical examination

Physical examination findings will be reported as relevant medical history/baseline condition (i.e., a condition already existent before intake of trial drug) or as AE and will be summarised as such.

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

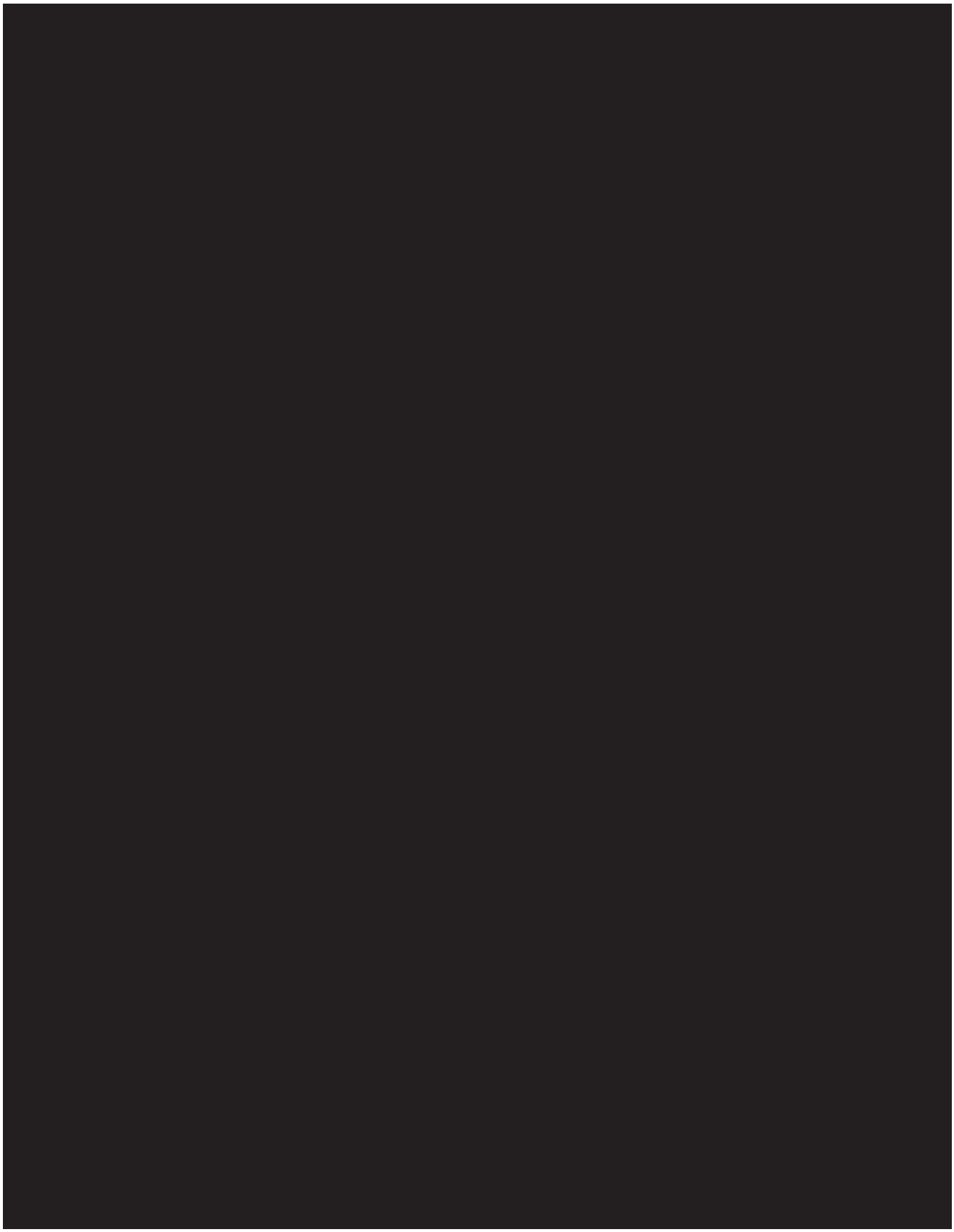
# 8. TIMEPOINT OF RELEASE OF TREATMENT INFORMATION

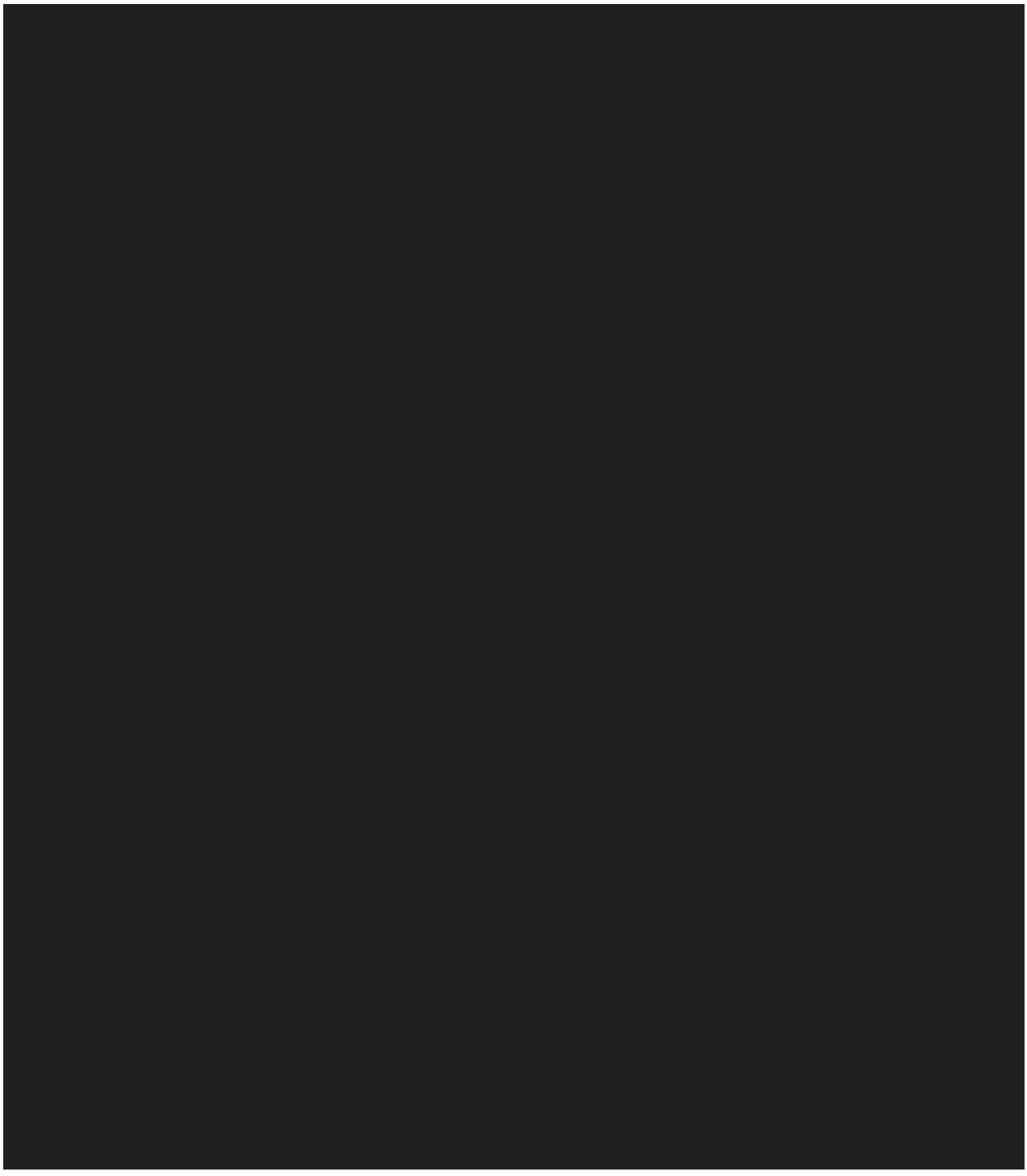
The treatment information will be loaded into the trial database at trial initiation, i.e., the database will be handled open-label in accordance with the CTP.

