TRIAL STATISTICAL ANALYSIS PLAN

c30677999-01

BI Trial No.:	1386-0022
Title:	A Phase I, open-label, Positron Emission Tomography study in healthy male subjects to explore the inhibition of monoamine oxidase B in the brain after multiple oral doses of BI 1467335 (non-randomized, open-label, parallel-group study) Revised protocol 2.0
Investigational Product:	BI 1467335
Responsible trial statistician:	Phone: Fax:
Date of statistical analysis plan:	17 JAN 2020 SIGNED
Version:	1

1. TABLE OF CONTENTS

LIST OF TABLES

2. LIST OF ABBREVIATIONS

Term	Definition / description
ADME	Absorption, distribution, metabolism, and excretion
ADS	Analysis data set
AE	Adverse Event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
$AUC_{0\text{-}24,N}$	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 to 24 h
BI	Boehringer Ingelheim
CDR	Clinical Data Repository
C_{max}	Maximum measured concentration of the analyte in plasma
$C_{max,N}$	Maximum measured concentration of the analyte
CRF	Case report form
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
CV	Arithmetic coefficient of variation
DNA	Desoxyribonucleic acid
ECG	Electrocardiogram
EDC	Electronic data capture
eCRF	Electronic case report form
gCV	geometric coefficient of variation
gMean	Geometric mean
ICH	International Conference On Harmonisation
iPD	Important protocol deviation
IQRMP	Integrated quality and risk management plan
MAO-B	Monoamine oxidase B

Term	Definition / description
MedDRA	Medical Dictionary For Regulatory Activities
NIMP	Non-investigational medicinal product
PD	Pharmacodynamic(s)
PDS	Pharmacodynamic Set
PET	Positron emission tomography
PETS	PET set
PK	Pharmacokinetic(s)
PKS	Pharmacokinetic parameter set
RAGe	Report appendix generator
ROI	Region of interest
SAE	Serious adverse event
SD	Standard Deviation
SOC	System Organ Class
TAC	Time activity curve
TS	Treated set
TSAP	Trial Statistical Analysis Plan
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 protocol, and to include detailed procedures for executing the statistical analysis of the primary and secondary variables and other data.

This 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, randomization.

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 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).

PK parameters will be calculated by means of noncompartmental analysis using Phoenix WinNonlin™ software (current version Phoenix 6.3 or higher, Certara USA Inc., Princeton, NJ, USA). Outputs for the CTR will be generated using SAS™ (current Version 9.4, by SAS Institute Inc., Cary, NC, USA).

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

All analyses as planned in the CTP will be performed and are described in more detail in this TSAP.

In addition, a pharmacodynamic set (PDS) has been introduced for analysis of MAO-B inhibition in platelet rich plasma.

5. ENDPOINTS

5.1 PRIMARY ENDPOINT

The primary endpoint is measured by PET scans and is defined in Section 2.1.2 of the CTP:

- *% reduction in MAO-B availability upon treatment with BI 1467335 on the last treatment day (Day 28 for the 10 mg dose group and Day 42 for the 3 mg dose group) compared to baseline.*

The % reduction in MAO-B availability refers to the whole brain.

5.2 SECONDARY ENDPOINTS

5.2.1 Key secondary endpoints

Not applicable.

5.2.2 Secondary endpoints

CTP, Section 2.1.3:

The following secondary endpoints will be determined:

- *% reduction in MAO-B availability upon treatment with 10 mg BI 1467335 on Day 14 compared to baseline.*
- *% reduction in MAO-B availability upon treatment with 3 mg BI 1467335 on Day 28 compared to baseline.*
- *MAO-B inhibition in platelet rich plasma at Day 14 (10 mg dose group only), Day 28, and Day 42 (3 mg dose group only) compared to baseline.*
- $C_{max,N}$ *(maximum measured concentration of the analyte) and* $AUC_{0\text{-}24,\,N}$ *(area under the concentration-time curve of the analyte over the time interval from 0 to 24 h) on Day 14 (10 mg dose group only), Day 28 and Day 42 (3 mg dose group only).*

The % reduction in MAO-B availability refers to the whole brain.

