TRIAL STATISTICAL ANALYSIS PLAN

c28958859-01

BI Trial No.:	1402-0008
Title:	Safety, tolerability and pharmacokinetics of single rising oral doses of BI 1358894 in healthy Japanese male subjects (double-blind, randomised, placebo-controlled parallel dose group design)
Investigational Product:	BI 1358894
Responsible trial statisticians:	Phone: Fax:
Date of statistical analysis plan:	14 AUG 2019 SIGNED
Version:	Final

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2. LIST OF ABBREVIATIONS

See Medicine Glossary:
website: glossary

Term	Definition / description
ALT	Alanine Aminotransferase
ANCOVA	Analysis of covariance
AST	Aspartate Aminotransferase
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
$AUC_{0-\infty}$	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity
BMI	Body mass index
BP	Blood pressure
CARE	Clinical Analysis and Reporting Environment
CI	Confidence Interval
C_{max}	Maximum measured concentration of the analyte in plasma
CV	Arithmetic Coefficient of Variation
DB	Dose Proportionality, Between-Subject Design
DILI	Drug induced liver injury
ECGPCS	ECG Pharmacokinetic Concentration Set
gCV	Geometric Coefficient of Variation
gMean	Geometric Mean
HR	Heart rate
IQRMP	Integrated Quality and Risk Management Plan
LLT	Lower Level Term
Max	Maximum
MedDRA	Medical Dictionary For Regulatory Activities
Min	Minimum
N	Number non-missing observations
P10	10^{th} percentile
P90	90^{th} percentile
PKS	Pharmacokinetic parameter analysis set

Term	Definition / description
PR	Pulse rate
Q1	1st quartile
Q3	3rd quartile
QD	Quaque die, once daily
RAGe	Report Appendix Generator system
REP	Residual Effect Period
RR	Respiratory rate
SAS®	Statistical Analysis System
SD	Standard Deviation
SOC	System Organ Class
TS	Treated Set
ULN	Upper Limit of Normal
WHO-DD	World Health Organization Drug Dictionary

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 endpoints and other data.

This trial statistical analysis plan (TSAP) assumes familiarity with the Clinical Trial Protocol (CTP). 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 (including data entered in the RAVE EDC system and external data provided by suppliers) will be stored in a Clinical Data Repository (CDR).

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

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 adverse event (AE) data or laboratory data; Report Appendix Generator system (RAGe) for compilation/formatting of the CTR appendices).

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

All analyses described in the TSAP are outlined in the CTP. The following changes compared to the protocol will be made:

In the protocol, it is stated that the medical examination at screening will include alcohol history. However, alcohol history is not captured in the eCRF, and thus, will neither be listed nor included in tables.

5. ENDPOINTS

5.1 PRIMARY ENDPOINT

Section 2.1.2 of the CTP:

The primary endpoint for assessment of safety and tolerability of BI 1358894 is the number [N (%)] of subjects with drug related adverse events.

5.2 SECONDARY ENDPOINTS

5.2.1 Key secondary endpoints

This section is not applicable as no key secondary endpoints have been defined in the CTP.

5.2.2 Secondary endpoints

Section 2.1.3 of the CTP:

The following pharmacokinetic parameters will be determined for BI 1358894 if feasible:

- *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 time point t_z)*
- *$AUC_{0-\infty}$ (area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity)*
- *C_{max} (maximum measured concentration of the analyte in plasma)*

6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENTS

It is planned that in total 24 Japanese healthy male subjects participate in this study, according to 3 sequential dose groups comprising 8 subjects per group. Within each dose group, 6 subjects will receive BI 1358894 and 2 will receive placebo.

For details of dosage and formulation see Table 6.1: 1 below.

Table 6.1: 1 Labels for treatments for use in the CTR

Dose group	Treatment		Short label
1-3	P*	Placebo, tablet, qd	Placebo
1	A	BI 1358894, 2*25 mg tablet, po, qd	BI 50mg
2	B	BI 1358894, 1*100 mg tablet, po, qd	BI 100mg
3	D	BI 1358894, 2*100 mg tablet, po, qd	BI 200mg

'qd' means here a single drug administration, not a regular drug administration per day.

*: The placebo group in the safety evaluation will consist of all placebo treated subjects, regardless of the dose group in which they were treated.

The following separate study phases will be defined for the analyses of AEs:

- **Screening** (ranging from 0:00h (midnight) on day of informed consent until administration time of study drug (BI or Placebo))
- **On treatment**
  - **BI/Placebo treatment** (separately for each treatment, ranging from the time of administration of BI 1358894 or Placebo until 0:00h (midnight) on the day after trial termination date)

Please note that all AEs reported between start of trial drug administration and the trial termination date will be considered on treatment (i.e. no follow-up period is considered in this trial).