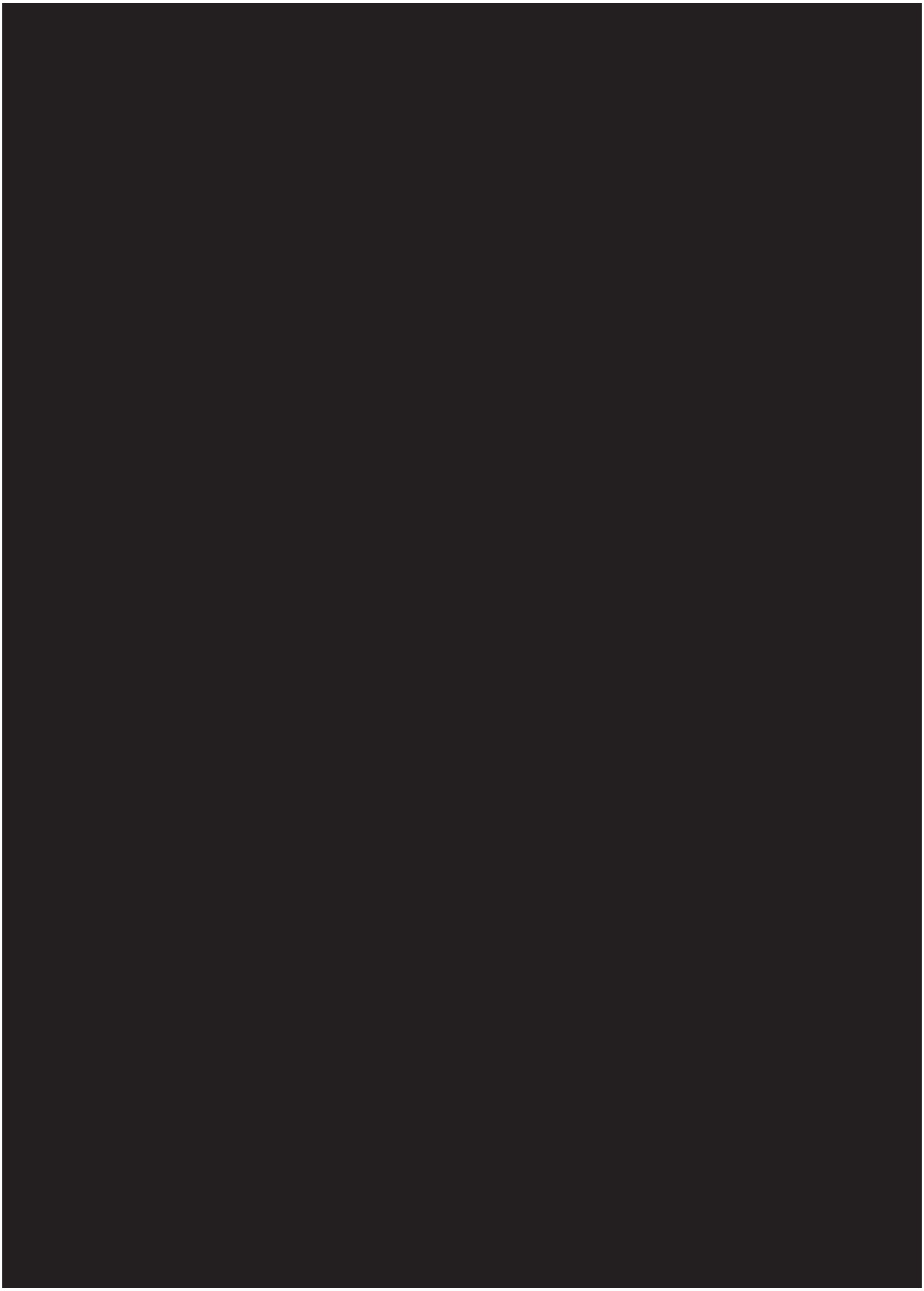
# 9. REFERENCES


| | |
|---|---|
| 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 | *BI-VQD-12045_40-413:* "Identify and Manage Important Protocol Deviations (iPD)", current version, group / owning department "Med Clinical Development & Operations", DMS for controlled documents. |
| 3 | *KM Asset BI-KMED-BDS-TMP-0059*: "iPD specification document (sdtm-dv-domain-specification)", template, current version, Group "Clinical Operations", KMED. |
| 4 | *BI-VQD-12682-S-G_50-415_AD-03:* "Clinical Trial Analysis Decision Log (template)", current version, group / owning department "Med Biostatistics & Data Sciences", DMS for controlled documents. |
| 5 | *KM Asset BI-KMED-BDS-HTG-0035:* "Handling of missing and incomplete AE dates", current version; KMED |
| 6 | *KM Asset BI-KMED-TMCP-MAN-0014:* "Noncompartmental Pharmacokinetic / Pharmacodynamic Analyses of Clinical Studies", current version; KMED |
| 7 | *KM Asset BI-KMED-TMCP-MAN-0010:* "Description of Analytical Transfer Files, PK/PD Data Files and ADA files", current version; KMED |
| 8 | *KM Asset BI-KMED-BDS-HTG-0045:* "Standards for Reporting of Clinical Trials and Project Summaries", current version; KMED |
| 9 | *KM Asset BI-KMED-TMCP-OTH-0003:* "Graphs and Tables for Clinical Pharmacokinetics and Pharmacodynamic Noncompartmental Analyses", current version; KMED |
| 10 | *KM Asset BI-KMED-BDS-HTG-0023:* "Standard Table Shells for Inferential and Descriptive Analyses - Company Standard Displays (CSD-Catalogue)", current version; KMED |
| 11 | *KM Asset BI-KMED-BDS-HTG-0041:* "Analysis and Presentation of Adverse Event Data from Clinical Trials – Display Template", current version; KMED |
| 12 | *KM Asset BI-KMED-BDS-HTG-0066:* "Analysis and Presentation of AE data from clinical trials", current version; KMED |
| 13 | *CPMP/ICH/137/95*: "Structure and Content of Clinical Study Reports", ICH Guideline Topic E3; Note For Guidance on Structure and Content of Clinical Study Reports, current version, EMA webpage. |
| 14 | *KM Asset BI-KMED-BDS-HTG-0042:* "Handling, Display and Analysis of Laboratory Data", current version; KMED |

| | |
|---|---|
| 15 | Garnett C, Bonate PL, Dang Q, Ferber G, Huang D, Liu J, et al. *Scientific white paper on concentration-QTc modeling. J Pharmacokinet Pharmacodyn.* 2018. 45(3): 383-397. [R18-0143] |







# 11. HISTORY TABLE

Table 11: 1 History table

| Version | Date (DD-MMM-YY) | Author | Sections changed | Brief description of change |
|---|---|---|---|---|
| 1.0 | **15-DEC-23** | [redacted] | None | This is the final TSAP. |