TRIAL STATISTICAL ANALYSIS PLAN

c38232923-01

BI Trial No.:	1450-0002
Title:	Absolute bioavailability, safety, tolerability, and pharmacodynamics following subcutaneous (SC) injection of 100 mg BI 765080 relative to intravenous (IV) dose in healthy male subjects Including Protocol Amendment 2 [c35408932-03]
Investigational Product:	BI 765080
Responsible trial statistician:	[redacted] Phone: [redacted] Fax: [redacted]
Date of statistical analysis plan:	08-Apr-2022 SIGNED
Version:	1

1. TABLE OF CONTENTS

[redacted]

LIST OF TABLES

2. LIST OF ABBREVIATIONS

Term	Definition / description
AE	Adverse Event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
$AUC_{0-\infty}$	Area under the concentration-time curve of the analyte in serum over the time interval from 0 extrapolated to infinity
AUC_{0-tz}	Area under the concentration-time curve of the analyte in serum over the time interval from 0 to the last quantifiable data point
BI	Boehringer Ingelheim
C_{max}	Maximum measured concentration of the analyte in serum
COVID	Coronavirus disease
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
CV	Arithmetic coefficient of variation
ECG	Electrocardiogram
gCV	geometric coefficient of variation
gMean	Geometric mean
ICH	International Conference On Harmonisation
IPD	Important protocol deviations
MedDRA	Medical Dictionary For Regulatory Activities
[redacted]	
PK	Pharmacokinetics
PKS	Pharmacokinetic parameter analysis set
RAGe	Report appendix generator
RPM	Report Planning Meeting
SAE	Serious adverse event
SD	Standard Deviation
SOC	System Organ Class
TS	Treated set
TSAP	Trial Statistical Analysis Plan

Term	Definition / description
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 revised 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 and its 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 revised 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 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, 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 CTR appendices).

PK parameters will be calculated using Phoenix WinNonlin™ software (version Phoenix 8.1, [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 revised CTP.

In this trial, PK [redacted] are measured in serum. However, at some places in the CTP 'plasma' was written where actually it should be 'serum', e.g. in the definition of PK endpoints.

In this TSAP these passages were corrected, i.e. 'plasma' was replaced by 'serum'.

5. ENDPOINTS

5.1 PRIMARY ENDPOINT

Primary endpoints are PK endpoints of BI 765080, as defined in Section 2.1.2. of the **CTP**:

- *AUC_{0-tz} (area under the concentration-time curve of the analyte in* serum *over the time interval from 0 to the last quantifiable data point)*
- *C_{max} (maximum measured concentration of the analyte in* serum*)*

5.2 SECONDARY ENDPOINTS

5.2.1 Key secondary endpoints

Not applicable.

5.2.2 Secondary endpoints

Secondary PK endpoint of BI 765080, is as defined in Section 2.1.3 of the **CTP**:

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

Secondary endpoint for assessment of safety and tolerability of BI 765080 is the occurrence (absolute number and percentage) of drug-related adverse events.