Two types of AE displays will be provided in the report:

A) Section 15.3 and Appendix 16.1.13.1.8 (for ClinicalTrials.gov) of the CTR displays:

In these displays, the on treatment phase will be analysed (labelled with the name of the study treatment (short label)). Screening will not be included in this analysis.
The following totals will be provided in addition:

- a total over all BI treated phases (**"BI Total"**)

- a total over all on treatment phases included in this analysis ("**Total on treatment**") (Section 15.3 only)

B) Section 15.4 and Appendix 16.1.13.1.8 (except for ClinicalTrials.gov) of the CTR displays:

- Screening
- On treatment (labelled with the name of the study treatment (short label))

In Section 16.1.13.1.8 AE tables, the following totals will be provided in addition:

- a total over all BI treated phases (**"BI Total"**)
- a total over all study phases ("**Total**")

Tables of vital signs, ECG and laboratory values will present results by the above mentioned on treatment phase.

For detailed information on the handling of the treatments refer to Technical TSAP ADS (analysis data set) plan and Analysis Data Reviewer`s guide.

6.2 IMPORTANT PROTOCOL DEVIATIONS

Data discrepancies and deviations from the CTP will be identified for all treated subjects.

Section 7.3 of the CTP: *Important protocol deviations* (iPDs) *categories will be specified in the IQRMP,* iPDs *will be identified no later than in the Report Planning Meeting, and the* iPD *categories will be updated as needed.*

Consistency check listings (for identification of deviations 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 Report Planning Meeting (RPM). At this meeting, all manual deviations identified at the sites by the CRAs and deviations too complex to program will be reviewed by the trial team to decide which are considered important. For definition of important protocol deviations (iPD), and for the process of identification of these, refer to the Boehringer Ingelheim (BI) SOP "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 RPM minutes via an accompanying Excel spreadsheet (3). 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.

The iPDs will be summarised and listed.

6.3 SUBJECT SETS ANALYSED

- Treated set (TS):
  This subject set includes all subjects who were dispensed study medication and were documented to have taken at least one dose of investigational treatment.
  This is the full analysis set population in the sense of ICH-E9 (1). It is used for demographics, baseline characteristics, and safety analyses.
  The ECG analyses are performed on the TS, except for the exposure-response analyses, which are performed on the ECGPCS defined below.

Section 7.3 of the CTP: *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.*

Relevant protocol deviations may be

- *Incorrect trial medication taken, i.e., the subject received at least one dose of trial medication the subject was not assigned to*
- *Incorrect dose of trial medication taken*
- *Use of restricted medications*

Plasma concentrations and/or parameters of a subject will be considered as non-evaluable, if for example

- *The subject experienced emesis that occurred at or before two times median t_{max} of the respective treatment (Median t_{max} is to be determined excluding the subjects experiencing emesis),*
- *Missing samples/concentration data at important phases of PK disposition curve.*

Plasma/urine concentration data and parameters of a subject which is flagged for exclusion will be reported with its individual values but will not be included in the statistical analyses.

- Pharmacokinetic parameter analysis set (PKS):
  The pharmacokinetic parameter analysis set (PKS) includes all subjects from the TS receiving BI 1358894 who provide at least one PK endpoint that was not excluded according to the description above.
  It is used for assessment of dose proportionality and the descriptive analyses of PK parameters.

The descriptive analysis of PK concentrations will be based on the ADS ADPC. The descriptive and model based analysis of PK parameters will be based on the ADS ADPP.

- ECG Pharmacokinetic Concentration Set (ECGPCS):
  This subject set includes all subjects from the TS for whom at least one pair of a valid drug plasma concentration of BI 1358894 and a corresponding (i.e. time-matched) ECG endpoint to be used in the exposure-response analyses was provided. For placebo subjects, the plasma concentration is set to zero and hence always considered as valid. The decision whether a time deviation between PK blood sampling and ECG recording is acceptable (and thus whether the pair of values will be used) is to be made no later than at the RPM before data-base lock.

Table 6.3: 1 Analysis sets for endpoints/data description

Endpoint/data description	Analysis set		
	TS	PKS	ECGPCS
Primary and further safety endpoints (incl. ECG)	X		
ECG endpoints and plasma concentrations used in exposure-response analysis			X
Secondary PK endpoints		X	
Demographic/baseline data	X		
Important protocol deviations	X		
Disposition	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

Handling of missing data and outliers will be performed as described in the CTP, Section 7.5.

