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TRIAL STATISTICAL ANALYSIS PLAN

Document No.:	**c43868454-01**
BI Trial No.:	**1397-0026**
Title:	Investigation of pharmacokinetics and absolute oral bioavailability of BI 1291583 administered as an oral dose with an intravenous microtracer dose of [^{14}C]-BI 1291583 in healthy male volunteers Including Protocol Amendment 1 [c41814759-02]
Investigational Product(s):	BI 1291583
Responsible trial statistician(s):	[redacted] Phone: [redacted] Fax: [redacted]
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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
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
BA	Bioavailability
BI	Boehringer Ingelheim
BMI	Body mass index
BP	Blood pressure
CI	Confidence interval
C_{max}	Maximum measured concentration of the analyte in plasma
COVID	Coronavirus disease
CRF	Case Report Form, paper or electronic (sometimes referred to as 'eCRF')
CTP	Clinical trial protocol
CTR	Clinical trial report
CV	Arithmetic coefficient of variation
DILI	Drug induced liver injury
ECG	Electrocardiogram
EoS	End of Study (synonym for End of Trial)
eCRF	Electronic case report form
EudraCT	European Clinical Trials Database
F	Absolute bioavailability factor
gCV	Geometric coefficient of variation
gMean	Geometric mean
ICH	International Conference On Harmonisation
IPD	Important protocol deviations

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Term	Definition / description
LLOQ	Lower limit of quantification
MedDRA	Medical Dictionary For Regulatory Activities
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PKS	Pharmacokinetic parameter analysis set
PR	Pulse rate
R	Reference treatment
RAGe	Report appendix generator
REP	Residual effect period
RPM	Report Planning Meeting
SAE	Serious adverse event
SD	Standard Deviation
SDL	Subject Data Listing
SOC	System Organ Class
T	Test product or treatment
TS	Treated set
TSAP	Trial Statistical Analysis Plan
$t_{1/2}$	Terminal half-life of the analyte in plasma
ULN	Upper limit of normal range

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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 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 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 or higher, [redacted]).

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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.

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5. ENDPOINT(S)

5.1 PRIMARY ENDPOINT(S)

The primary endpoint will be analysed in plasma for [^{14}C]-BI 1291583 after intravenous and for BI 1291583 after oral administration (2 dose groups: 1 mg and 5 mg), as defined in **Section 2.1.2** of the **CTP**:

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

5.2 SECONDARY ENDPOINT(S)

5.2.1 Key secondary endpoint(s)

Not applicable.

5.2.2 Secondary endpoint(s)

The following secondary endpoints will be evaluated in plasma for [^{14}C]-BI 1291583 after intravenous and for BI 1291583 after oral administration (2 dose groups: 1 mg and 5 mg), as defined in **Section 2.1.3** of the **CTP**:

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



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6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENT(S)

For basic study information on the treatments to be administered, cf. **Section 4** of the **CTP**. All subjects will receive an oral dose of either 1 mg or 5 mg BI 1291583 (Treatment T) first followed by an intravenous infusion of 50 µg BI 1291583 (C-14) (Treatment R).

CTP Section 1.2.2: *"Based on PK and PD data from trial 1397-0002 and 1397-0011 [redacted] the REP of BI 1291583 was defined as [redacted]. However, in this trial with the administration of a [redacted] (BI 1291583 oral dose of [redacted] BI 1291583 (C-14)) no relevant pharmacodynamics effects are expected. Considering the $t_{1/2}$ of [redacted] of BI 1291583, highest dose, a REP [redacted] appears appropriate."*

For statistical analysis of AEs, laboratory data, vital signs and local tolerability 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, vital signs and local tolerability

Study analysis phase	Label	Start (inclusive)	End (exclusive)
Screening[1]	Screening	Date of informed consent	Date/time of oral administration of treatment T
On-treatment	1mg BI tab + BI iv or 5mg BI tab + BI iv	Date/time of oral administration of treatment T	End date/time of intravenous infusion of treatment R + residual effect period (10 days) or 12:00 a.m. on day after last contact date (whichever occurs first)
Follow up	F/U 1mg BI tab + BI iv or F/U 5mg BI tab + BI iv	End date/time of intravenous infusion of treatment R + residual effect period (10 days)	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 and vital signs.

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

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In AE tables in CTR Section 15.3 (but not for EudraCT and CT.gov AE tables), the following total will be provided in addition:

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

The AE displays for ClinicalTrials.gov and EudraCT (in Appendix 16.1.13.1) will be provided for the on-treatment phase only without total, screening and follow-up phase.

