TRIAL STATISTICAL ANALYSIS PLAN

c34271221-01

BI Trial No.:	1402-0015
Title:	A phase I, open-label trial to investigate metabolism and pharmacokinetics of a single dose of [^{14}C] BI 1358894 administered as oral solution (Part 1) and multiple doses of BI 358894 administered as film-coated tablets (Part 2) in healthy male volunteers Final protocol [c31118084-01]
Investigational Product(s):	BI 1358894
Responsible trial statistician(s):	[redacted] Phone: [redacted] Fax: [redacted]
Date of statistical analysis plan:	11 MAR 2021 SIGNED
Version:	1

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2. LIST OF ABBREVIATIONS

Term	Definition / description
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC_{0-24}	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 to 24
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
$AUC_{\tau,ss}$	Area under the concentration-time curve of the analyte in plasma at steady state over a uniform dosing interval τ
BI	Boehringer Ingelheim
BP	Blood pressure
C_{max}	Maximum measured concentration of the analyte in plasma
$C_{max,ss}$	Maximum measured concentration of the analyte in plasma at steady state
C-SSRS	Columbia-Suicide Severity Rating Scale
CV	Arithmetic coefficient of variation
fe_{0-t2}	Fraction of administered drug excreted unchanged over the time interval from 0 to t_2
gCV	geometric coefficient of variation
gMean	Geometric mean
PKS	Pharmacokinetic parameter set
PR	Pulse rate
RAGe	Report appendix generator
REP	Residual Effect Period
RPM	Report Planning Meeting
SD	Standard deviation
TS	Treated set
ULN	Upper limit of normal range

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 CTP, and to include detailed procedures for executing the statistical analysis of the primary variables and other data.

This TSAP assumes familiarity with the 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.

The trial consists of two parts. The analyses of both parts (Part 1 and Part 2) are described in the TSAP.

Study data as collected in the eCRF will be stored in a trial database within the RAVE EDC system. All study data also including external data will then be uploaded to the CDR data warehouse.

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

PK parameters will be calculated using Phoenix WinNonlin™ software (version Phoenix 6.3, [redacted]).

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 CTP.

5. ENDPOINTS

5.1 PRIMARY ENDPOINTS

Primary endpoints for Part 1 are the PK endpoints of BI 1358894 as defined in **CTP Section 2.1.2:**

- *Mass balance recoveries of [^{14}C] BI 1358894 total radioactivity in urine and faeces after single oral dose*
- *Amount of radioactivity excreted as a percentage of the administered dose (fe_{0-t2}) for urine and faeces*

No primary endpoint is defined for Part 2.

5.2 SECONDARY ENDPOINTS

5.2.1 Key secondary endpoint

Not applicable.

