TRIAL STATISTICAL ANALYSIS PLAN

c28983597-01

BI Trial No.:	1430-0001
Title:	Safety, tolerability and pharmacokinetics of single rising oral doses of BI 764122 (single-blind, partially randomised, placebo-controlled, parallel (sequential) group design) and the effect of food on BI 764122 (open-label, randomised, single-dose, two-period, two-sequence crossover design) in healthy male subjects
Investigational Product:	BI 764122
Responsible trial statisticians:	Phone: Fax:
Date of statistical analysis plan:	13 SEP 2019 SIGNED
Version:	"Final"

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2. LIST OF ABBREVIATIONS

Term	Definition / description
AE	Adverse Event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ANOVA	Analysis of variance
$AUC_{0-\infty}$	Area under the concentration-time curve of the analyte over the time interval from 0 extrapolated to infinity
BLQ	Below the lower limit of quantification
BMI	Body mass index
BI	Boehringer Ingelheim
BP	Blood pressure
CARE	Clinical data analysis and reporting environment
C_{max}	Maximum measured concentration of the analyte in plasma
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
CV	Arithmetic coefficient of variation
ECG	Electrocardiogram
ECGPCS	Electrocardiogram plasma concentration set
eCRF	Electronic case report form
FE	Food effect
gCV	Geometric coefficient of variation
gMean	Geometric mean
HR	Heart rate
ICH	International Conference On Harmonisation
IPD	Important protocol deviation
LLT	Lower level term
MedDRA	Medical Dictionary For Regulatory Activities
PK	Pharmacokinetics
PKS	Pharmacokinetic parameter analysis set
PR	Pulse rate

Term	Definition / description
QRS complex	Combination of the Q, R, and S waves
QT interval	Time between start of the Q-wave and the end of the T-wave in an electrocardiogram
QTcB	QT interval, heart rate corrected according to Bazetts formula
QTcF	QT interval, heart rate corrected according to Fridericias formula
Q1	Lower Quartile
Q3	Upper Quartile
RAGe	Report appendix generator
RPM	Report Planning Meeting
RR interval	ECG interval from the peak of the R wave to the peak of the subsequent R wave
SD	Standard Deviation
SRD	Single-rising dose
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 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 amendment. In particular, the TSAP is based on the planned analysis specification as written in CTP Section 7 "Statistical Methods and Determination of Sample Size". Therefore, TSAP readers may consult the CTP for more background information on the study, e.g., on study objectives, study design and population, treatments, definition of measurements and variables, planning of sample size, randomisation.

Study data will be stored in a trial database within the Medidata Rave system.

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; RAGe system for compilation/formatting of the CTR appendices).

PK parameters will be calculated using Phoenix WinNonlin™ software (version 6.3, Certara USA Inc., Princeton, NJ, USA).

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

All analyses described in this TSAP are in accordance with the statistical methods described in the CTP.

5. ENDPOINTS

5.1 PRIMARY ENDPOINT

Primary endpoint is the percentage of subjects with drug-related adverse events.

5.2 SECONDARY ENDPOINTS

5.2.1 Key secondary endpoint

Not applicable.

5.2.2 Secondary endpoints

Secondary endpoints are $AUC_{0-\infty}$ and C_{max} in plasma for BI 764122.

5.3.2 Safety parameters

Further safety parameters will be used as defined in Section 2.2.2.1 of the CTP:

CTP:

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

12-lead ECG endpoints

For the definition of baseline value and a clear presentation of measurement time points scheduled for ECG recording and central evaluation refer to Section 6.7.