The only exceptions where imputation might be necessary for safety evaluation are AE dates. Missing or incomplete AE dates are imputed according to BI standards.

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

If single cardiac cycles of an ECG (out of the generally four) are missing, the arithmetic mean for this single ECG will be computed with the reduced (1, 2 or 3) number of cardiac cycles.

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

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. In case of a missing qualitative ECG finding at baseline, a finding observed on treatment will be categorized as ‘new onset’.

For placebo subjects, the missing plasma concentration values will be replaced by 0 for the exposure-response analyses. For subjects on active drug, missing plasma concentration values with ‘BLQ’ in the comment field will be replaced by ½ LLOQ (post treatment values) or by 0 (predose values).

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

The baseline value is defined as the last measurement before administration of BI 1358894 or Placebo.

Section 6.1 of the CTP: *Exact times of measurements outside the permitted time windows will be documented. The acceptable time windows for screening and the end of trial examination are provided in the* CTP *Flow Chart.*

Study measurements and assessments scheduled to occur ‘before’ trial medication administration on Day 1 are to be performed and completed within a 2 h-period prior to the trial drug administration except PK sample. A blank sample for PK will be collected within 3 h before drug administration.

The acceptable deviation from the scheduled time for vital signs, orthostatic testing and ECG will be ± 10 min and laboratory tests will be ± 30 min for the first 4 h after trial drug administration and ± 30 min thereafter.

[…]

Adherence to time windows will be checked via the consistency check listings at the RPM.

Unscheduled measurements of laboratory data or vital signs 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.

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

Section 5.2.4.1 of the CTP: *Triple ECGs will be recorded (within 180 sec) at all-time points on Day 1 to Day 3 (48 h) for Dose Groups 1 and 2 or on Day 1 to Day 7 (144h) for Dose Group 3. At all remaining time points, single ECGs will be recorded.*

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

Visit	Day	Planned time [hh:mm] (relative to drug administration)	Study phase	Central evaluation
1	-28 to -1		Screening	NA
2	1	-01:00	Baseline	all 3 single ECGs of the triplicate
		00:30	On treatment	first of three replicate ECG
		01:00		first of three replicate ECG
		01:30		first of three replicate ECG
		02:00		first of three replicate ECG
		03:00		first of three replicate ECG
		04:00		first of three replicate ECG
		05:00		first of three replicate ECG
		06:00		first of three replicate ECG
		08:00		first of three replicate ECG
		12:00		first of three replicate ECG
	2	16:00		first of three replicate ECG
		24:00		first of three replicate ECG
		34:00		first of three replicate ECG
	3	48:00		first of three replicate ECG
	4	72:00**		first of three replicate ECG**
	5	96:00**		first of three replicate ECG**
	6	120:00**		first of three replicate ECG
	7	144:00**		first of three replicate ECG
3	10 to 14* 29 to 33**		End of trial examination	NA

*for dose groups 1 and 2
**for dose group 3

The baseline value of an ECG variable is defined as the mean of the triplicate ECG measurements prior to drug administration.

Section 5.2.4.1 of the CTP: *A centralised evaluation (during study or post study) of all 12-lead ECGs recorded on Day 1 to Day 3 (48h) for Dose Groups 1 and 2 or on Day 1 to Day 7*

(144h) for Dose Group 3 will be performed by an independent ECG laboratory. This analysis will include the determination of cardiac axis (automatic evaluation based on a validated GE-12-SL-algorithm or equivalent) as well as the intervals RR, PR, QRS and QT measured semi-automatically. With the exception of the first triple ECG (used as baseline before the drug administration), only the first of the three replicate ECGs at a single assessment time will be 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. HR change from baseline and the plasma concentration measured at planned time 0:30 will build one pair. Whether a time deviation between PK blood sampling time and corresponding ECG recording is too big and the pair has to be excluded from the analysis will be decided no later than at the RPM. This critical time deviation depends on the PK properties. When plasma concentrations are expected to change only little around a given time point, the acceptable time deviation between ECG recording and PK blood sampling may be bigger.

7. PLANNED ANALYSIS

The placebo group in the safety evaluation will consist of all placebo treated subjects, regardless of the dose group in which they were treated.

Safety analysis (refer to Section 7.8) will be performed by and will be presented in Sections 15.1 to 15.4 of the CTR and in Appendix 16.2 and 16.1.13.1.

Inferential statistical analyses of PK endpoints (refer to Section 7.5.2) will also be performed by and will be presented in Section 15.5 of the CTR and in Appendix 16.1.13.3.