5.2.2 Secondary endpoints

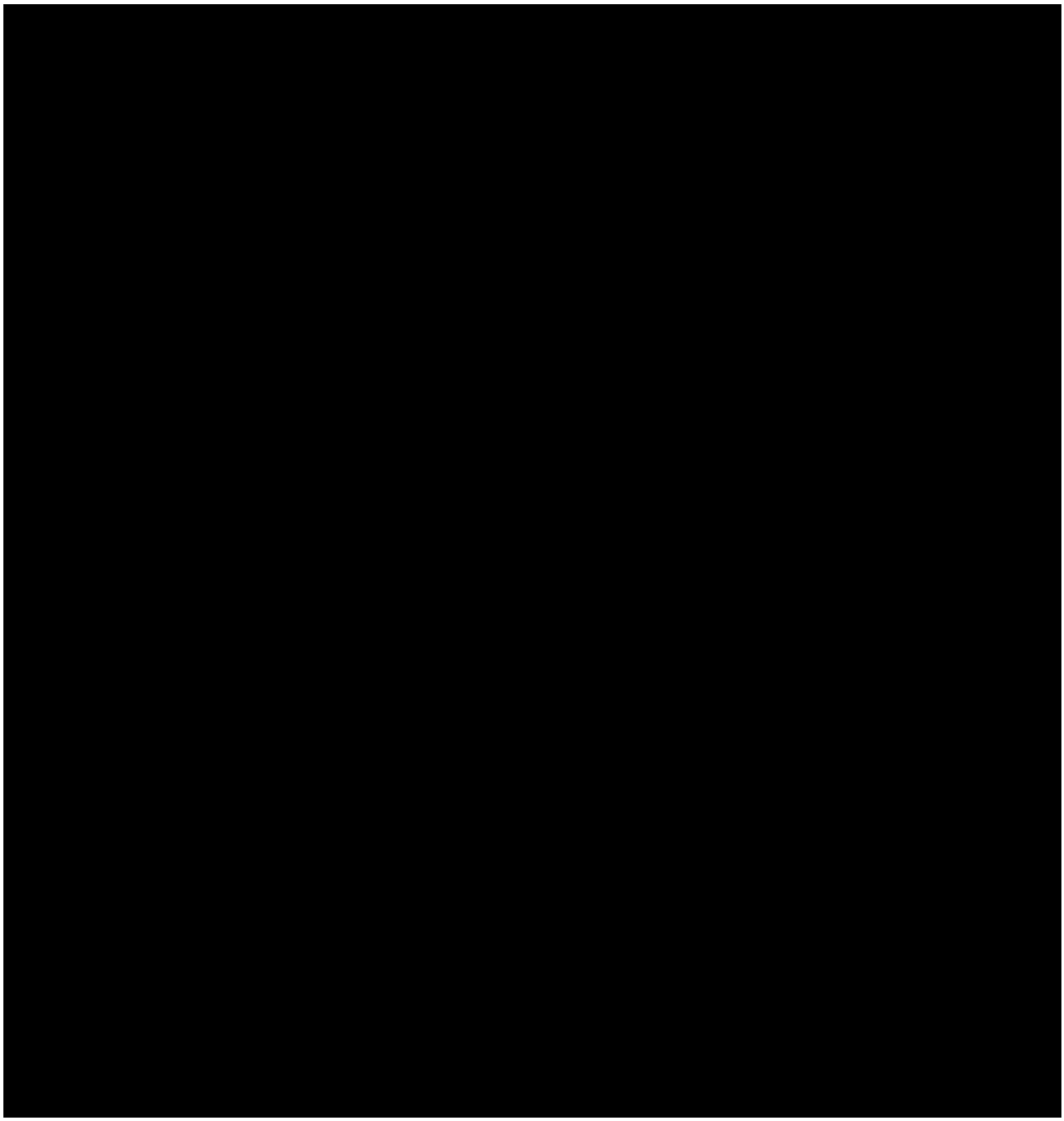
For Part 1, the secondary PK endpoints will be determined for total [^{14}C] BI 1358894 and BI 1358894 after single dose administration, as defined in **Section 2.1.3 of the CTP**:

- *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)*
- *C_{max} (maximum measured concentration of the analyte in plasma)*

For Part 2, the secondary PK endpoints will be determined for BI 1358894, as defined in **Section 2.1.3 of the CTP**:

- *AUC_{0-24} (area under the concentration-time curve of the analyte in plasma over the time interval from 0 to 24)*
- *C_{max} (maximum measured concentration of the analyte in plasma)*
- *$AUC_{\tau,ss}$ (area under the concentration-time curve of the analyte in plasma at steady state over a uniform dosing interval τ)*
- *$C_{max,ss}$ (maximum measured concentration of the analyte in plasma at steady state over a uniform dosing interval τ)*

[redacted]



6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENTS

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

The trial consists of Part 1 and Part 2 and the two parts will be analysed separately.

In Part 1, subjects are planned to be treated with a single dose of BI 1358894 mixed with [14C] BI 1358894.

For statistical analyses of AEs, safety laboratory data, and vital signs the following separate analysis phases will be defined for each subject:

Table 6.1: 1 Part 1 - Analysis phases for statistical analysis of AEs, safety laboratory data and vital signs

Study analysis phase	Label	Start (inclusive)	End (exclusive)
Screening	**Screening**	Date of informed consent	Date/time of administration of study drug
On-treatment	**BI 1358894 SD**	Date/time of administration of study drug	Date/time of administration of study drug + REP (14 days * 24 h)
Follow-up	**F/U BI 1358894 SD**	Date/time of administration of study drug + REP (14 days * 24 h)	12:00 a.m. on day after trial completion date

SD = Single Dose

In Part 2, subjects are planned to be treated with multiple dose of 100 mg BI 1358894 as 2 film-coated tablets once daily (2 tablets x 50 mg, q.d.) from Day 1 to Day 21.