Quantitative ECG endpoints:

The following quantitative ECG endpoints will be determined for the ECG variables QT, HR, PR, QRS, RR, QTcF and QTcB derived as described in Additional Section 9.1:

- absolute values (per time point)
- changes from baseline (per time point)
- percent changes from baseline (per time point; for HR, PR, QRS)

Categorical ECG endpoints

The following categorical ECG endpoints will be determined based on the quantitative ECG endpoints:

- New onset (meaning that this or a higher category was not present at baseline) of maximum QTcF interval > 450 to 480 msec, > 480 to 500 msec, or > 500 msec on treatment.
  For assignment of a particular subject to one of the above categories, all time points on-treatment (refer to Table 6.7: 1) will be considered.
- Maximum change from baseline of QT ≤ 60 msec, or > 60 msec on treatment
- Maximum change from baseline of QTcF ≤ 30 msec, > 30 to ≤ 60 msec, or > 60 msec on treatment

The occurrence of any of the following will be viewed as "notable findings":

- New onset (not present at baseline) of uncorrected QT interval > 500 msec at any time on treatment
- New onset of QTcF interval > 500 msec at any time on treatment
- Change from baseline of QTcF > 60 msec at any time on treatment
- Percent change from baseline of HR ≥ 25%, when corresponding on-treatment value of HR is > 100 beats/min, or percent change from baseline of HR ≤ - 25%, when corresponding on-treatment value of HR is < 50 beats/min, at any time on treatment
- Percent change from baseline of PR ≥ 25%, when corresponding on-treatment value of PR interval is > 200 msec, at any time on treatment
- Percent change from baseline of QRS ≥ 10%, when corresponding on-treatment value of QRS complex is > 110 msec, at any time on treatment

6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENTS

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

Subjects were planned to be treated with

SRD part:

- either a single dose of 4, 12, 25, 50, 100, 200, 300 or 400 mg of BI 764122 (test treatments)
  or
- a single dose of placebo (reference treatment)

All placebo subjects will be analysed in one pooled placebo group (i.e. no distinction between dose groups will be made for placebo subjects).

FE part:

- single dose of 50 mg BI 764122 in fed state (test treatment T) and in fasted state (reference treatment R) with a wash-out period of at least 7 days between treatments

Subjects will randomly be assigned to the treatment sequence (T-R) or (R-T).

For statistical analysis of AEs, safety laboratory data, vital signs and ECG, the following analysis phases are defined for each subject:

Table 6.1: 1 Flow chart of analysis phases for statistical analyses of AEs, safety laboratory data, ECG and vital signs

SRD part:

Study analysis phase	Label	Start (inclusive)	End (exclusive)
Screening	**Screening**	Date of informed consent	Date/time of first administration of study drug
On-treatment	**Pbo,** **4 mg BI**, **12 mg BI**, **25 mg BI**, **50 mg BI,** **100 mg BI**, **200 mg BI**, **300 mg BI** or **400 mg BI** respectively	Date/time of first administration of study drug	Date/time of last administration of study drug + 7 * 24 h (i.e., REP of 7 days) or 0:00 AM on day after subject's trial termination date whatever occurs earlier
Follow-up	**F/U Pbo,** **F/U 4 mg BI**, **F/U 12 mg BI**, **F/U 25 mg BI**, **F/U 50 mg BI,** **F/U 100 mg BI**, **F/U 200 mg BI**, **F/U 300 mg BI** or **F/U 400 mg BI** respectively	Date/time of last administration of study drug + 7 * 24 h	0:00 AM on day after subject's trial completion date

FE part:

Study analysis phase	Label	Start (inclusive)	End (exclusive)
Screening	**Screening**	Date of informed consent	Date/time of first administration of study drug
On-treatment	**BI fed,** **BI fasted**	Date/time of first administration of study drug of respective treatment	Date/time of administration of study drug in next period or date/time of administration of study drug + 7 * 24 h (i.e., REP of 7 days) or 0:00 AM on day after subject's trial completion date whatever occurs earlier
Follow-up	**F/U BI**	Date/time of administration of study drug + 7 * 24 h	Date/time of second administration of study drug or 0:00 AM on day after subject's trial completion date

CTR Section 15, Appendix 16.1.13.1.8.2 and Appendix 16.1.13.1.8.3 AE displays will present results for the on-treatment phase only. Appendix 16.1.13.1.8.1 will present results for the screening, on-treatment and follow-up phase.