5.3.3 Safety and Tolerability endpoints

Safety and tolerability of BI 1467335 will be assessed based on parameters defined in Section 2.2.2.2 of the CTP:

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

5.4.1 Demographic and other baseline characteristics

The following demographic variables and baseline characteristics will be reported in the eCRF: Sex, ethnicity, race, birth year, age, smoking status, alcohol history, height, weight, relevant medical history and concomitant therapy.
Body mass index will be calculated as weight [kg] / height $[m]^2$.

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.

Each subject is planned to be treated daily over a period of 4 or 6 weeks with BI 1467335 film-coated tablets:

Table 6.1: 1 Dosage and treatment schedule

Substance	Formulation	Unit strength	Dosage
BI 1467335	Film-coated tablet	10 mg	2 tablets (5 mg) qd for 28 days
BI 1467335	Film-coated tablet	3 mg	3 tablets (1 mg) qd for 42 days

In addition to the two investigational treatments stated above, the following non-investigational PET tracer will be used:

- PET tracer (NIMP)
  ≤ 100 µg [^{11}C]-L-deprenyl-D2 as solution for injection for a predose assessment and about 1,5 h after dosing of BI 1467335 on Day 14 (10 mg dose group only), Day 28 and Day 42 (3 mg dose group only).

For statistical analyses of AEs, the following separate analysis phases will be defined for each subject:

Table 6.1: 2 Analysis phases for statistical analysis of AEs

Study analysis phase	Label	Start	End
Screening	**Screening**	Date of informed consent	Date/time of first administration of BI 1467335
On treatment	**BI 1467335**	Date/time of first administration of BI 1467335	12:00 a.m. on day after subject's end of study participation date.

In CTR Section 15, AE displays will be presented for the on-treatment phase only.

In CTR Section 15, AE tables, the following totals will be provided in addition:

- "**Total on treatment**", defined as the total over all on-treatment phases

AEs during the screening phase will be listed in CTR Section 16.2 but not tabulated.

Statistical analyses of safety laboratory tests and vital signs will be conducted with clear differentiation between baseline (cf. Section 6.7) and on-treatment measurements.

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 Report Planning Meeting. 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 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 minutes of the Report Planning Meeting 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 Report Planning Meeting.

iPDs will be summarized and listed. Table 6.2: 1 below specifies which kind of iPDs could potentially lead to exclusion from which analysis set. The decision on exclusion of patients from analysis sets will be made at the latest at the Report Planning Meeting, after discussion of exceptional cases and implications for analyses.

Table 6.2: 1 Handling of iPDs

iPD code	iPD Category & Brief Description	Excluded from which analysis set
iPD B1	Informed consent not available/not done	All
iPD B2	Informed consent too late	None
iPD A1	Inclusion Criteria not met	PKS, PDS, PETS
iPD A2	Exclusion Criteria met	PKS, PDS, PETS
iPD C1	Randomisation not followed	Not applicable
iPD C2	Non-compliance	PKS, PDS, PETS
iPD C3	Incorrect intake of trial medication	PKS, PDS, PETS
iPD D1	Prohibited medication use	PKS, PDS, PETS
iPD D2	Improper washout of concomitant medication	PKS, PDS, PETS
iPD E1	Certain violations of procedures used to measure primary or secondary data	PKS, PDS, PETS
iPD F1	Certain violations of time schedule used to measure primary or secondary data	PKS, PDS, PETS
iPD G1	PDs affecting safety and rights of subjects	PKS, PDS, PETS

6.3 SUBJECT SETS ANALYSED

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 study drug. 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 and was not excluded due to a protocol deviation relevant to the evaluation of PK or due to PK non-evaluability (as specified in the following subsection ‘Pharmacokinetics’). Thus, a subject will be included in the PKS, even if he/she contributes only one PK parameter value to the statistical assessment. Analyses of PK parameters will be based on the PKS.
- Pharmacodynamic analysis set (PDS): This set includes all subjects in the treated set (TS) who provide at least one post-baseline measurement of MAO-B inhibition in

platelet rich plasma which were not excluded due to a protocol deviation relevant to the evaluation of PD.