Table 6.1: 2 Part 2 - Analysis phases for statistical analysis of AEs, safety laboratory data and vital signs

Study analysis phase	Label	Start (inclusive)	End (exclusive)
Screening	**Screening**	Date of informed consent	Date/time of first administration of study drug
On-treatment	**BI 1358894 MD**	Date/time of first administration of study drug	Date/time of last administration of study drug + REP (14 days * 24 h)
Follow-up	**F/U BI 1358894 MD**	Date/time of last administration of study drug + REP (14 days * 24 h)	12:00 a.m. on day after trial completion date

MD = Multiple Doses

AE displays in CTR Section 15.3, Appendix 16.1.13.1.8.2 and Appendix 16.1.13.1.8.3 will present results for the on-treatment phase only.

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

6.2 IMPORTANT PROTOCOL DEVIATIONS

Consistency check listings (for identification of deviations from 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 RPM. At this meeting, it will be decided whether a discrepant data value can be used in the analyses or whether it must be corrected in the clinical database. Each protocol deviation must be assessed to determine whether it is an iPD. For definition of iPDs, and for the process of identification of these, refer to the BI reference document "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 decision log. Categories which are considered to be iPDs in this trial are defined in the DV domain. If the data show other iPDs, the definition in the DV domain will be supplemented accordingly by the time of the RPM.

iPDs will be summarized and listed. In the DV domain it is also specified which kind of iPDs could potentially lead to exclusion from which analysis set. The decision on exclusion of subjects from analysis sets will be made at the RPM at the latest after discussing exceptional cases and implications for the analyses.

Non important Covid-19 related protocol deviations will be listed.

6.3 SUBJECT SETS ANALYSED

All entered subjects who received study medication will be included in the safety analysis and in the PK analysis depending on the availability of measurement values, and on their adherence to the CTP.

The following subject sets will be defined for statistical analysis:

- Treated set (TS):
  This subject set includes all subjects entered the study who were documented to have received at least one dose of study drug.

- Pharmacokinetic parameter set (PKS):
  This subject set includes all subjects in the TS who provide at least one primary or secondary PK parameter that was not excluded because of iPDs relevant to the statistical evaluation of PK endpoints as defined in Section 7.3 of the CTP.

The two trial parts (Part 1 and Part 2) will be analysed separately. Therefore, the two analysis sets will be split into TS/PKS of Part 1 and TS/PKS of Part 2.

- The discussion of all exceptional cases and problems and the decisions on the allocation of subjects to analysis sets will be made at latest at the RPM.

Table 6.3: 1 Subject sets analysed

	Subject set	
Class of endpoint	TS	PKS
Disposition	X	
IPDs	X	
Demographic/baseline endpoints	X	
Primary and secondary PK endpoints		X
Further PK endpoints		X
Safety parameters and treatment exposure	X	

[redacted]

6.5 POOLING OF CENTRES

This section is not applicable, because the trial is performed in only one centre.

6.6 HANDLING OF MISSING DATA AND OUTLIERS

Data of screened subjects who were withdrawn from the trial prior to first administration of any study drug will not be reported in the CTR.

Data of subjects who failed to complete all periods of the study (dropouts or withdrawals) will be reported in the CTR as far as their data are available. All withdrawals will be documented and the reason for withdrawal reported in the CTR.

CTP Section 7.5.1: *It is not planned to impute missing values for safety parameters.*

One exception where imputation might be necessary for safety evaluation are AE dates. Missing or incomplete AE dates are imputed according to BI standards (3).

Missing data and outliers of PK data are handled according to BI standards (4) and (5)

CTP Section 7.5.2: *PK parameters that cannot be reasonably calculated based on the available drug concentration-time data will not be imputed.*

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

The last non-missing value determined prior to first BI 1358894 administration will be defined as baseline (in both parts).

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

7. PLANNED ANALYSIS

The format of the listings and tables will follow the BI guideline "Reporting of clinical trials and project summaries" (6)

The individual values of all subjects will be listed. Listings will be sorted by treatment group, subject number and visit (if visit is applicable in the respective listing). AE listings will be sorted by treatment group, subject number and AE onset date (see Section 7.8.1 below for details). The listings will be contained in Appendix 16.2 (SDL) of the CTR.