In CTR Section 15 AE tables (but not in Appendix 16.1.13.1.8.2 and Appendix 16.1.13.1.8.3 AE tables), the following totals will be provided in addition:

SRD part:

- "**Total BI**", defined as the total over all on-treatment phases involving BI
- "**Total on-trt SRD**", defined as the total over all on-treatment phases, including placebo

FE part:

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

Additionally, the following total will be provided in CTR Section 16.1.13.1.8.1 AE tables:

- "**Total SRD**", defined as the total over all study phases (incl. screening, on-treatment, and follow-up) of the SRD part

- "**Total FE**", defined as the total over all study phases (incl. screening, on-treatment, and follow-up) of the FE part

For disclosure outputs in CTR Section 16.1.13.1 (but not for AE tables) the following total will be provided:

- "**Study Total**", defined as the total over all study phases (screening, on-treatment and follow-up) for the SRD and FE part combined (only for disclosure outputs)

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 violations of time windows) and a list of protocol deviations (e.g. deviations in drug administration, in blood sampling times, etc.) will be provided to be discussed at the RPM. At this meeting, it will be decided whether a discrepant data value can be used in 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 the process of identification and managing iPDs refer to the BI reference document "Identify and Manage Important Protocol Deviations (iPD)" (2). For a detailed specification of PDs and iPDs of this trial refer to the Integrated Quality and Risk Management Plan (IQRMP) Section 4.1.

If any iPDs are identified, they are to be summarised into categories and will be captured in the decisions log. 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 RPM.

iPDs will be summarised 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 subjects from analysis sets will be made at the latest at the RPM, after discussion of exceptional cases and implications for analyses.

Table 6.2: 1 Handling of iPDs

iPD code	iPD Category & Brief Description	Possible exclusion from analysis set
A1	Inclusion Criteria Not Met	PKS,
A2	Exclusion Criteria Not Met	PKS,
B1	Informed consent not available/not done	TS, PKS,
B2	Informed consent too late	None
C2	Randomization not followed	PKS
C3	Non-compliance	PKS,
C5	Incorrect intake of trial medication	PKS,
C6	Improper washout between treatments	PKS
D1	Prohibited medication use	PKS,
E1	Certain violations of procedures used to measure primary or secondary data	PKS
F1	Certain violations of time schedule used to measure primary or secondary data	PKS
G1	Incorrect intake of meal	PKS

6.3 SUBJECT SETS ANALYSED

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

The subject sets as defined in detail in the CTP, Section 7.3 will be used. These include the Treated set (TS) and Pharmacokinetic parameter analysis set (PKS) for the SRD and FE part, and the ECG Pharmacokinetic Concentration Set (ECGPCS) and
for the SRD part.

Table 6.3: 1 Subject sets analysed

	Subject set		
Class of endpoint	TS	PKS	ECGPCS
Disposition	X		
Exposure	X		
IPDs	X		
Demographic/baseline endpoints	X		
Primary endpoint	X		
Other safety parameters	X		
Secondary PK endpoints		X	
ECG endpoints and plasma concentrations used in exposure-response analysis			X

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

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

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

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

The only exception where imputation might be necessary for safety evaluation are AE dates. Missing or incomplete AE dates are imputed according to BI standards (3) [001-MCG-156_RD-01].

No imputation will be done for ECG endpoints. If replicate ECG recordings are missing, the arithmetic means per time point will be computed with the reduced (1 or 2) number of recordings. If single cardiac cycles (also denoted as beats or waveforms) are missing, the

arithmetic mean per single ECG will be computed with the reduced (1, 2 or 3) number of cardiac cycles.

For the classification of the on-treatment QTc/QT intervals into 'no new onset' / 'new onset' categories, a missing value is obtained only in case that

(i) all on-treatment values are missing and

(ii) the baseline value is less than or equal to 500 msec, or missing.

If condition (i) is fulfilled but the baseline value is greater than 500 msec, this case will be categorized as 'no new onset'. If baseline is missing and the maximum on-treatment QTc interval is greater than 450 msec (or 500 msec for QT interval, respectively), this is classified as a 'new onset' in the respective category. If baseline is missing and the maximum QTc interval is less than or equal to 450 msec (or 500 msec for QT interval, respectively), this will be categorized as 'no new onset'. If baseline is missing, a QTc/QT interval > 500 msec at any time on treatment will be a notable finding.