- PET set (PETS): This set includes all subjects in the treated set (TS) who provide at least one PET scan at baseline and one on-treatment, i.e. the reduction in MAO-B availability can be calculated for at least one post-baseline measurement (either 14 or 28 or 42 days)

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

Table 6.3: 1 Subject sets analyzed

	Subject set			
Class of endpoint	TS	PETS	PDS	PKS
Primary endpoint		X		
Secondary MAO-B availability from PET scan endpoints		X		
Secondary MAO-B inhibition in platelet rich plasma endpoint			X	
Secondary PK endpoints				X
Safety parameters & treatment exposure	X			
Demographic/baseline endpoints	X			
Important protocol deviations	X			

6.5 POOLING OF CENTRES

This section is not applicable, because the study 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 investigational study drug will not be reported in the CTR.

Data of subjects who drop out or withdraw from the trial 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.

CTP Section 7.5.2: *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 data are handled according to BI standards (4).

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

A separate baseline is defined for each study treatment. The baseline is the last available value before first administration of BI 1467335.

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

Unscheduled measurements of laboratory data or 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.
Descriptive statistics of laboratory data will be calculated by planned time point based on the worst value of the subject at that planned time point (or assigned to that planned time point).
For vital signs, descriptive statistics will be calculated by planned time point based on the last value of the subject at that planned time point (or assigned to that planned time point).

7. PLANNED ANALYSIS

The format of the listings and tables will follow the standards defined in the BI standards with the exception of those generated for PK-calculations (6).

The individual values of all subjects will be listed. Listings will be sorted by treatment, subject number and visit (if visit is applicable in the respective listing). AE listings will be sorted by assigned treatment (see Section 7.8.1 below for details). The listings will be contained in Appendix 16.2 (SDL) 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 PD parameters the CV (arithmetic coefficient of variation) will additionally be calculated.

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 report.

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.

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

7.4 PRIMARY ENDPOINT

CTP Section 7.3.1: *Image analysis will be used to generate the outcome parameter for the PET data (proportional to the target availability at each PET scan), using the PET emission and the metabolite corrected arterial plasma input function, within an appropriate kinetic model. Tissue time-activity curves (TACs) for each region of interest (ROI) will be analysed together with arterial blood data, processed to generate metabolite-corrected arterial plasma input function curves. Kinetic modelling techniques will then be applied to the input function and TAC data to estimate parameters relating to the level of target availability for each PET scan. For scans following 14, 28 or 42 days of dosing with BI 1467335, fractional occupancy values will be generated for each post-dose PET scan by comparing the outcome parameters for baseline and post-dose scans for a subject (primary endpoint).*

7.4.1 Primary analysis of the primary endpoint

The primary endpoint will be analyzed based on the PETS.

Individual line plots of reduction of MAO-B availability over time by dose group and median reduction of MAO-B availability by dose group over time will be created. Descriptive statistics will be provided.

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

An Emax model will be fitted for plasma concentration against % reduction of MAO-B availability. The analysis will be performed on the PKS.

The model is defined as follows:
% reduction = E0 + Emax*Concentration**N / (Concentration**N+ED50**N),
with E0 (basal effect) being set to 0. Parameters to be estimated are Emax (maximum effect), ED50 (concentration which produces half of Emax) and N (Hill factor).

SAS procedure PROC NLIN will be used for this analysis.

```
PROC NLIN DATA = indata METHOD = marquardt;
PARAMETERS  IMAX = imax.-5 to imax.+5 by 2.5
                    IC50 = ic50.*0.8 to ic50.*1.2 by ic50.*0.1.
                    HILL = 1 to 10 by 3;
MODEL reduct = 0+(IMAX*conc**HILL)/(IC50**HILL+conc**HILL);
RUN;
```

Starting values will use a range for IMAX, IC50 and HILL. The imax starting value will be estimated as the maximum value of MAO-B % reduction across all time points and subjects. This value will be increased and decreased by an absolute 2.5 twice to both sides to get a range of starting values (values above 100 will be set to 100). The HILL factor will be set to 1, 4, 7, and 10. The ic50 starting value will be estimated as the median plasma concentration across all time points and for all subjects. This value will be decreased and increased by a relative 10% twice to both sides to come to an adequate starting value range (values less than 0 will be set to 0).

The Emax model will also be presented graphically.