If not stated otherwise, the data of Part 1 and Part 2 will be analysed separately.

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	3^{rd} quartile
P90	90^{th} 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. Percentages will be rounded to one decimal place. The category missing will be displayed if and only if there actually are missing values. Percentages will be based on all subjects in the respective subject set whether they have non-missing values or not.

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Only descriptive statistics are planned for this section of the CTR.

7.2 CONCOMITANT DISEASES AND MEDICATION

Concomitant diseases will be coded according to the most recent version of MedDRA. Concomitant medication will be coded according to the most recent version of the World Health Organisation – Drug Dictionary. Concomitant non-drug therapies will be coded according to the most recent version of MedDRA.

A medication will be considered concomitant, if it

- is ongoing at the time of first study drug administration, or
- 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.

CTP Section 7.3.4: *Previous and concomitant therapies will be presented per treatment group without consideration of time intervals and treatment periods.*

Only descriptive statistics are planned for this section of the CTR.

7.3 TREATMENT COMPLIANCE

Treatment compliance will not be analyzed as a specific endpoint (cf. Section 5.4.2). Any deviations from complete intake will be addressed in the RPM (cf. Section 6.2) and described in the CTR.

7.4 PRIMARY ENDPOINTS

7.4.1 Primary analysis of the primary endpoint

The primary endpoints of Part 1 will be analysed descriptively (cf. Section 7.3.1 of the CTP).

The analysis is performed according to BI standards (4) and will be based on the PKS.

Exclusion of PK parameters (applies to Part 1 and Part 2)

The ADS ADPP contains column variables APEXC and APEXCO indicating inclusion/exclusion (APEXC) of a PK parameter and an analysis flag comment (APEXCO). All analyses based on the PKS are based on PK parameter values which are not flagged for exclusion, i.e. with APEXC equal to "Included".

Exclusion of plasma/urine concentrations (applies to Part 1 and Part 2)

The ADS ADPC (PK concentrations per time-point or per time-interval) contains column variables ACEXC or 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 only; the value is included for all other analyses. 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" (4) and "Description of Analytical Transfer Files and PK/PD Data Files" (5).

7.4.2 Sensitivity analysis, subgroup analysis, exploratory analysis of the primary endpoints

Not applicable.

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 CTP.

7.5.2 Secondary endpoints

Secondary PK endpoints of both parts will be assessed descriptively. This will be based on the PKS. The analysis of PK parameters is performed according to BI standards (4).

See Section 7.4.1 of this TSAP for details regarding exclusion of PK parameters and plasma concentrations.

7.7 EXTENT OF EXPOSURE

For Part 1 treatment exposure will only be listed by means of the date and time of drug administration

For Part 2 descriptive statistics are planned for this section of the report.

7.8 SAFETY ANALYSIS

All safety analyses will be performed on the TS.

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. All analyses of AEs will be based on the number of subjects with AEs and not on the number of AEs.

For further details on summarization of AE data, please refer to "Analysis and Presentation of Adverse Event Data from Clinical Trials" (7) and "Handling of missing and incomplete AE dates" (3).

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

An overall summary of AEs will be presented. This overall summary will comprise summary statistics for the class of AESIs.

CTP Section 5.2.6.1.3: *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*

The investigator had to classify on the eCRF whether an observed AE was an AESI or not.

According to ICH E3 (8) in addition to deaths and SAEs, "other significant" AEs need to be listed in the CTR. These will be any non-serious adverse event that led to an action taken with study drug (e.g. discontinuation or dose reduced or interrupted).

The frequency of subjects with AEs will be summarised by treatment, primary SOC and preferred term. AEs which were considered by the investigator to be drug related will be summarised separately. AEs will also be summarized by maximum intensity. Separate tables will be provided for subjects with SAEs and subjects with AESIs.

The SOCs will be sorted by total frequency; preferred terms will be sorted by total 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 preferred term. 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.

For support of lay summaries, the frequency of subjects with drug-related SAEs will be summarized by treatment, primary SOC and preferred term.

If the subject reports headaches during the treatment period further information about the duration of headache, location, characteristics, and signs and symptoms were recorded. These data will be summarized with descriptive statistics. Headache episodes with onset during screening and Follow-up phase will be listed only.