Safety laboratory data, vital signs, local tolerability and PK parameters 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: 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 (RPM). At this meeting, it will be decided whether a discrepant data value can be used in analyses, must be corrected in the clinical database or constitutes a PD.

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 specification. If the data show other iPDs, the definition in the DV domain specification 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 specification. The decision on exclusion of participants from analysis sets will be made at the latest at the RPM, after discussion of exceptional cases and implications for analyses. If the data show other iPDs, this table will be supplemented accordingly by the time of the RPM.

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

A description of handling of iPDs in the analysis is included in the DV domain specification and stored within the TMF in EDMS.

6.3 INTERCURRENT EVENTS

Section is not applicable since no intercurrent events were defined in the **CTP**.

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6.4 SUBJECT SETS ANALYSED

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

Table 6.4: 1 Subject sets analysed

	Subject set	
Class of analysis	TS	PKS
Disposition	X	
iPDs	X	
Demographic/baseline characteristics	X	
Treatment exposure	X	
Primary PK endpoints		X
Secondary PK endpoint		X
Further PK endpoints		X
Safety parameters	X	

[redacted]

6.6 HANDLING OF MISSING DATA AND OUTLIERS

CTP Section 3.3.4: *"If a subject is removed from or withdraws from the trial prior to the first administration of trial medication, the data of this subject will not be entered in the case report form (CRF) and will not be reported in the clinical trial report (CTR).*
If a subject is removed from or withdraws from the trial after the first administration of trial medication, this will be documented and the reason for discontinuation must be recorded in the CRF; in addition, trial data will be included in the CRF and will be reported in the CTR."

CTP Section 7.3.1: "*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 data are handled according to BI standards (4) and (5).

CTP Section 7.3.2: *"PK parameters that cannot be reasonably calculated based on the available drug concentration-time data will not be imputed."*

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6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

In all analyses (safety and PK analyses), the baseline is defined as the last available value prior to the first study drug administration. Time windows are defined in **Section 6.1** of the **CTP**. Adherence to time windows will be checked at the Report Planning Meeting.

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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 assigned treatment group (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 and urine 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 and urine 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 integer numbers. The category missing will be displayed only if there are actually missing values. Percentages will be based on all subjects in the respective subject set whether they have non-missing values or not.

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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 and non-drug therapies will be coded according to the most recent version of MedDRA. Concomitant medications 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 or 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 as well as non-drug therapies will be listed. Subjects without any concomitant disease or concomitant therapy will be marked with a "No" in the respective column.

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 analysed as a specific endpoint. Any deviations from complete intake will be addressed in the RPM (cf. Section 6.2) and described in the CTR.

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."*

7.4 PRIMARY OBJECTIVE ANALYSIS

7.4.1 Main analysis

The primary and secondary endpoints will be analysed as described in the **CTP Section 7.2.2** and **Section 7.2.3**.

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CTP Section 7.2.2: *"The statistical model used for the analysis of the primary endpoint for each dose group will be an analysis of variance (ANOVA) model on the logarithmic scale. That is, the PK endpoints will be log-transformed (natural logarithm) prior to fitting the ANOVA model. This model will include effects accounting for the following sources of variation: subjects and treatment. The effect 'subjects' will be considered as random, whereas the other 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 measured on subject m receiving treatment k,*
μ = *the overall mean,*
s_m = *the effect associated with the* m^{th} *subject, m = 1, 2, ..., n,*
τ_k = *the* k^{th} *treatment effect, k = 1, 2,*
e_{km} = *the random error associated with the* m^{th} *subject who received treatment k*

where $s \sim N(0, \sigma)$ *i.i.d.,* $e \sim N(0, \sigma)$ *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 [...] 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."

CTP Section 7.1: *"The absolute bioavailability of either* [redacted] *BI 1291583 administered as* [redacted] *(test treatment T) compared with* [redacted] *BI 1291583 (C-14) (reference treatment R) administered as* [redacted] *will be estimated by the ratio of the geometric means (test/reference) for primary and secondary dose-normalized PK endpoints, and their corresponding 2-sided 90% confidence intervals (CIs) will be provided."*

The SAS code is presented in Section 10.1.

The analysis of primary and secondary endpoints will be based on the PKS.
Subjects in the PKS may not contribute data to every statistical analysis of PK endpoints, in case specific PK endpoints of this subject are missing or excluded for the following reasons.

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).

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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 will be included in the statistical pharmacokinetic (PK) analyses if they are not flagged for exclusion due to a protocol deviation relevant to the evaluation of PK (to be decided no later than in the Report Planning Meeting) or due to PK non-evaluability (as revealed during data analysis, based on the criteria specified below). Exclusion of a subject's data will be documented in the CTR."*

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)

[redacted]

7.4.4 Supplementary analysis

This section is not applicable as no supplementary analysis has been specified in the **CTP**.

