TRIAL STATISTICAL ANALYSIS PLAN

c26650906-01

BI Trial No.:	1289-0038
Title:	Thorough QT study to evaluate the effects of BI 409306 as single doses on cardiac safety parameters in healthy male and female subjects. A randomized, placebo controlled, double-blind, five-period crossover study with (open-label) moxifloxacin as positive control
Investigational Product(s):	BI 409306
Responsible trial statistician(s):	Phone: Fax: Phone:
Date of statistical analysis plan:	18 NOV 2019 SIGNED
Version:	"Final"

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2. LIST OF ABBREVIATIONS

Term	Definition / description
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BRAVE	BI Rave system
CARE	Clinical data Analysis and Reporting Environment
CT	Concomitant Therapy
DBP	Diastolic blood pressure
ECGS	ECG analysis Set
HR	Heart Rate
IQRMP	Integrated Quality and Risk Management Plan
MMRM	Mixed effects Model for Repeated Measurements
PR interval	ECG interval from the onset of P wave to the beginning of the QRS
QRS duration	Duration of the QRS complex in the ECG (corresponding to the depolarization of the right and left ventricles)
QT interval	ECG interval from the beginning of the QRS complex to the end of the T wave
QTcB [msec]	QT interval, heart rate corrected according to Bazett's formula
QTcF [msec]	QT interval, heart rate corrected according to Fridericia's formula

Term	Definition / description
	correction factor derived from individual subject data
Q1	Lower Quartile
Q3	Upper Quartile
RAGe	Report Appendix Generator system
REP	Residual Effect Period
RR interval	ECG interval from the peak of the R wave to the peak of the subsequent R wave
SA	Statistical Analysis
SBP	Systolic Blood Pressure
SD	Standard Deviation
SDL	Subject Data Listings
SOC	System Organ Class
TS	Treated Set
ULN	Upper limit of normal range

3. INTRODUCTION

As per ICH E9 (1), the purpose of this document is to provide a more technical and detailed elaboration of the principal features of the analysis described in the protocol, and to include detailed procedures for executing the statistical analysis of the primary and secondary variables and other data.

This Trial Statistical Analysis Plan (TSAP) assumes familiarity with the Clinical Trial Protocol (CTP), including Protocol Amendments. In particular, the TSAP is based on the planned analysis specification as written in CTP Section 7 “Statistical Methods and Determination of Sample Size”. Therefore, TSAP readers may consult the CTP for more background information on the study, e.g., on study objectives, study design and population, treatments, definition of measurements and variables, planning of sample size, randomization.

Study data will be stored in the BI Rave (BRAVE) system.

The statistical analyses will be performed within the validated working environment Clinical data Analysis and Reporting Environment (CARE), including SAS™ (current Version 9.4, by SAS Institute Inc., Cary, NC, USA), and a number of SAS™-based tools (e.g., macros for the analyses of AE data or laboratory data; Report Appendix Generator system (RAGe) for compilation/formatting of the CTR appendices).

Pharmacokinetic (PK) parameters will be calculated using Phoenix WinNonlin™ software (version Phoenix 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

No efficacy endpoints will be evaluated in this trial.

General remarks regarding ECG endpoints derived from interval measurements:
The derivation of HR, QTcI and QTcF endpoints is described in Section 9.1.

Throughout this section, the term "baseline" refers to the mean of the pre-dose ECG measurements at Visits 2-6 (i.e. a separate baseline for each period which is also denoted as "period baseline"; see Section 6.7). Each ECG measurement per time point is defined as the mean value of 3 single ECGs with 4 cardiac cycles each.

5.1 PRIMARY ENDPOINTS

CTP Section 5.2.1.1: *The primary endpoint will be derived based on the changes from baseline in QTcF at each time point between 20 min to 24 hours after drug administration of BI 409306 and placebo. For each of the 2 doses of BI 409306, the relevant outcome is the maximum mean difference between BI 409306 and placebo in the QTcF changes from baseline.*

5.2 SECONDARY ENDPOINTS

5.2.1 Key secondary endpoints

Not applicable. There are no key secondary endpoints specified in the CTP.

