TRIAL STATISTICAL ANALYSIS PLAN

Document No.:	**c42762777-01**
BI Trial No.:	1447-0004
Title:	Safety, tolerability and pharmacokinetics of single rising oral doses and multiple oral doses of BI 1569912 in healthy male Japanese subjects (single-blind, partially randomized within dose groups, placebo-controlled, parallel-group design) Revised protocol #03 [c33487150-03]
Investigational Product(s):	BI 1569912
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Date of statistical analysis plan:	15 NOV 2023 SIGNED
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2. LIST OF ABBREVIATIONS

Term	Definition / description
ADS	Analysis data set
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
$AUC_{\tau,ss}$	Area under the concentration-time curve of the analyte in plasma over the dosing interval τ at steady state
$AUC_{0-\infty}$	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity
AUC_{0-24}	Area under the concentration-time curve of the analyte in plasma from 0 to 24 h
BI	Boehringer Ingelheim
BP	Blood pressure
CADSS	Clinician Administered Dissociative States Scale
CARE	Clinical data analysis and reporting environment
CDR	Clinical Data Repository
CI	Confidence Interval
C_{max}	Maximum measured concentration of the analyte in plasma
$C_{max,ss}$	Maximum measured concentration of the analyte in plasma at steady state
COVID	Coronavirus disease
CRF	Case Report Form, paper or electronic (sometimes referred to as 'eCRF')
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
DILI	Drug-induced liver injury
ECG	Electrocardiogram
EDMS	Electronic Document Management System
EudraCT	European union drug regulating authorities clinical trials
HR	Heart rate
IPD	Important protocol deviations

Term	Definition / description
LLOQ	Lower limit of quantification
MD	Multiple Dose
MedDRA	Medical Dictionary For Regulatory Activities
PKS	Pharmacokinetic parameter analysis set
PR	Pulse rate
PKS	Pharmacokinetic parameter analysis set
PK	Pharmacokinetic(s)
PT	Preferred term
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
QTc	QT interval, heart rate corrected
QTcB	QT interval, heart rate corrected according to Bazetts formula
QTcF	QT interval, heart rate corrected according to Fridericias formula
RAGe	Report appendix generator
REP	Residual effect period
RR interval	ECG interval from the peak of the R wave to the peak of the subsequent R wave
RPM	Report Planning Meeting
SAE	Serious adverse event
SDL	Subject data listing
SOC	System organ class
SRD	Single Rising Dose
TS	Treated set
TMF	Trial Master File
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 revised clinical trial protocol (CTP), and to include detailed procedures for executing the statistical analysis of the primary variables and other data.

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

Study data as collected in the Case Report Form (eCRF) will be stored in a trial database within the RAVE EDC system. All study data also including external data will then be uploaded to the CDR data warehouse.

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

Pharmacokinetic (PK) parameters will be calculated using Phoenix WinNonlin™ software (version Phoenix 8.1.1, [redacted]).

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

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

The exploratory analysis of the relationship between plasma concentrations and ECG endpoints (including HR) will be included for the SRD and MD part.

5. ENDPOINTS

5.1 PRIMARY ENDPOINT(S)

SRD and MD part:

CTP Section 2.1.2: *The primary endpoint for assessment of safety and tolerability of BI 1566912 is the percentage of subjects with drug-related adverse events.*

Evening PK part:

Primary endpoints are PK endpoints of BI 1566912, as defined in **Section 2.1.2 of the CTP**.

- *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)*
- *C_{max} (maximum measured concentration of the analyte in plasma)*

5.2 SECONDARY ENDPOINT(S)

5.2.1 Key secondary endpoint(s)

Not applicable.

5.2.2 Secondary endpoint(s)

Secondary endpoints are the PK endpoints of BI 1569912 as defined in **CTP Section 2.1.3**:

SRD part:

- *$AUC_{0-\infty}$ (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)*

MD part:

After the first dose:

- *AUC_{0-24} (area under the concentration-time curve of the analyte in plasma from 0 to 24 h)*
- *C_{max} (maximum measured concentration of the analyte in plasma)*

After the last dose:

- *$AUC_{\tau,ss}$ (area under the concentration-time curve of the analyte in plasma over the dosing interval τ at steady state)*
- *$C_{max,ss}$ (maximum measured concentration of the analyte in plasma at steady state)*

Evening PK part:

- *The percentage of subjects with drug-related adverse events.*

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

5.3 FURTHER ENDPOINT(S)

5.3.1 Further endpoints of interest

Safety and tolerability of BI 1569912 will be assessed based on further safety parameters defined in **Section 2.2.2.1 and 2.2.2.2 of the CTP:**