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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**.

7.5.1.1 Main analysis

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



7.5.1.4 Supplementary 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 Pharmacokinetic endpoints

CTP Section 7.2.4.1: *"Further PK endpoints will be analysed descriptively."*

7.6.2 Safety parameters

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

7.7 EXTENT OF EXPOSURE

Since only single doses are 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 TS.

7.8.1 Adverse Events

AEs will be coded using the most recent version of MedDRA.

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The analyses of AEs will be descriptive in nature. All analyses of AEs will be based on the number of subjects with at least one AE 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 either the screening, on-treatment or follow-up phase as defined in Section 6.1. AEs will be analysed based on actual treatments on the recorded time of AE onset, as defined in Table 6.1: 1.

An overall summary of AEs will be presented. This summary will include summary statistics for the class of adverse events of special interest (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 aminotransferase) and/or ALT (alanine aminotransferase) ≥3-fold ULN combined with an elevation of total bilirubin ≥2-fold ULN measured in the same blood sample, or in samples drawn within 30 days of each other, or*
- *Aminotransferase (ALT, and/or AST) elevations ≥10-fold ULN*

These lab findings constitute a hepatic injury alert and the participants showing these lab abnormalities need to be followed up according to the 'DILI checklist' provided in the ISF. In case of clinical symptoms of hepatic injury (icterus, unexplained encephalopathy, unexplained coagulopathy, right upper quadrant abdominal pain, etc.) without lab results (ALT, AST, total bilirubin) available, the investigator should make sure that these parameters are analysed, if necessary in an unscheduled blood test. Should the results meet the criteria of hepatic injury alert, the procedures described in the DILI checklist should be followed."

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 events 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. Separate tables will be provided for subjects with

- AEs, which were considered by the investigator to be drug related
- SAEs

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- AESIs
- AEs summarized by worst 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 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 "Handling, 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 compared to their reference ranges. Values outside the reference range will be highlighted in the listings.

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 analysed as such.

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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 analysed as such.

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 post-baseline 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 post-baseline measurement (e.g. for follow-up visits) 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 post-baseline measurement, this measurement will be listed but will be ignored for the calculation of descriptive statistics.
In descriptive statistics of the Screening visit the planned time points will be used. However, if an unscheduled measurement on the same day as the screening visit exists then the unscheduled assessment will be used in descriptive statistics of Screening visit.

7.8.4 ECG

ECG recordings will be checked by the investigator for pathological results. Clinically relevant abnormal findings in ECG will be reported as baseline conditions (at screening) or as AEs (after first administration of study treatment) if judged clinically relevant by the investigator, and will be analysed as such.

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

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.

7.8.5.2 Body weight

Body weight will only be listed.

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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."*

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

7.9 OTHER ANALYSIS

Not applicable

7.9.1 Biomarker analyses

Not applicable

7.9.2 PK / PD analyses

Not applicable

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8. TIMEPOINT OF RELEASE OF TREATMENT INFORMATION

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

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9. REFERENCES

1	*CPMP/ICH/363/96: "Statistical Principles for Clinical Trials", ICH Guideline Topic E9, Note For Guidance on Statistical Principles for Clinical Trials, current version*
2	*BI-VQD-12045_40-413: "Identify and Manage Important Protocol Deviations (iPD)", current version, group / owning department "Med Clinical Development & Operations", DMS for controlled documents*
3	*KM Asset BI-KMED-BDS-HTG-0035: "Handling of missing and incomplete AE dates", current version, DMS for controlled documents*
4	*KM Asset BI-KMED-TMCP-MAN -0014: "Noncompartmental PK/PD Analyses of Clinical Studies", current version, DMS for controlled documents*
5	*KM Asset BI-KMED-TCMP-MAN-0010: "Description of Analytical Transfer Files, PK/PD Data Files and ADA files", current version, DMS for controlled documents*
6	*KM Asset BI-KMED-BDS-HTG-0045: "Standards for Reporting of Clinical Trials and Project Summaries", current version, DMS for controlled documents*
7	*KM Asset BI-KMED-BDS-HTG-0066: "Analysis and Presentation of Adverse Event Data from Clinical Trials", current version, DMS for controlled documents*
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, EMA webpage.*
9	*KM Asset BI-KMED-BDS-HTG-0042: "Handling, Display and Analysis of Laboratory Data", current version, DMS for controlled documents*

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11. HISTORY TABLE

Table 11: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
1.0	**25-Mar-2024**	[redacted]	None	This is the final TSAP.