Descriptive data analysis of PK parameters and concentrations will be performed by . The individual values of all subjects and descriptive statistics will be presented in Appendix 16.1.13.5 and Section 15.6 of the CTR, respectively.

The format of the listings and tables will follow the standards defined in the BI standards with the exception of those generated for PK-calculations (6).

The individual values of all subjects will be listed, sorted by treatment group, subject number, and visit.
The listings except PK evaluations will be included in Appendix 16.2 of the CTR.

For end-of-text tables, the set of summary statistics for non-PK parameters is:

N	number non-missing observations
Mean	arithmetic mean
SD	standard deviation
Min	minimum
Median	median
Max	maximum

For analyte concentrations, 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:

CV	arithmetic coefficient of variation
gMean	geometric mean
gCV	geometric coefficient of variation
P10	10th percentile
Q1	1st quartile
Q3	3rd quartile
P90	90th 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 (%) for each treatment group. Percentages will be rounded to one decimal place and will be based on all subjects in the respective subject set whether they have non-missing values or not. The category 'missing' will be displayed only if there are actually missing values.

Units of variables should be given in the titles or column/row descriptors in square brackets (e.g. [mg]).

Exclusion of PK parameters

The ADS ADPP (PK parameters) contains column variables indicating inclusion/exclusion (APEXC) of a PK parameter and an analysis flag comment (APEXCO). All analyses based on the PKS will include parameters if they are not flagged for exclusion, that is APEXCO is equal to “Included”.

Exclusion of PK 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 (and, as a consequence, any calculation that relies on λ_z) only; the value is included for all other analyses.

Further details are given in 001-MCS-36-472_RD-01 "Noncompartmental Pharmacokinetic / Pharmacodynamic Analyses of Clinical Studies" (4) and 001-MCS-36-472_RD-03 "Description of Analytical Transfer Files and PK/PD Data Files" (5).

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Only descriptive statistics are planned for this section of the report, based on the TS.

The data will be summarised by treatment group and in total.

7.2 CONCOMITANT DISEASES AND MEDICATION

Frequency tables are planned for this section of the report, based on the TS.

Concomitant diseases will be coded using the latest version of the coding system of the Medical Dictionary for Drug Regulatory Activities (MedDRA). Medications will be coded using the latest version of the World Health Organization Drug Dictionary (WHO-DD). The coding version number will be displayed as a footnote in the respective output.

The diagnoses and medications will be listed. Subjects without any concomitant diagnoses or concomitant therapies should 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

Section 4.3 of the CTP: *Compliance will be assured by administration of all trial medication in the study centre under supervision of the investigating physician or a designee. The measured plasma concentrations will provide additional confirmation of compliance.*

It is not intended to list the compliance separately. Any deviations from complete intake will be addressed in the RPM and described in the CTR.

7.4 PRIMARY ENDPOINTS

Refer to TSAP Section 7.8 for a description of the analysis of safety and tolerability of BI 1358894.

7.5 SECONDARY ENDPOINTS

7.5.1 Key secondary endpoints

This section is not applicable as no key secondary endpoints have been specified in the CTP.

7.5.2 Secondary endpoints

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

All safety analyses will be performed on the TS.

If not stated otherwise, the safety results will be sorted by treatment group.

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

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 and will be based on BI standards.

The standard AE analyses 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 provided that all of the following applies:

- All AE attributes are identical (lower level term (LLT), intensity, action taken, therapy required, seriousness, reason for seriousness, relationship, outcome, AE of special interest (AESI))
- The occurrences were time-overlapping or time-adjacent (time-adjacency of two occurrences is given if the second occurrence started within one hour after end of the first occurrence).

Section 5.2.6.1.5 of the CTP: *The AESI for this trial is hepatic injury, as 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*
- *Aminotransferase (ALT, and/or AST) elevations ≥10-fold ULN*

These lab findings constitute a hepatic injury alert and the subjects 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 analysis of adverse events will be based on the concept of treatment emergent AEs.

Section 1.2.6 of the CTP: *The residual effect period (REP) for BI 1358894, the time interval when measureable drug levels or pharmacodynamics (PD) effects are still likely to be present after the last administration, is not known at this early stage of development.*

Section 7.3.4 of the CTP: *Therefore, measurements planned or AEs recorded prior to intake of trial medication will be assigned to the screening period, those between trial medication intake until the trial termination date will be assigned to the treatment period.*

For more details see the TSAP ADS plan.

According to ICH E3 (7), 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 investigator or Clinical Trial Leader at the RPM.

An overall summary of AEs (including AESIs) will be presented.

