TRIAL STATISTICAL ANALYSIS PLAN

Document No.:	**c41522791-01**
BI Trial No.:	**1305-0030**
Title:	Investigation of pharmacokinetics and absolute oral bioavailability of BI 1015550 administered as an oral dose with an intravenous microtracer dose of [^{14}C]-BI 1015550 in healthy male volunteers Protocol #01 [c38933360-01]
Investigational Product(s):	BI 1015550
Responsible trial statistician(s):	[redacted] Phone: [redacted] Fax: [redacted]
Date of statistical analysis plan:	07 JUN 2023
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2. LIST OF ABBREVIATIONS

Term	Definition / description
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
[redacted]	[redacted]
BI	Boehringer Ingelheim
[redacted]	[redacted]
CDR	Clinical data repository
CI	Confidence interval
C_{max}	Maximum measured concentration of the analyte in plasma
COVID	Coronavirus disease
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
CV	Arithmetic coefficient of variation
DILI	Drug induced liver injury
DV	Data validation
ECG	Electrocardiogram
(e)CRF	(Electronic) case report form
EDC	Electronic data capture
EDMS	Electronic management system
gCV	geometric coefficient of variation
gMean	Geometric mean
[redacted]	[redacted]
ICH	International Conference On Harmonisation
iPD	Important protocol deviations
i.v.	intravenous

Term	Definition / description
[redacted]	[redacted]
MedDRA	Medical Dictionary For Regulatory Activities
PD	Protocol deviation
PK	Pharmacokinetics
PKS	Pharmacokinetic parameter analysis set
p.o.	After oral
[redacted]	[redacted]
RAGe	Report appendix generator
RPM	Report Planning Meeting
SAE	Serious adverse event
SD	Standard Deviation
SOC	System Organ Class
TMF	Trial master file
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 Clinical Trial Protocol (CTP), 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 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 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 or higher, [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.

In accordance with CTP section 7.2.2 and in contrast to CTP section 7.1, no p-values will be computed or displayed for the primary and secondary endpoint analyses since this is an explorative analysis with a small sample size.

The dose-normalised further PK endpoint, C_{max} of [^{14}C]-BI 1015550 after intravenous administration, will be used as comparison to the dose-normalised secondary endpoint, C_{max} of BI 1015550 p.o., in the secondary endpoint analysis since it is the PK parameter of the reference treatment corresponding to the secondary endpoint.

5. ENDPOINTS(S)

5.1 PRIMARY ENDPOINT(S)

Primary endpoints are as defined in Section 2.1.2 of the **CTP**.

The following pharmacokinetic parameters will be determined for [^{14}C]-BI 1015550 in plasma after intravenous (i.v.) administration as well as for BI 1015550 after oral (p.o.) administration:

- *$AUC_{0-\infty}$ of [^{14}C]-BI 1015550 i.v.*
- *$AUC_{0-\infty}$ of BI 1015550 p.o.*

5.2 SECONDARY ENDPOINT(S)

5.2.1 Key secondary endpoint(s)

No key secondary endpoints have been specified in the CTP hence this section is not applicable.

5.2.2 Secondary endpoint(s)

The following pharmacokinetic parameter is the secondary endpoint and will be determined for BI 1015550 after oral administration, as defined in Section 2.1.3 of the **CTP**:

- *C_{max} (maximum measured concentration of the analyte in plasma) of BI 1015550 p.o.*

5.3 FURTHER ENDPOINT(S)

5.3.1 Safety parameters

Safety and tolerability of BI 1015550 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 and pulse rate)*
- *Local tolerability of injection site (based on swelling, induration, heat, redness, pain, and other clinically relevant findings reported as AE after intravenous infusion)*

Local tolerability will be assessed by the investigator and reported as AE in case of clinically relevant findings see **CTP** Section 5.2.5.1.

6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENT(S)

For basic study information on the treatment to be administered, and selection of dose, **cf. Section 4 of the CTP**. For information of overall trial design, **cf. Section 3.1 of the CTP**.

CTP Section 3.1:

The trial will be performed as a non-randomised, open-label, single period, single arm trial in healthy male subjects in order to compare the test treatment (T) to the reference treatment (R). […] Both treatments will be given in the fasted state. Drug administration of treatment R will start [redacted] *after drug administration of treatment T.*

For details of dosage and formulation see below:

Table 6.1: 1 Treatments and labels used in the analysis

Treatment		Short label
R	[redacted] BI 1015550 (C-14), intravenous microtracer solution	BI C14
T	[redacted] BI 1015550, film-coated tablet	BI Tab

The sequence for “R-T” is named “BI Tab / BI C14” accordingly.