5.2.2 Secondary endpoints

CTP Section 5.2.1.2:

- *The QTcF changes from baseline at each time point between 20 min to 24 hours after drug administration of moxifloxacin and placebo (for assessment of assay sensitivity). The relevant outcome is the maximum mean difference between moxifloxacin and placebo in the QTcF changes from baseline for the time points 2, 3, and 4 hours after dosing.*
- *The changes from baseline in HR at each time point between 20 min to 24 hours after drug administration of BI 409306 and placebo. For each dose of BI 409306, the relevant outcomes are the maximum and the minimum mean differences between BI 409306 and placebo in HR changes from baseline after dosing. HR will be derived from the RR interval* (see Section 9.1).

6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENTS

For basic information on treatments to be administered and assignment of treatment groups, refer to Section 4 of the CTP.

For the statistical analysis of AEs, the following analysis phases specified in Table 6.1: 1 will be defined for each subject.

Table 6.1: 1 Analysis phases for statistical analysis of AEs

Study analysis phase	Label	Start	End
Screening	**Screening**	Date of informed consent	Date/time of first administration of study drug in period 1
On-treatment	**Placebo 1**, **Placebo 2**, **BI 50 mg**, **BI 250 mg,** or **Mox 400 mg,** respectively	Date/time of administration of study drug	Date/time of administration of study drug + residual effect period or Date/time of administration of study drug in the next treatment period or 12:00 a.m. on day after subject's end of study participation date, whatever comes first
Follow-up	**FUP Placebo 1**, **FUP Placebo 2**, **FUP BI 50 mg**, **FUP BI 250 mg**, or **FUP Mox 400 mg**, respectively	End of the respective on-treatment period (see line above)	Date/time of administration of study drug in the next treatment period, if applicable, otherwise 12:00 a.m. on day after subject's end of study participation date

CTP Section 1.2.4: *The Residual Effect Period (REP) of BI 409306 is 24 hours. The REP of moxifloxacin is 4 days.*

For Placebo, the REP is set to 24 hours, i.e. equal to that of BI 409306.

In CTR Section 15 and Appendix 16.1.13.1.8, AE displays will present results for the on-treatment phase only.

In CTR Section 15 AE tables (but not in Appendix 16.1.13.1.8 AE tables), the following totals will be provided in addition:

- "**Total Pbo**", defined as the total over all on-treatment phases involving treatment with placebo
- "**Total BI**", defined as the total over all on-treatment phases involving treatment with BI 409306
- "**Total**", defined as the total over all on-treatment phases

The treatments will be presented in Section 15 AE tables in the following sort order: Placebo 1, Placebo 2, BI 50 mg, BI 250 mg, Mox 400 mg, Total Pbo, Total BI, Total.

Statistical analyses of vital signs will be conducted by treatment (Placebo 1, Placebo 2, BI 50 mg, BI 250 mg, Mox 400 mg), with clear differentiation between baseline (see Section 6.7) and on-treatment measurements.

Statistical analyses of ECG data will include the single periods involving BI treatment (or treatment with moxifloxacin, respectively) together with summarised Placebo and BI periods (see also Section 7.6.1).

More details on the technical implementation of these analyses are provided in the Analysis Data Set Plan of this TSAP.

6.2 IMPORTANT PROTOCOL DEVIATIONS

Consistency check listings (for identification of deviations from pre-specified 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 the analyses or whether it must be corrected in the clinical database. Each protocol deviation must be assessed to determine whether it is an important protocol deviation (iPD). For definition of iPDs, and for the process of identification of these, refer to the BI reference document "Identify and Manage Important Protocol Deviations (iPD)" (2).

If any iPDs are identified, they are to be summarised into categories and will be captured in the minutes of the RPM. 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 summarized and listed. Table 6.2: 1 below specifies which kind of iPDs could potentially lead to exclusion from which analysis set. The decision on exclusion of subjects from analysis sets will be made at the latest at the RPM, after discussion of exceptional cases and implications for analyses.

Decisions made at the RPM will be documented within the decision log and stored within the eTMF in the DMS.