The frequency of subjects with AEs will be summarized by treatment, primary system organ class (SOC) and preferred term (PT). Separate tables will be provided for subjects with other significant AEs according to ICH E3 (7), for subjects with serious AEs, for subjects with drug-related AEs, for subjects with drug related serious adverse events and for subjects with AESIs.

The SOC and PTs will be sorted by frequency (within SOC). The MedDRA version number will be displayed as a footnote in the respective output.

In addition, frequencies of subjects with non-serious AEs that had an incidence of > 5% for at least one treatment will be summarised by treatment, primary SOC and PT.

7.8.2 Laboratory data

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

Laboratory data will be analysed qualitatively via comparison of laboratory data to their reference ranges. Values outside the reference range as well as values defined as possible clinically significant will be flagged in the data listings.

Clinically relevant findings in laboratory data will be reported as baseline conditions (at screening) or as AEs (during the trial) if judged clinically relevant by the investigator, and will be analysed as such.

It is the investigator's responsibility to decide whether a lab value is clinically significant abnormal or not (at the RPM at the latest).

Descriptive statistics of laboratory data 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).

The mean normalised values and SD over time for all laboratory parameters, except for parameters that are measured at a single time point will be displayed graphically. The time span is from baseline to post examination.

7.8.3 Vital signs

Descriptive statistics over time including change from baseline will be performed for vital signs (blood pressure and pulse rate), as well as respiratory rate (RR) and orthostatic tests. In the listing the difference from baseline will also be displayed.

Descriptive statistics will be calculated by planned time point based on the last value of the subject at that planned time point (or assigned to that planned time point).

Clinically relevant findings in vital signs will be reported as AEs.

7.8.4 ECG

Continuous safety ECG monitoring (by investigator)

Clinically relevant abnormal findings will be reported as AEs.

No separate listing or analysis of continuous ECG monitoring will be prepared.

12-lead ECG

Abnormal findings, irrespective of whether they originate from central or local evaluation, will be reported as baseline conditions (at screening) or as AEs (during the trial) if judged clinically relevant by the investigator.

All evaluations of ECG data will be based on the TS, except the exposure-response analyses, which are 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.

For QTcF and HR changes from baseline, the relationship to the corresponding plasma concentrations will be evaluated using a random coefficient model. For subjects in the ECGPCS, all time points with available ECG endpoints and valid time-matched drug plasma concentrations will be included. For the handling of missing values, see Section 6.6.

The response variable will be the 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 Statistical Appendix of the CTR), as well as for means per active treatment (presented in the End-of-Text part of the CTR).

The relationship between BI 1358894 plasma concentrations and QTcF changes from baseline will be investigated in an exploratory manner using a random coefficient model to estimate the difference in means between BI 1358894 and placebo of QTcF change from baseline 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. (8) with ΔQTcF as response variable, centered 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 Section 9.3.

For visualization, a scatterplot of the BI 1358894 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 and 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.).

All of the above described graphical and statistical analyses will be also performed for HR in place of QTcF.

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 QTcF vs 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

7.8.5.1 Physical examination

Physical examination findings will be reported as relevant medical history/baseline condition (i.e. a condition already existent before intake of study drug) or as AE and will be summarised as such.

No separate listing or analysis of physical examination findings will be prepared.

7.8.5.2 Visual Analogue Scale (VAS) - Bowdle

The VAS will be used at screening and at end of trial examination, as well as at the planned times -1:00, 2:00, 4:00, 8:00, 24:00, 34:00, 48:00, 96:00 (only DGs 1-2) and 144:00 (only DG3). The last VAS assessments before drug administration will be considered as baseline.

Descriptive statistics of the 13 individual Bowdle scales at screening and post examination and for the difference from baseline will be provided. Other assessments will be listed only.

Furthermore, the change from baseline of the individual scales will be presented graphically over time (arithmetic means + standard deviation).

7.8.5.3 Suicidality assessment - Columbia Suicidal Severity Rating scale (C-SSRS)

The C-SSRS will be done at

- Screening
- Treatment period
- End of trial examination

The results will be listed only.

8. 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.	*001-MCS-40-413:* "Identify and Manage Important Protocol Deviations (iPD) ", current version, BIRDS
3.	*BI-KMED-COPS-TMP-0001:* "iPD log", 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.	*001-MCS 36-472*: "Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics", current version; IDEA for CON.
7.	*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
8.	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.	Ring A. Statistical models for heart rate correction of the QT interval. Stat Med (2010) [R10-2920]

10. HISTORY TABLE

Table 10: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
Final	14-AUG-2019		None	This is the final TSAP without any modification