For subjects on active drug, missing plasma concentration values with 'BLQ' in the comment field will be replaced by ½ LLOQ. For placebo subjects, the missing plasma concentration values will be replaced by 0 for the exposure-response analyses.

Missing data and outliers of PK data are handled according to BI standards (4) [001-MCS-36-472_RD-01] and (5)

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

In all analyses (except for analyses of ECG variables), the last available off-treatment value determined prior to the first dosing of trial medication of the respective treatment period will be defined as baseline. This means that a separate baseline is defined for each study treatment of the FE part. Off-treatment in this context means that a value measured within an on-treatment phase, as defined in Table 6.1: 1, will not be used as baseline for any study treatment.

There will be a centralised evaluation of all 12-lead ECG recordings for the SRD part at the time points specified in Table 6.7: 1:

Table 6.7: 1 Time schedule of 12-lead ECG recordings with centralised evaluation

Visit	Day	Planned time [hh:mm] (relative to respective drug administration)	Study phase
2	1	-00:30	Baseline
		00:10	On-treatment
		00:30	
		00:45	
		01:00	
		01:30	
		02:00	
		03:00	
		04:00	
		06:00	
		08:00	
		10:00	
		12:00	
	2	24:00	

Three triplicate ECGs will be recorded as the baseline before the first drug administration, but only the first ECG of each of the 3 triplicates will be evaluated. The baseline value of an ECG variable is defined as the mean of the transferred baseline ECG measurements prior to drug administration. At all other time points, 1 triplicate ECG will be recorded, but only the first ECG of the triplicate will be centrally evaluated.

For the exposure response analyses, pairs of ECG variables and corresponding plasma concentrations will be built using the same planned time points, e.g., the HR change from baseline and the plasma concentration measured at planned time 0:30 will build one pair. Note, there is a time-matched PK sample planned at each planned time of ECG recordings as outlined in Table 6.7: 1 above, see also Flow Chart in the CTP. Whether a time deviation between PK blood sampling time and corresponding ECG recording is too big for a reliable assessment and the pair has to be excluded from the analysis will be decided no later than at the RPM.

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

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, sorted by treatment or sequence group, subject number and visit. 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	10^{th} percentile
Q1	1^{st} quartile
Q3	3^{rd} quartile
P90	90^{th} percentile

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 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 are actually 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. 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.

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

A medication will be considered concomitant, if it

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

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

7.3 TREATMENT COMPLIANCE

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

7.4 PRIMARY ENDPOINT

Refer to Section 7.8.1 for a description of the analysis of AEs, and in particular the analysis of the percentage of subjects with drug related AEs, which is the primary endpoint of this trial.

7.5 SECONDARY ENDPOINTS

7.5.1 Key secondary endpoint

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

7.5.2 Secondary endpoints

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

The PK endpoints will be assessed descriptively. The analysis of standard PK parameters is performed according to BI standards (4) [001-MCS-36-472_RD-01].

Exclusion of PK parameters

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

Exclusion of plasma 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 CTP trial 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)

7.7 EXTENT OF EXPOSURE

Descriptive statistics are planned for this section of the report, by fasting state and overall for the FE part. For the SRD part a listing will be sufficient.

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 electronic case report form (eCRF) will be collapsed into an AE event provided that all of the following applies:

- All AE attributes are identical (LLT, 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).

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 the screening or treatment phases 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 other significant AEs according to ICH E3 (8) and for the class of AESIs.

CTP: *Hepatic injury*
A hepatic injury is defined by the following alterations of hepatic laboratory parameters::

- *An elevation of AST (aspartate transaminase) and/or ALT (alanine transaminase) ≥3-fold ULN combined with an elevation of total bilirubin ≥2-fold ULN measured in the same blood sample, or*
- *Aminotransferase (ALT, and/or AST) elevations ≥10 fold ULN*

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

According to ICH E3 (8), 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 system organ class 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 (8)). AEs will also be summarized by maximum intensity.