CTP Section 1.2.3: *The Residual Effect Period (REP) of BI 1015550 is* [redacted]*. This is the period after the last dose during which measurable drug levels and/or pharmacodynamic effects are still likely to be present.*

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

Table 6.1: 2 Analysis phases for statistical analysis of AEs, and actual treatment for analysis of laboratory data and vital signs

Study analysis phase	Label	Start (inclusive)	End (exclusive)
Screening[1]	**Screening**	Date of informed consent	Date/time of administration of BI 1015550 tablet (test treatment)
On treatment	**BI Tab + BI C14**	Date/time of administration of BI 1015550 tablet (test treatment)	Date/time of end of infusion of BI 1015550 (C-14) (reference treatment) + residual effect period [redacted] or 12:00 a.m. on day after date/time of trial termination (whichever occurs first)
Follow-up	**F/U**	Date/time of administration of BI 1015550 tablet (test treatment) + residual effect period [redacted] or date/time of end of infusion of BI 1015550 (C-14) (reference treatment) + residual effect period [redacted] (whichever occurs later)	12:00 a.m. on day after trial termination date

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

CTP Section 7.2.5: *Note that AEs occurring after the last per protocol contact but entered before database lock of 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:

A) Section 15.3 and Appendix 16.1.13.1.8 (for ClinicalTrials.gov and EudraCT only) of the CTR displays:
In these displays (AE summary tables), the on treatment phase will be analysed (labelled with the name of the study treatment (short label) as in Table 6.1:2). Screening and follow-up periods will not be included in this analysis.

B) Section 15.4 of the CTR displays:

- Screening
- On treatment (labelled with the name of the study treatment (short label) as in Table 6.1:2)
- Follow-up (labelled as “F/U”)

Safety laboratory data and vital signs will be analysed 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 phase as defined in Table 6.1: 2.

More details on the technical implementation of these analyses are provided in the ADS Plan of this TSAP and Analysis Data Reviewers guide.

6.2 IMPORTANT PROTOCOL DEVIATIONS

Documentation of iPD categories and handling of iPDs in analysis is included in the DV domain specifications and stored within the TMF in EDMS. The iPDs will be summarized and listed in the CTR.

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 (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 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 RPM.

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 RPM, after discussion of exceptional cases and implications for analyses.

Non-important COVID-19 related PDs will only be listed.

Handling of iPDs in analysis is included in the DV domain specifications and stored within the TMF in EDMS.

6.3 INTERCURRENT EVENTS

This Section is not applicable since no estimands or intercurrent events were defined in the CTP.

6.4 SUBJECT SETS ANALYSED

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

- *Treated set (TS): The treated set includes all subjects who were treated with at least one dose of trial 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 that was not excluded due to a protocol deviation relevant to the evaluation of PK or due to PK non-evaluability (as specified in Section 7.2.1.2). Thus, a subject will be included in the PKS, even if he contributes only one PK parameter value to the statistical assessment. Descriptive and model-based analyses of PK parameters will be based on the PKS.*

Table 6.4: 1 Subject sets analysed

	Subject set	
Class of endpoint	Treated set	PKS
Primary endpoints		X
Secondary [redacted] endpoints		X
Further safety parameters [redacted]	X	
Disposition	X	
iPDs	X	
[redacted]	[redacted]	

[redacted]

6.6 HANDLING OF MISSING DATA AND OUTLIERS

Handling of missing data and outliers will be performed as described in **Section 7.3 of the CTP.**

CTP Section 7.3.1: *It is not planned to impute missing values for safety parameters.*

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

CTP Section 7.3.2: *Handling of missing PK data will be performed according to the relevant BI internal procedures. 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) and (10).

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

CTP Section 7.2.5:

[…] The last non-missing measurement prior to study treatment will be used as baseline for safety variables.

Time windows are defined in Section 6.1 of the CTP. Adherence to time windows will be checked via the consistency check listings 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 or sequence group, 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 PK parameters, the following descriptive statistics will additionally be calculated:

P10	10th percentile
Q1	1st 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 (unless otherwise specified, all subjects in the respective subject set whether they have non-missing values or not). Percentages will be rounded to integer numbers. Percentages will be based on all subjects in the respective subject set whether they have non-missing values or not. The category missing will be displayed only if there are actually missing values.

Exclusion of PK parameters

The ADS ADPP contains column variables APEX and APEXCO indicating inclusion/exclusion (APEX) 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 APEX equal to "Included".

CTP Section 7.2.1.2: *Plasma concentration data and parameters of a subject which are flagged for exclusion will be reported with its individual values but will not be included in the statistical analyses.*

Exclusion of PK concentrations

The ADS ADPC (PK concentrations per time-point or per time-interval) contains column variables ACEX or 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. 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).

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

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

7.2 CONCOMITANT DISEASES AND MEDICATION

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 and drug therapies will be coded according to the most recent version of the World Health Organisation – Drug Dictionary (WHO-DD). The coding version number will be displayed as a footnote in the respective output.

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

CTP Section 7.2.5: *Previous and concomitant therapies will be presented per treatment group without consideration of time intervals and treatment periods.*

A drug and non-drug therapy will be considered concomitant to a treatment, 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 treatments and analysis phases).

The diagnoses and drug and non-drug therapies will be listed. Subjects without any concomitant disease or concomitant therapy should be marked with a "No" in the respective column.

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

7.3 TREATMENT COMPLIANCE

CTP Section 4.3: *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.*

Treatment compliance will not be analysed as a specific endpoint, but judged by observed analyte concentrations. Any deviations from complete medication intake (incorrect duration of infusion) will be addressed in the RPM (cf. Section 6.2) and described in the CTR.