- *AEs (including clinically relevant findings from the medical examination)* [includes findings of mental and neurological examination]
- *Safety laboratory tests*
- *12-lead ECG*
- *Continuous ECG monitoring (SRD-Part, only)* [only as part of AE analysis]
- *Vital signs (blood pressure, pulse rate, respiratory rate, body temperature)*

Further BI 1569912 specific endpoints of safety and tolerability

- *Columbia-Suicide Severity Rating Scale (C-SSRS)*
- *Standardized medical assessment* [only as part of AE analysis]
- *Assessment of dissociative symptoms (e.g. CADSS)*
- *Electroencephalogram (EEG)*

CADSS

CTP Section 5.2.5.3: *Dissociative symptoms will be assessed via the 'Clinician Administered Dissociative States Scale' (CADSS) […]. The CADSS is a clinician n administered measure of perceptual, behavioural and attentional alterations during active dissociative experiences. The scale contains 23 subjective items, each rated from 0 (not at all) to 4 (extremely).*

The total score of the CADSS will be defined as the sum of the 23 item scores, ranging from 0 to 92. For the total score and each component, a higher score represents a more severe condition. Statistical analysis of the CADSS will be based on the total score.

12-lead ECG endpoints

For the definition of baseline and a summary of time points please 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 10.1:

- 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, Table 6.7: 2), and Table 6.7: 3) will be considered.
- Maximum change from baseline in QT interval of ≤ 60 msec, or > 60 msec on treatment
- Maximum change from baseline in QTcF interval of ≤ 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 duration is > 110 msec, at any time on treatment

For a detailed description of ‘new onset’, refer to Additional Section 10.2.

[redacted]

6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENT(S)

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

SRD part:

Subjects in SRD Part will receive 2.5 mg, 5 mg, 10 mg or 20 mg BI 1569912 in tablet format or a matching placebo.

All placebo subjects from SRD Part will be analysed in one pooled placebo group.

MD part:

Subjects in MD Part will receive 20 mg BI 1569912 q.d. in tablet format for 14 days or matching placebo.

Evening PK part:

Subjects in evening PK part will receive 5 mg BI 1569912 in the morning (Reference treatment (R) and 5 mg BI 1569912 in the evening (Test treatment (T)) in tablet format. Subjects will be randomly allocated to the 2 treatment sequences T-R (Evening PK part I) or R-T (Evening PK part II). [redacted]

SRD part, MD part, and evening PK part will be analysed separately.

The residual effect period (REP) is estimated [redacted]

For statistical analysis of AEs regarding SRD part, the following analysis phases will be defined for each subject.

Table 6.1: 1 Analysis phases for statistical analysis of AEs, and actual treatment for analysis of laboratory data and other safety assessment (SRD Part)

Study analysis phase	Actual treatment label	Start (inclusive)	End (exclusive)
Screening[1]	**Screening**	Date of informed consent	Date/time of administration of study drug
On treatment	**Placebo SRD,** **2.5 mg BI SRD,** **5 mg BI SRD,** **10 mg BI SRD,** **20 mg BI SRD,**	Date/time of administration of study drug	Date/time of administration of study drug + REP [redacted] or 12:00 a.m. on day after subject's trial termination date, whichever occurs earlier
Follow-up	**F/U Placebo SRD,** **F/U 2.5 mg BI SRD,** **F/U 5 mg BI SRD,** **F/U 10 mg BI SRD,** **F/U 20 mg BI SRD**	Date/time of administration of study drug + REP [redacted]	12:00 a.m. on day after trial termination date

[1] See Section 6.7 for definition of baseline.

For statistical analysis of AEs regarding MD part, the following analysis phases will be defined for each subject.

Table 6.1: 2 Analysis phases for statistical analysis of AEs, and actual treatment for analysis of laboratory data and other safety assessments (MD Part)

Study analysis phase	**Actual treatment label**	**Start (inclusive)**	**End (exclusive)**
Screening[1]	**Screening**	Date of informed consent	Date/time of first administration of study drug
On treatment	**Placebo MD,** **20 mg BI MD**	Date/time of first administration of study drug	Date/time of last administration of study drug + REP [redacted] or 12:00 a.m. on day after subject's trial termination date, whichever occurs earlier
Follow-up	**F/U Placebo MD,** **F/U 20 mg BI MD**	Date/time of last administration of study drug + REP [redacted]	12:00 a.m. on day after trial termination date

[1] See Section 6.7 for definition of baseline.

For statistical analysis of AEs regarding evening PK part, the following analysis phases will be defined for each subject.