7.8.2 Laboratory data

The analyses of laboratory data will be descriptive in nature and will be based on BI standards "Display and Analysis of Laboratory Data" (9).

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.

Descriptive statistics of laboratory values over time and for the difference from baseline (see Section 6.7) will be provided for the on-treatment phase. Frequency tables of changes between baseline and last value on treatment with respect to the reference range will be presented. Qualitative urinalysis results will be listed only.

CTP Section 7.3.4: *Values outside the reference range as well as values defined as possibly clinically significant will be highlighted in the listings*.

Unscheduled measurements of laboratory 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. Descriptive statistics 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).

Possibly clinically significant abnormal laboratory values are only those identified either in the Investigator's comments or at the RPM at the latest. It is the Investigator's responsibility to decide whether a lab value is clinically significant abnormal or not. Standard or project-specific rules for flagging clinically significant values in an automated manner will not be applied in this study.

Clinically relevant findings in laboratory 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 analyzed as such.

7.8.3 Vital signs

The analyses of vital signs (blood pressure and 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.

Unscheduled measurements of vital signs will be assigned to planned time points as follows:

- Unscheduled measurements prior to the first scheduled measurement within a visit will be assigned to the planned time point of the first scheduled measurement of that visit.

- Other unscheduled measurements will be assigned to the planned time point of the previous, most recent scheduled measurement.

Unscheduled measurements of vital signs will be used in calculation of descriptive statistics by planned time point as follows:

- If an unscheduled measurement is the last available off-treatment value before study drug administration, this unscheduled measurement will be used in the statistical analysis as baseline (as this is in accordance with the definition of baseline, cf. Section 6.7).

- At post-baseline time points, descriptive statistics by planned time point will be calculated based on the last value of the subject within 20 minutes of the scheduled measurement of that planned time point. The rationale for this rule is that these measurements are interpreted to be repeat measurements of the scheduled measurement (e.g. for confirmation of a particular value).

  An unscheduled measurement more than 20 minutes after the time of the scheduled measurement of that planned time point will be listed, but will not be used in calculation of descriptive statistics. These measurements are interpreted as off-schedule vital signs measurements, taken for other reasons.

  If an unscheduled measurement is taken at exactly the same time as the scheduled measurement, this unscheduled measurement will be considered to be done after the scheduled measurement, and will potentially qualify to be the "last value of the subject within 20 minutes of the scheduled measurement of that planned time point".

  If the time of measurement is missing for a scheduled measurement, the scheduled measurement will be used in calculation of descriptive statistics (as time difference between scheduled and unscheduled cannot be assessed).
  If the time of measurement is missing for an unscheduled measurement, this measurement will be listed but will be ignored for the calculation of descriptive statistics.

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 analyzed as such.

7.8.4 ECG

Relevant ECG findings 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.

7.8.5 Others

Suicidality assessment

Suicidality monitoring will be performed as described in Section 5.2.5.1 of the CTP, results will only be listed. No further analysis will be prepared. Findings will also be reported as AEs.

Physical and neurological examinations

Physical examination findings including neurological examination finding 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 physical examination findings 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_1.0:* "Identify and Manage Important Protocol Deviations (iPD)", current version; IDEA for CON
3.	*KM Asset BI-KMED-BDS-HTG-0035:* "Handling of missing and incomplete AE dates", current version; KMED
4.	*KM Asset BI-KMED-TMCP-MAN-0014*: "Noncompartmental PK/PD Analyses of Clinical Studies", current version; KMED
5.	*KM Asset BI-KMED-TMCP-MAN-0010:* "Description of Analytical Transfer Files, PK/PD Data files and ADA files", current version; KMED
6.	*KM Asset BI-KMED-BDS-HTG-0045:* "Standards for Reporting of Clinical Trials and Project Summaries", current version; KMED
7.	*KM Asset BI-KMED-BDS-HTG-0041:* "Analysis and Presentation of Adverse Event Data from Clinical Trials", current version; KMED
8.	*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
9.	*KM Asset BI-KMED-BDS-HTG-0042: "Display and Analysis of Laboratory Data", current version; KMED*

10. HISTORY TABLE

Table 10: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
1	**11-MAR-21**	[redacted]	None	This is the final TSAP