The system organ classes will be sorted by total frequency, preferred terms will be sorted by total frequency (within system organ class).

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 system organ class and preferred term. The frequency of subjects with SAEs will also be summarised.

For disclosure of AE data in the EudraCT register, the frequency of AEs, the frequency of non-serious AEs with an incidence of greater than 5 % (in preferred terms) and the frequency of SAEs will be summarised.

For support of lay summaries, the frequency of subjects with drug-related SAEs will be summarised by treatment, primary system organ class and preferred term.

7.8.2 Laboratory data

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

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 on the eCRF or at the RPM at the latest. It is the Investigator's responsibility to decide whether a lab value is clinically significant abnormal or not. Standard or project-specific rules for flagging clinically significant values will not be applied in this study.

Clinically relevant findings in laboratory data will be reported as AEs and will be analysed as part of AE analysis.

7.8.3 Vital signs

The analysis of vital signs 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 study drug administration) or as AEs (during the trial) if judged clinically relevant by the investigator, and will be analysed as such.

7.8.4 ECG

Abnormal findings will be reported as baseline conditions (prior to first study drug administration) or as AEs (during the trial) if judged clinically relevant by the investigator.

Descriptive analysis of ECG endpoints will be based on the TS. The evaluation of the relationship between plasma concentration and change in ECG endpoints (exposure-response analysis) will be based on the ECGPCS.

Listing of individual data

For all quantitative endpoints, listings of individual data will be shown in Appendix 16.2. For QTcB and RR, only listings will be provided. Occurrences of notable findings will be flagged.

Comments regarding the ECGs will be listed.

Categorical endpoints

For the categorical endpoints, frequency tables will be provided.

For all subjects with any notable finding in ECG intervals, a separate listing will be created as end-of-text display (based on the same display template as in Appendix 16.2), and the corresponding time profiles will be shown.

Quantitative endpoints

Descriptive statistics (N, mean, SD, min, median, max) will be provided for the changes from baseline over time of QTcF, HR, QT, PR and QRS. The time profiles of mean and SD for the changes from baseline on treatment will be displayed graphically by treatment group.

Exposure-response analysis

To analyse the relationship between changes from baseline in QTcF and HR and the time-matched plasma concentrations a random coefficient model will be applied to the ECGPCS, including placebo treated subjects. For a list of time points with scheduled ECG assessments and a time-matched plasma concentration, refer to Table 6.7: 1.

For the handling of missing values, see Section 6.6.

The remaining Section describes the analysis for QTcF only, however the same analysis will be performed for HR.

The response variable will be change from baseline in QTcF (ΔQTcF). The placebo subjects will be included in the analysis, setting their plasma concentrations to zero.

As a first step, it is investigated if there is a potential delayed or accelerated (e.g. due to metabolites) effect of the drug on QTcF. A general visual impression will be provided by overlaying time profiles of plasma concentrations and QTcF changes from baseline (ΔQTcF). These figures will be generated for each subject (presented in the Statistical Appendix of the CTR), as well as for means per treatment group (presented in the End-of-Text part of the CTR).

The relationship between BI 764122 plasma concentrations and QTcF changes from baseline will be investigated in an exploratory manner using a random coefficient model to estimate the difference in mean QTcF change from baseline between BI 764122 and placebo and its

90% confidence interval at the geometric mean of C_{max} for each dose. Additionally, the estimated overall slope with its 90% confidence interval will be provided. The used random coefficient model is based on a white paper from Garnett et. al. [R18-0143] (10) with ΔQTcF as response variable, centred baseline QTc and plasma concentration as continuous covariates, treatment and time as fixed categorical effects, and a random intercept and slope for each subject. For more details refer to Additional Section 9.2.

For visualization, a scatterplot of the BI 764122 plasma concentration against the following individual QTcF values will be provided: For each subject on active treatment and each time point, subtract the mean value of all individual observed ΔQTcF values from the placebo group for this time point from the individual observed ΔQTcF value for this subject and time point. This results in estimates for "individual ΔΔQTcF" values, which should only be used for plotting purposes. The corresponding regression line and its pointwise confidence bands as well as the geometric mean of C_{max} for each dose will additionally be displayed in the plot.