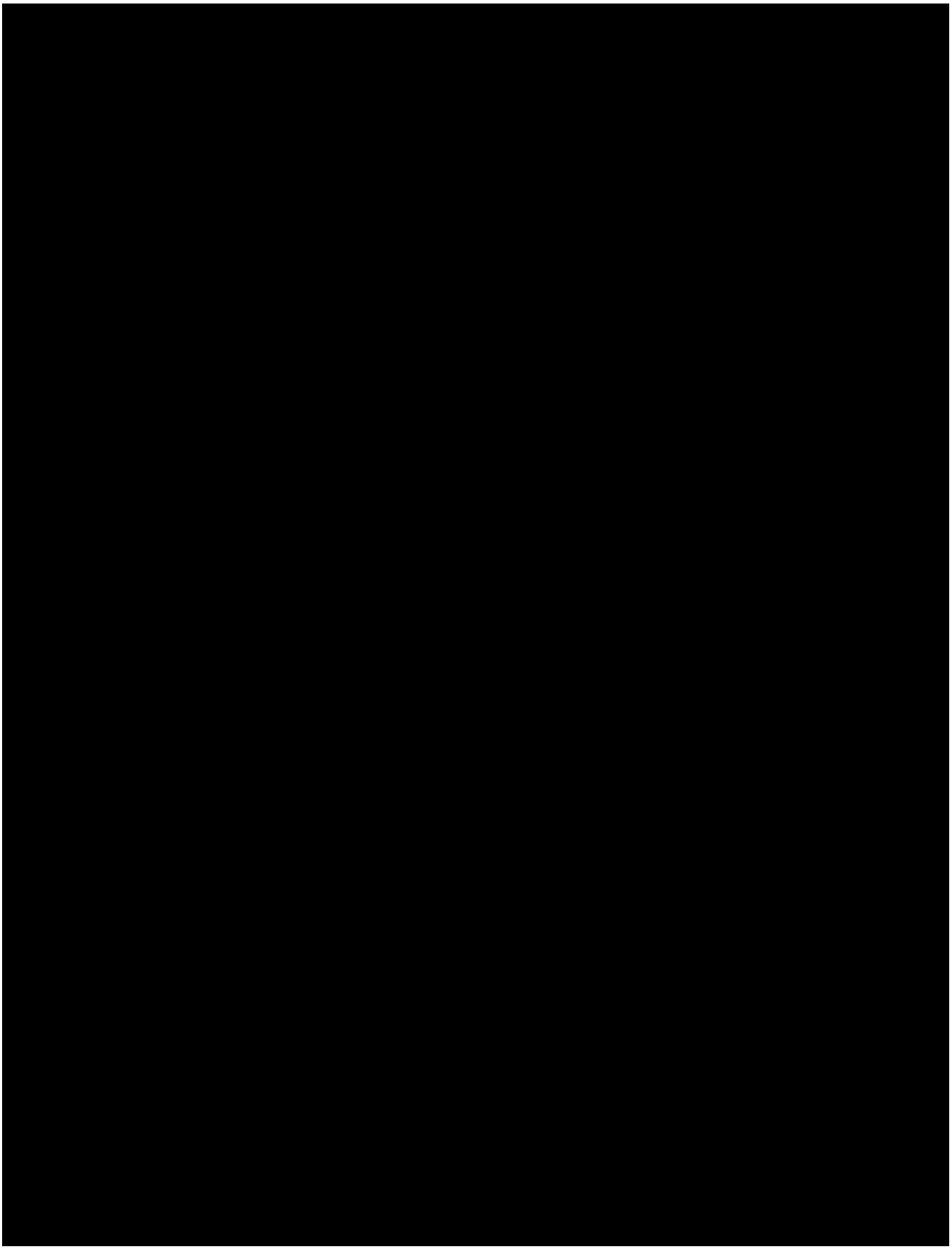
[redacted]

5.3.1 Safety parameters

Safety and tolerability of BI 765080 will be assessed based on further safety parameters defined in Section 2.2.2.2 of the **CTP:**

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

[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.

Subjects will receive 100 mg BI 765080 either as

- subcutaneous injection as bolus (Test Treatment T)

or as

- 30 minute intravenous infusion (Reference Treatment R)

For statistical analysis of AEs, the following analysis phases are defined for each subject.

Table 6.1: 1 Analysis phases for statistical analysis of AEs, and actual treatment for analysis of laboratory data and vital signs

Study analysis phase	Label	Start	End
Screening[1]	Screening	Date of informed consent	Date/time of start of administration of study drug
On-treatment	BI SC or BI IV	Date/time of start of administration of study drug	12:00 a.m. on day after last contact date

[1] See Section 6.7 for definition of baseline, which will be used in the statistical analyses of safety laboratory data, ECG and vital signs.