7.4 PRIMARY OBJECTIVE ANALYSIS

7.4.1 Main analysis

CTP Section 7.2.2: *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 logtransformed (natural logarithm) prior to fitting the ANOVA model. This model will include effects accounting for the following sources of variation: 'subjects' and 'formulation'. The effect 'subjects' will be considered as random, whereas the 'formulation' effect will be considered as fixed. The model is described by the following equation:*

$y_{km} = \mu + s_m + \tau_k + e_{km}$, *where*

y_{km} = *logarithm of response (dose normalized) measured on subject m receiving formulation k,*

μ = *the overall mean,*

s_m = *the effect associated with the* m^{th} *subject,* $m = 1, 2, ..., 8$

τ_k = *the* k^{th} *formulation effect (either tablet or i.v.),* $k = 1, 2,$

e_{km} = *the random error associated with the* m^{th} *subject who received formulation k.*

where $s_m \sim N(0, \sigma_B^2)$ *i.i.d.,* $e_{km} \sim N(0, \sigma_W^2)$ *i.i.d. 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 CTP *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.

The implementation for this analysis will be accomplished by using the CSD macros based on the PKS.

[redacted]

7.4.5 Secondary endpoint analysis

CTP Section 7.2.3: *The secondary endpoints (refer to* CTP *Section 2.1.3) will be calculated according to the relevant BI internal procedures and will be assessed statistically using the same methods as described for the primary endpoints.*

The further endpoint C_{max} of [^{14}C]-BI 1015550 i.v. will be used as reference treatment to secondary endpoint C_{max} of BI 1015550 p.o in the statistical analysis.

The analysis of secondary PK endpoints will be based on the PKS.

7.5 SECONDARY OBJECTIVE ANALYSIS

7.5.1 Key secondary objective analysis

This section is not applicable as no key secondary objective has been specified in the CTP.

7.5.2 Secondary objective analysis

This section is not applicable as no secondary objective has been specified in the CTP.

7.6 FURTHER OBJECTIVE ANALYSIS

7.6.1 Safety parameters

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

[redacted]

7.7 EXTENT OF EXPOSURE

Since only [redacted] dose per treatment formulation (tablet or infusion) is administered per subject a listing will be sufficient to give account of the extent of exposure.

7.8 SAFETY ANALYSIS

All safety analyses will be performed on the treated set.

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 phase and follow-up phase 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 include summary statistics for the class of AESIs.

CTP Section 5.2.6.1.4: *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 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*
- *Vasculitis*
  In this trial protocol vasculitis is defined as any adverse event term included in the MedDRA SMQ Vasculitis (broad). This includes clinical and pathological features related to primary or secondary vasculitis syndromes and involving any type, size, and location of blood vessels. The investigator should monitor for any signs and symptoms of vasculitis at all times and specifically as part of the AE questioning. In case of (suspected) event of vasculitis, further work-up and management as outlined has to be followed, including biopsy, appropriate imaging/angiography, laboratory measures (e.g., ESR, additional lab sample for immunological and further inflammation markers).
- *Severe infections, serious infections, opportunistic or mycobacterium tuberculosis infections (refer to Appendix 10.1 for a list of severe infections considered as AESI)*

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 and listed 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.

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 "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).

Laboratory data will be analysed qualitatively via comparison of laboratory data to their reference ranges. Values outside the reference range as well as possible clinically significant values will be highlighted in the listings. Possibly clinically significant abnormal laboratory values will be listed separately in Section 15.4.1.

It is the Investigator's responsibility to decide whether a lab value is clinically significant abnormal or not. Clinically significant abnormal laboratory values are identified either in the Investigator's comments or at the Report Planning Meeting at the latest. They will be reported as baseline conditions (prior to first administration of study drug) or as AEs (after first administration of study treatment).

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 in the same way as described above for laboratory data. However, 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). 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 via Investigator comments or at the RPM at the latest, and will be analyzed as such.

7.8.4 ECG

ECG recordings will be checked by the investigator for pathological results. Clinically relevant abnormal findings for ECG will be listed under 'Relevant Medical History / Baseline Conditions' (when they occurred during screening) or will be reported as AEs (when they occurred during treatment), and will be analysed as such. No separate ECG listing will be provided.

7.8.5 Others

7.8.5.1 Physical examination

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.

[redacted]

7.8.5.3 Local tolerability

CTP Section 5.2.5.1: *Local tolerability will be assessed by the investigator on the basis of swelling, induration, heat, redness, pain, and other findings. Local findings assessed as clinically relevant by the investigator must be recorded as AE.*

The results of the local tolerability assessments themselves will not be entered in the CRF/database and will not be reported in the CTR. Only abnormal findings will be reported as AEs.

8. TIMEPOINT OF RELEASE OF TREATMENT INFORMATION

The treatment information will be loaded into the trial database at trial initiation.

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-TCMP-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.	KM Asset BI-KMED-TMCP-HTG-0025: “Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics” ", current version; KMED

11. HISTORY TABLE

Table 11: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
1.0	**07-JUN-23**	[redacted]	None	This is the final TSAP.