Table 6.2: 1 Handling of iPDs

iPD code	iPD Category & Brief Description	Potentially excluded from which analysis set
A1	Inclusion Criteria Not Met	ECGS, PKS
A2	Exclusion Criteria Met	ECGS, PKS
B1	Informed consent not available/not done	TS
B2	Informed consent too late	None
C1	Incorrect trial medication taken	ECGS, PKS
C2	Randomisation not followed	ECGS, PKS
C3	Non-compliance	ECGS, PKS
C4	Medication code broken inappropriately	None
C5	Incorrect intake of trial medication	ECGS, PKS
C6	Improper washout between treatments	ECGS, PKS
D1	Prohibited medication use	ECGS, PKS
D3	Improper washout of concomitant medication	ECGS, PKS
E1	Certain violations of procedures used to measure primary or secondary data	ECGS
F1	Certain violations of time schedule used to measure primary or secondary data	ECGS
G1	Incorrect intake of meal	PKS

6.3 SUBJECT SETS ANALYSED

CTP Section 7.3: *The following analysis sets will be defined:*

- *Treated Set (TS): This subject set includes all randomised subjects who have received at least one dose of any study drug.*

- *ECG Set (ECGS): This subject set includes all subjects in the TS who have at least one on-treatment value for at least one ECG endpoint, which is not excluded due to ECG relevant iPDs. Such iPDs may be e.g. the use of pro-arrhythmic medications. Exclusion of single ECG values due to relevant iPDs is to be decided no later than in*

the Blinded Report Planning Meeting (BRPM) before data base lock and will be documented in the CTR.

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 subjects who failed to complete all periods of 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 Section 7.4.1: *With respect to safety evaluations, it is not planned to impute missing values.*

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

ECG

If single cardiac cycles (generally four) are missing, the arithmetic means per single ECG will be computed with the reduced (1, 2 or 3) number of cardiac cycles.

If replicate ECG recordings (generally three) are missing, the arithmetic means per time-point will be computed with the reduced number (1 or 2) of recordings.

If a period baseline is missing the arithmetic mean of the remaining other period baselines will be used.

In the repeated measures analyses, the subject baseline will be calculated based on the non-missing period baselines used in the respective comparison. Imputed period baseline values will not be used for creation of subject baselines.

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

6.7.1 Baseline

If not otherwise stated, baseline is defined as the last measurement prior to first drug administration.

ECG interval data:

CTP Section 7.1: *Throughout the study protocol, the term "baseline" (if not specified further) refers to the 3 pre-dose triplicate ECG measurements at Visits 2-6 (i.e. a separate baseline for each period will be derived from the 9 ECG recordings that comprise 4 cardiac cycles each).*

The mean of the values calculated for the 3 pre-dose time points per period is also denoted as 'period baseline'. 'Change from baseline' always refers to the period baseline. An additional 'subject baseline' is defined as the arithmetic mean of the period baselines per subject and will only be used in the context of MMRM analyses; for further details see Section 7.4.

6.7.2 Time windows

Time windows are defined in Section 6.1 of the CTP.

Adherence to time windows will be checked at the RPM.

The following tables summarize the time points of interval extractions from the 12-lead Holter recordings as well as the planned time intervals for Holter evaluations with regard to cardiac arrhythmia events.

Table 6.7.2: 2 Time schedule for extractions of triplicate ECGs from Holter recording during treatment periods

	Planned times [hh:mm] relative to administration of study drug	
Visit	Pre-dose	On treatment
2-6	-0:50, -0:35, -0:20	0:20, 0:40, 1:00, 1:30, 2:00, 2:30, 3:00, 4:00, 8:00, 12:00, 24:00

7. PLANNED ANALYSIS

For End-Of-Text (EoT) tables, the set of summary statistics is: N / Mean / SD / Min / Q1 (lower quartile) / Median / Q3 (upper quartile) / Max.

For tables that are provided for endpoints with some extreme data, median, quartiles and percentiles should be preferred to mean, standard deviation, minimum and maximum.

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).

The precision for percentages should be one decimal point. The category missing will be displayed only if there are actually missing values.