7.5 SECONDARY ENDPOINTS

7.5.1 Key secondary endpoint(s)

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

7.5.2 (Other) Secondary endpoint(s)

The descriptive analysis of all secondary endpoints referring to MAO-B availability will follow the principles of analysis of the primary endpoint. Where applicable, all time points will be summarized in the same table or figure.

Pharmacodynamic parameters

MAO-B inhibition in platelet rich plasma will be analysed descriptively by department Translational Medicine and Clin. Pharmacology at BI according to BI standards (4) [001-MCS-36-472_RD-01].

Exclusion of measurements of MAO-B inhibition in platelet rich plasma

The ADS ADYC (PD values per time-point or per time-interval) contains column variables ACEXC or ACEXCO indicating inclusion/exclusion (ACEXC) of a measurement and an analysis flag comment (ACEXCO). Exclusion of a measurement 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 measurements. 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.

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).

Pharmacokinetic parameters

Analysis of BI 1467335 concentrations in plasma will be performed by department Translational Medicine and Clin. Pharmacology at BI.

CTR Section 7.3.2: *The secondary endpoints C_{max} and AUC_{0-24} of BI 1467335 will be only evaluated descriptively. The following descriptive statistics will be calculated: N, arithmetic mean, standard deviation, minimum, median, maximum, arithmetic coefficient of variation, geometric mean, and geometric coefficient of variation. 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 3 significant digits in the clinical trial report.*

Exclusion of plasma concentrations

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.

Exclusion of PK parameters

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".

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).

7.6.1 Safety parameters

Safety and tolerability will be analysed as described in Section 7.8 of this TSAP.

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 analysis, multiple AE occurrence data on the eCRF will be collapsed into one event provided that all of the following applies:

- All AE attributes are identical (lower level term, intensity, action taken, therapy required, seriousness, reason for seriousness, relationship, outcome, AESI)
- The occurrences were time-overlapping or time-adjacent (time-adjacency of two occurrences is given if the second occurrence started at most 1 hour after the first occurrence ended)

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

An overall summary of AEs will be presented. This overall summary will comprise summary statistics for the class of other significant AEs according to ICH E3 (7) and for the class of AESIs.

CTP, Section 5.2.6.1.4: "*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 (7), AEs classified as "other significant" need to be reported and will include those non-serious and non-significant AEs
(i) which are marked haematological or other lab abnormalities, or
(ii) which were reported with "action taken = discontinuation" or "action taken = reduced", or
(iii) which lead to significant concomitant therapy as identified by the Clinical Monitor/Investigator at a Medical Quality Review Meeting.

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. Separate tables will also be provided for subjects with SAEs, subjects with AESIs and subjects with other significant AEs (according to ICH E3 (7)). The frequency of subjects with AEs will also be summarised by maximum intensity, primary SOC and preferred term.

The SOCs and preferred terms within SOCs will be sorted by descending frequency over all treatment groups.

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 summarized.

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

7.8.2 Laboratory data

The analyses of laboratory data will be descriptive in nature and will be based on BI standards.

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. Frequency tables of changes between baseline and last value on treatment with respect to the reference range will be presented.

Possibly clinically significant abnormal laboratory values are only those identified either in the Investigator's comments or at the Report Planning Meeting 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.

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. No separate listing or analysis of ECG findings will be prepared.

7.8.5 Others

Physical examination 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. 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:* "Identify and Manage Important Protocol Deviations (iPD) ", current version, BIRDS
3.	*BI-KMED-COPS-TMP-0001:* "iPD log", current version; KMED
4.	*001-MCS-36-472_RD-01*: "Noncompartmental Pharmacokinetic/Pharmacodynamic Analyses of Clinical Studies", current version; IDEA for CON.
5.	*001-MCS-36-472_RD-03:* "Description of Analytical Transfer Files and PK/PD Data Files", current version; IDEA for CON.
6.	*001-MCS 36-472*: "Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics", current version; IDEA for CON.
7.	*CPMP/ICH/137/95*: "Structure and Content of Clinical Study Reports", ICH Guideline Topic E3; Note For Guidance on Structure and Content of Clinical Study Reports, current version

10. HISTORY TABLE

Table 10: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
1	**17-JAN-2020**		None	This is the final TSAP