To check model assumptions, the conditional residuals will be plotted and presented in the Statistical Appendix of the CTR. In case of non-linearity or if there is evidence for a delayed effect, further models will be explored in order to better characterise the PK-ECG relationship (e.g. effect compartment models, non-linear models, etc.).

Appropriateness of heart rate correction methods of QT interval

To evaluate the appropriateness of the heart rate correction methods, the slope of the relationship of QTcF interval versus RR interval (values log-transformed using the natural logarithm) will be estimated by applying the random coefficient model described in Section 9.1 using all time points. A scatterplot of ln(QTcF) vs ln(RR) including the overall regression line will be included in the Statistical Appendix of the CTR. The resulting (fixed effect) slope together with two-sided 95% confidence intervals will be included in the footnote for this plot.

7.8.5 Others

Physical examination findings will be reported as relevant medical history/baseline condition (i.e., a condition already existent before intake of first study drug) or as AE and will be summarised 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 Design, Conduct, Analysis and Evaluation of Clinical Trials, current version
2	*001-MCS-40-413_1.0:* "Identify and Manage Important Protocol Deviations (iPD)", current version; IDEA for CON
3	*KM Asset BI-KMED-BDS-HTG-0035:* "Handling of missing and incomplete AE dates", current version; KMED
4	*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	*KM Asset BI-KMED-BDS-HTG-0045:* "Reporting of Clinical Trials and Project Summaries", current version; KMED
7	*KM Asset BI-KMED-BDS-HTG-0041:* "Analysis and Presentation of Adverse Event Data from Clinical Trials", current version; KMED
8	*CPMP/ICH/137/95:* "Structure and Content of Clinical Study Reports", ICH Guideline Topic E3; Note For Guidance on Structure and Content of Clinical Study Reports, current version
9	*KM Asset BI-KMED-BDS-HTG-0042:* "Display and Analysis of Laboratory Data", current version; KMED
10	Garnett C, Bonate PL, Dang Q, Ferber G, Huang D, Liu J, et al. Scientific white paper on concentration-QTc modeling. J Pharmacokinet Pharmacodyn. 2018,45(3):383-397 [R18-0143]

9. ADDITIONAL SECTIONS

9.1 DETAILED DESCRIPTION OF ENDPOINTS FOR ECG

QT, PR, QRS and RR baseline and on-treatment measurements (see Table 6.7: 1) are included in the centralised ECG evaluation.

For each single ECG, measurements of QT, PR, QRS and preceding RR interval of four cardiac cycles will be determined and stored in the database as raw data. Their mean values will be used as the QT, PR, QRS, and RR interval values, respectively, for this ECG.

QTcF, HR and QTcB will be calculated based on the derivation rules as follows:

From the four cardiac cycles of a single ECG, the HR (measured in beats per minute, beats/min) will be calculated as

$$HR\ [beats/min] = \frac{60\ 000}{\overline{RR}}$$

where $\overline{RR}$ is the mean of the four RR intervals (measured in msec).

Similarly, the QT interval corrected for HR according to Fridericia's formula (QTcF) for a single ECG will be derived as

$$\overline{QTcF}\ [msec] = \left(\frac{1000}{\overline{RR}}\right)^{1/3} * \overline{QT}[msec],$$

where $\overline{QT}$ is the mean of the four QT intervals and $\overline{RR}$ is the mean of the corresponding preceding RR intervals of the four cardiac cycles for this ECG.

Likewise, the HR-corrected QT interval according to Bazett's formula (QTcB) for a single ECG is given by

$$\overline{QTcB}\ [msec] = \left(\frac{1000}{\overline{RR}}\right)^{1/2} * \overline{QT}[msec].$$

In case of triplicate ECGs at a time point, the respective ECG variable will be averaged over the triplicate ECG measurements at this time point (arithmetic mean). Note that in case of missing values the averaging is simply done for the available values.

10. HISTORY TABLE

Table 10: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
Final	**13-Sep-19**		None	This is the final TSAP without any modification