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

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

7.2 CONCOMITANT DISEASES AND MEDICATION

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

7.3 TREATMENT COMPLIANCE

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

7.4 PRIMARY ENDPOINT(S)

7.4.1 Primary analysis of the primary endpoint(s)

CTP Section 7.1.3: *For the analysis of the QTcF changes from baseline at each time point between 20 min to 24 hours after dosing, a linear mixed-effects model for repeated measurements (MMRM) will be used.* The analyses will be based on the ECG set.

The comparison between each dose of BI 409306 and placebo will be performed pairwise, i.e. data not relevant for the comparison of interest will be excluded. Data from both placebo periods per subject will be included simultaneously in the analysis, using the same treatment code 'placebo' but differentiated by the respective period numbers. This means that the model defined below can directly be used for estimating the treatment contrast between the active drug under consideration and placebo, using the observations from both placebo periods. In the following, the 'subject baseline' is defined as the arithmetic mean of the period baselines per subject (only from the periods involved in the comparison, i.e. the period baseline of the active treatment period and those of the 2 placebo periods).

The MMRM is based on Schall and Ring (14) *and includes the fixed categorical effects of 'treatment', 'period' and 'time', the 'treatment-by-time' interaction and 'period-by-time'*

interactions, as well as the continuous fixed covariates 'period baseline' and 'subject baseline', and the 'period baseline-by-time' interaction and 'subject baseline-by-time' interaction. Subject is included as a random effect on the intercept. For the repeated effect 'time', an unstructured covariance pattern is chosen, using the blocking factor 'subject-by-period'. Note that the 'subject baseline' is included in the model to avoid cross-level bias affecting treatment comparisons; see Kenward and Roger (13).

More precisely, the model is given by

$$Y_{ikm(j)} = \mu + \gamma B_{im} + \gamma' \bar{B}_i + \pi_m + \tau_j + \zeta_k + \gamma_k B_{im} + \gamma'_k \bar{B}_i + (\pi\zeta)_{mk} + (\tau\zeta)_{jk} + s_i + e_{ikm},$$

$$s_i \sim N(0, \sigma_s^2),\ (e_{i1m}, \ldots, e_{iKm}) \sim N_K\ (\mathbf{0}, \Psi),$$

where *i=1,...,I* indicates the subject, *k=1,...,K* the time point within period, *m=1,...,M* the period and *j=1,2* the treatment,

$Y_{ikm(j)}$	the QTcF change from period baseline for subject *i* receiving treatment *j* in period *m* at repeated measures time point *k*,
μ	the overall intercept,
B_{im}	the baseline value for subject *i* in period *m* (period baseline),
γ	the associated covariate effect of period baseline,
$\bar{B}_i$	the subject baseline value (mean of 3 period baselines) for subject *i*,
γ'	the associated covariate effect of subject baseline,
π_m	the effect of period *m*,
τ_j	the effect of treatment *j*,
ζ_k	the effect of time *k*,
γ_k	the interaction effect of period baseline and time,
γ'_k	the interaction effect of subject baseline and time,
$(\pi\zeta)_{mk}$	the interaction effect of period and time,
$(\tau\zeta)_{jk}$	the interaction effect of treatment and time,
s_i	the random effect of subject *i* on intercept, assumed mutually independent across subject,
e_{ikm}	the random error associated with subject *i* for time *k* and period *m,* assumed

independent across period and subject (indices *m, i*), and

Ψ an unstructured *K-by-K* covariance matrix.

The random subject effects s_i and the random errors e_{ikm} are assumed to be independent of one another.

CTP Section 7.3.1: *For the pairwise comparisons between each dose of BI 409306 and placebo, mean treatment differences in the QTcF changes from baseline at each time point will be estimated by the differences in the corresponding least-squares means. Two-sided 90% confidence intervals based on the t-distribution will also be computed for each time point. The null hypothesis will be rejected if the maximum upper confidence limit for the mean difference in the QTcF changes from baseline between BI 409306 and placebo is less than 10 msec.*

7.5 SECONDARY ENDPOINT(S)

7.5.1 Key secondary endpoint(s)

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

7.5.2 (Other) Secondary endpoint(s)

7.5.2.1 Assessment of assay sensitivity

CTP Section 7.3.2.1: *The effect of moxifloxacin on the QTcF changes from baseline in comparison with placebo will be assessed using the same MMRM as applied in the primary analysis.*

For this analysis, only the data from the moxifloxacin and placebo periods will be used.