AE summary tables will present results for the on-treatment phase only. All AEs will be listed.

In AE tables in CTR Section 15.3 (but not in Appendix 16.1.13.1.8.1), the following total will be provided in addition:

- "**Total**", defined as the total over on-treatment phases BI injection and BI infusion

Safety laboratory data, vital signs and PK [redacted] parameters will be analysed based on treatment groups with clear differentiation between baseline (cf. Section 6.7) and on-treatment measurements. Measurements will be considered on-treatment, if they were taken within the on-treatment phases as defined in Table 6.1: 1.

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 important PD (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) and the DV domain template.

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 template. If the data show other IPDs, the definition in the DV domain template will be supplemented accordingly by the time of the Report Planning Meeting.

IPDs will be summarized and listed. Which kind of IPDs could potentially lead to exclusion from which analysis set is specified in the DV domain template. The decision on exclusion of subjects from analysis sets will be made at the latest at the Report Planning Meeting, after discussion of exceptional cases and implications for analyses.

Non-important COVID-19 related PDs will also be summarised and listed.

6.3 SUBJECT SETS ANALYSED

The treated set (TS) and pharmacokinetic parameter analysis set (PKS) will be used as defined in the CTP, Section 7.3.

Table 6.3: 1 Subject sets analyzed

	Subject set		[redacted]
Class of endpoint	TS	PKS	
Disposition	X		
iPDs	X		
Primary PK endpoints		X	
Secondary PK endpoint		X	
Secondary Safety endpoint	X		
[redacted]			
Safety parameters	X		
Local tolerability	X		
Demographic/baseline characteristics	X		
[redacted]			

6.5 POOLING OF CENTRES

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

6.6 HANDLING OF MISSING DATA AND OUTLIERS

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

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

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

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

CTP: "*Pharmacokinetic 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

In all analyses, baseline is defined as the last available value prior to start of infusion/injection.

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, 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 serum 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 serum 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. These will be based on the TS.

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.

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

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

A medication will be considered concomitant to study drug, if it

- is ongoing at the time of study drug administration, or
- starts within the analysis phase of the respective treatment (see Section 6.1 for a definition of analysis phases).

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

7.3 TREATMENT COMPLIANCE

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

7.4 PRIMARY ENDPOINTS

7.4.1 Primary analysis of the primary endpoints

The analysis of primary endpoints will be based on the PKS.

CTP: *The statistical model used for the analysis of the primary endpoints will be an analysis of variance (ANOVA) model on the logarithmic scale. That is, the PK endpoints will be log-transformed (natural logarithm) prior to fitting the ANOVA model. This model will include effects accounting for the following source of variation: treatment and matching pair. The effect of treatment will be considered as fixed. For each matched pair in the study a pair number will be assigned for analysis purpose. The resulting variable 'matched pair' will be considered as random effect. The model is described by the following equation:*

$y_{km} = \mu + \tau_k + s_m + e_{km}$, *where*
y_{km} = *logarithm of response measured on subject m receiving treatment k*

μ = the overall mean,
τ_k = the k^{th} treatment effect, k = 1, 2,
s_m = the effect associated with the m^{th} matching pair, m = 1, 2,..., 14,
e_{km} = the random error associated with the m^{th} subject who received treatment k.
where $s \sim N(0,\sigma_B^2)$ i.i.d., $e \sim N(0, \sigma_W^2)$ i.i.d., σ_W^2 and s_m , e_{km} are independent random variables.

Point estimates for the ratios of the geometric means (test/reference) for the primary endpoints (see Section 2.1) and their two-sided 90% confidence intervals (CIs) will be provided.
For each endpoint, the difference between the expected means for log(T)-log(R) will be estimated by the difference in the corresponding adjusted means (Least Squares Means). Additionally their two-sided 90% confidence intervals will be calculated based on the residual error from the ANOVA and quantiles from the t-distribution. These quantities will then be back-transformed to the original scale to provide the point estimate and 90% CIs for each endpoint.