For describing the time course of the effect of moxifloxacin on QTcF, 90% confidence intervals for the mean differences of the QTcF changes from baseline between moxifloxacin and placebo will be provided.

For the formal test of assay sensitivity at level α=5%, the method by Hochberg (10) will be applied. To this end, the three single hypotheses that the mean difference in the QTcF change from baseline between moxifloxacin and placebo is less than or equal to 5 msec at a given time point (out of the three time points 2, 3, and 4 hours after drug administration) will be tested based on the results of the MMRM (fitted to the data for all time points). If the largest of the three p-values is less than 5% (=α), then all single hypotheses can be rejected. If the second largest p-value is less than 2.5% (=α/2), then the corresponding null hypothesis and the one regarding the test with the lowest p-value can be rejected. If the lowest p-value is less than 1.667% (=α/3), then only the null hypothesis corresponding to this p-value can be rejected. Note that it is sufficient to reject only one of the three single null hypotheses in order to reject the overall null hypothesis stated in CTP *Section 7.2 (i.e., the intersection of the three single hypotheses), and hence to show assay sensitivity.*

7.5.2.2 Analyses of the heart rate

For each dose of BI 409306, the HR changes from baseline at each time point between 20 min to 24 hours after dosing will be analysed by applying the same model as in the primary analyses and calculating the corresponding 90 % CIs for the mean difference between BI 409306 and placebo. For these analyses, only the HR data from the respective BI 409306 dose and placebo will be used.

7.7 EXTENT OF EXPOSURE

Descriptive statistics are planned for this section of the report based on the TS. The date and time of drug administration will be listed for each subject.

7.8 SAFETY ANALYSIS

CTP Section 7.3: *The TS will be used for all other safety summaries and all safety listings.*

7.8.1 Adverse events

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

Unless otherwise specified, the analyses of adverse events will be descriptive in nature. All analyses of AEs will be based on the number of subjects with AEs and NOT on the number of AEs.

For analysis multiple AE occurrence data on the eCRF will be collapsed into an AE provided that all of the following applies:

- All AE attributes are identical (lower level term, intensity, action taken, therapy required, seriousness, reason for seriousness, relationship, outcome, AE of special interest**).**
- The occurrences were time-overlapping or time-adjacent (time-adjacency of 2 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" (5) 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 or follow-up phases as defined in Section 6.1. AEs will be analysed based on actual treatments, as defined in Table 6.1: 1.

In addition to the presentation of AEs in separate study periods, both the events in the two placebo periods, and the events of the two periods of (the different doses of) BI 409306 (see Section 6.1) will be added. The interpretation of this summary for "Total BI" is "events following a dose of at least the therapeutic dose level". When comparing "Total Pbo" and "Total BI", "time under risk" is similar.

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 (6) and for the class of AESIs.

CTP Section 5.2.2.1: *The following is considered as AESI:*

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*

According to ICH E3 (6), AEs classified as 'other significant' needs to be reported and will include those non-serious and non-significant adverse events with
(i) 'action taken = discontinuation' or 'action taken = reduced', or
(ii) marked haematological and other lab abnormalities or lead to significant concomitant therapy as identified by the Clinical Monitor/Investigator at a Medical Quality Review Meeting.

The frequency of subjects with adverse events will be summarised by treatment, primary system organ class and preferred term. Separate tables will be provided for subjects with other significant adverse events according to ICH E3 (6), for subjects with AESIs and for subjects with serious adverse events. The frequency of subjects with AEs and the frequency of subjects with AEs considered by the investigator to be drug related will also be summarised by maximum intensity, primary SOC and preferred term.

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

For disclosure of AE data on ClinicalTrials.gov, the frequency of subjects with non-serious AEs occurring with an incidence of greater than 5 % (in preferred terms) will be summarised by treatment, primary SOC and preferred term. The frequency of subjects with SAEs will also be summarised.

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

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

7.8.2 Laboratory data

CTP: *Laboratory data will be listed only. Values outside the reference range as well as values defined as clinically relevant will be flagged.* Refer to the BI reference document "Display and Analysis of Laboratory Data" (7).

7.8.3 Vital signs

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

7.8.4 ECG

The statistical analyses of ECG endpoints selected as primary, secondary or further endpoints (see Sections 5.1, 5.2 and 5.3) are described in the respective sections of this TSAP (see Section 7.4, 7.5 and 7.6).

CTP Section 5.2.4.5: *ECG data from continuous 3-lead ECG recording will not be transferred to the clinical trial database.*

CTP Section 5.2.4.6: *Abnormal findings from safety 12-lead single ECGs, Holter recordings or 3-lead continuous ECG monitoring, irrespective of whether they originate from central or local evaluation, will be reported as AEs (during the trial) or recorded in the subject's medical history (at screening) if judged clinically relevant by the investigator.*

Listing of individual ECG data

The listings of individual ECG data will be based on the treated set.

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

For all subjects with any notable finding of quantitative ECG recordings, 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.

Comments regarding the ECGs will be listed.

7.8.5 Others

Physical examination findings will be reported as relevant medical history/baseline condition (if a condition already exists before first administration of study treatment) or as AE (if condition emerges after first administration of study treatment) and will be summarized as such. No separate listing or analysis of physical examination findings will be prepared.

8. REFERENCES

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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:* "Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics", current version, Group "Biostatistics & Data Sciences", IDEA for CON.
5.	*KM Asset BI-KMED-BDS-HTG-0041:* "Analysis and Presentation of Adverse Event Data from Clinical Trials", current version; KMED
6.	*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
7.	*KM Asset BI-KMED-BDS-HTG-0042:* "Display and Analysis of Laboratory Data", current version; KMED
8.	Guidance for industry: E14 clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs. Rockville: U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER); 2005. [R07-4722]
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12.	Schall R, Ring A. Statistical characterization of QT prolongation. J Biopharm Stat 20 (3), 543 - 562 (2010) [R10-2954]
13.	Kenward MG, Roger JH. The use of baseline covariates in crossover studies. Biostatistics 11 (1), 1 - 17 (2010) [R10-4391]
14.	Schall R, Ring A. Mixed models for data from thorough QT studies: part 1. Assessment of marginal QT prolongation. Pharm Stat, (2010) [R10-5353]

15.	Ring A, Walter B, Larbalestier A, Chanter D. An efficient crossover design for thorough QT studies. GMS Med Inform Biometr Epidemiol 2010; 6(1):Doc05. [R12-0517]
16.	Garnett C, Bonate PL, Dang Q, Ferber G, Huang D, Liu J, et al. Scientific white paper on concentration-QTc modeling. J Pharmacokin Pharmacodyn (2017) [R18-0143]

9.1 DERIVATION OF HR AND QTC INTERVAL ENDPOINTS

CTP Section 7.3: *For the analysis of the ECG variables QT, RR, PR, and QRS, a 2-step averaging procedure will be performed. In the first step, the 4 cardiac cycles per 10-second ECG will be averaged.*

For each 10-second ECG, heart rate will then be derived from the calculated RR value as

HR[beats/min]=60000/RR[msec].

Likewise, for each ECG the heart rate corrected QT intervals QTcF and QTcI will be derived from the mean values of the 4 cardiac cycles for RR and QT, respectively (see Section 7.6.3).

In the second step, for obtaining one ECG variable value per subject per time point, the calculated values of the three 10-second ECGs (triplicate ECGs extracted from the Holter recordings) will be averaged.

For all quantitative ECG variables derived from the 10-second ECGs, further analyses are then performed on these aggregated data on time point level. Period baseline values are calculated as the means of the values derived for the 3 baseline time points per period.

10. HISTORY TABLE

Table 10: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
Final	18-NOV-19		None	This is the final TSAP