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".

CTP: *S*erum *concentration data and parameters of a subject which is flagged for exclusion will be reported with its individual values but will not be included in the statistical analyses.*

Exclusion of serum/urine 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.

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).

[redacted]

7.5 SECONDARY ENDPOINTS

7.5.1 Key secondary endpoints

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

7.5.2 Secondary endpoints

7.5.2.1 Secondary endpoint analysis

CTP: *The secondary PK endpoints (refer to Section 2.1.3) will be calculated according to the BI SOP 'Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics' and will be assessed statistically using the same methods as described for the primary endpoints.*

Drug-related adverse event will be presented descriptively by treatment group.

[redacted]

7.6.1 Safety parameters

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

[redacted]

7.7 EXTENT OF EXPOSURE

Only listings 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 or on-treatment phase as defined in Section 6.1. AEs will be analysed based on actual treatments, as defined in Table 6.1: 1.

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

CTP: *A potential severe Drug Induced Liver Injury (DILI) is considered an AESI in this trial. 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 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 in samples drawn within 30 days of each other, 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 Serious Adverse Events, 'other significant' AEs need to be listed in the clinical trial report. 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. Separate tables will also be provided for subjects with SAEs and subjects with AESIs. AEs will also be summarized by maximum intensity.

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

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).

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.

Laboratory data will be compared to their reference ranges. Values outside the reference range as well as possibly clinically significant values will be highlighted in the listings. Possibly clinically significant laboratory values will be listed in Section 15.4.1.

Clinically relevant findings in laboratory data will be reported as baseline conditions (prior to start of administration of study treatment) or as AEs (after start of 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, 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 in the same way as described above for laboratory data (i.e., they will be assigned to the previous planned time point).

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). This is based on the assumption, that the last value is a repeat measurement due to quality reasons and is therefore more reliable than the first measurement. The assumption of a repeat measurement due to quality reasons is only plausible if the unscheduled measurement is shortly after the scheduled measurement. In order to assess the time difference (during data validation and Report Planning Meeting), the date and clock time of both measurements has to be available. If the time of measurement is missing for a scheduled or unscheduled post-baseline measurement (or both), the scheduled measurement will be used in calculation of descriptive statistics (since it cannot be assessed whether the assumption of a repeat measurement for quality reasons is plausible, or not). All measurements will be listed.

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

7.8.4 ECG

Abnormal findings will be reported as baseline conditions (at screening) or as AEs (during the trial) if judged clinically relevant by the investigator and will be analyzed as such.
No separate listing or analysis of ECG data will be prepared.

7.8.5 Local tolerability

Local tolerability (absence or presence of "swelling", "induration", "heat", "redness", "pain", or "other findings") will be summarized with counts and percentages overall (i.e. over all on-treatment time points, cf. Section 6.1) as well as by time point.

7.8.6 Others

7.8.6.1 Physical examination

Physical examination findings will be reported as relevant medical history/baseline condition (if a condition already exists before start of administration of study treatment) or as AE (if condition emerges after start of administration of study treatment) and will be summarized 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 after completion of enrolment, i.e. the randomization has been completed.

9. REFERENCES

1	*CPMP/ICH/363/96*: "Statistical Principles for Clinical Trials", ICH Guideline Topic E9; Note For Guidance on Design, Conduct, Analysis and Evaluation of Clinical Trials, current version
2	*BI-VQD-12045_40-413:* "Identify and Manage Important Protocol Deviations (iPD)", current version; KMED
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-0066:* "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:* "Handling, Display and Analysis of Laboratory Data", current version; KMED

10. ADDITIONAL SECTIONS

Not applicable as no additional information is needed.

11. HISTORY TABLE

Table 11: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
1	**08-APR-22**	[redacted]	None	This is the final TSAP