Table 6.1: 3 Analysis phases for statistical analysis of AEs, and actual treatment for analysis of laboratory data and other safety assessments (evening PK Part)

Study analysis phase	**Period**	**Actual treatment label**	**Start (inclusive)**	**End (exclusive)**
Screening[1]		**Screening**	Date of informed consent	Date/time of first administration of study drug
On treatment	Period Reference (R)	**5 mg BI a.m.**	Date/time of administration of BI 1569912 (in Period R)	Date/time of administration of BI 1569912 + REP [redacted] in Period R or 12:00 a.m. on day after subject's trial termination date, whichever occurs earlier
Follow-up (Period R)		**F/U 5 mg BI a.m.**	Date/time of administration of BI 1569912 + REP [redacted] (in Period R)	Date/time of first administration of BI 1569912 in Period T if subject assigned to R/T or 12:00 a.m. on day after subject's trial termination date, whichever occurs earlier.
On treatment	Period Test (T)	**5 mg BI p.m.**	Date/time of administration of BI 1569912 (in Period T)	Date/time of administration of BI 1569912 + REP [redacted] in Period T or or 12:00 a.m. on day after subject's trial termination date, whichever occurs earlier.
Follow-up (Period T)		**F/U 5 mg BI p.m.**	Date/time of administration of BI 1569912 + REP [redacted] (in Period T)	Date/time of administration of BI 1569912 in Period R if subject assigned to T/R or 12:00 a.m. on day after subject's trial termination date, whichever occurs earlier.

[1] See Section 6.7 for definition of baseline.

AE displays in CTR Section 15.3, Appendix 16.1.13.1.8. will present results for the on-treatment phase (as defined in Table 6.1: 1, Table 6.1: 2, and Table 6.1: 3) only. Screening and follow-up will not be included in this analysis.

AEs will be listed, based on the “actual treatment” defined in these tables.

In AE tables in CTR Section 15.3 (but not in displays for ClinicalTrials.gov), the following totals will be provided in addition:

SRD part:

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

MD part:

- "**Total MD**", defined as the total over all on-treatment phases, including placebo

Evening PK part:

- "**Total BI PK**",

Safety laboratory data, vital signs, ECG, EEG or CADSS data will be analysed with clear differentiation between baseline (cf. Section 6.7) and post-baseline. An ECG measurement will be considered to be on-treatment, if it was taken within the on-treatment phase as defined in Table 6.7: 1, Table 6.7: 2, and Table 6.7: 3.
Follow-up laboratory measurements will be listed, but will not be used in descriptive summaries. Of note, no distinction will be made between on- or off-treatment assessments of a post-baseline visit in the by-visit-summaries of vital signs and ECG.

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

6.2 IMPORTANT PROTOCOL DEVIATIONS

Consistency check listings (for identification of deviations from time windows) and a list of protocol deviations (e.g. deviations in drug administration, in blood sampling times, etc.) will be provided to be discussed at the Report Planning Meeting (RPM). At this meeting, it will be decided whether a discrepant data value can be used in analyses or whether it must be corrected in the clinical database. Each protocol deviation (PD) must be assessed to determine whether it is an important PD (iPD). For definition of iPDs, and for the process of identification of these, refer to the BI reference document "Identify and Manage Important Protocol Deviations (iPD)" (2) and the DV domain template.

If any iPDs are identified, they are to be summarised into categories and will be captured in the decision log. Categories which are considered to be iPDs in this trial are defined in the DV domain template. If the data show other iPDs, the definition in the DV domain template will be supplemented accordingly by the time of the RPM.

IPDs will be summarized and listed. Which kind of iPDs could potentially lead to exclusion from which analysis set is specified in the DV domain template. The decision on exclusion of subjects from analysis sets will be made at the latest at the RPM, after discussion of exceptional cases and implications for analyses. If the data show other iPDs, this table will be supplemented accordingly by the time of the RPM.

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

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

6.3 INTERCURRENT EVENTS

This section is not applicable.

6.4 SUBJECT SETS ANALYSED

The treated set (TS), pharmacokinetic parameter analysis set (PKS), and pharmacokinetic parameter evening analysis set (PKS-E) will be used as defined in the **CTP, Section 7.3**.

PKS includes subject in SRD and MD part. The PKS-E includes subjects in evening PK part.

All ECG analyses are performed on the TS, except for the exposure-response analyses, which are performed on the ECGPCS defined below.

SRD and MD part:

- ECG pharmacokinetic concentration set (ECGPCS):
  This subject set includes all subjects from the TS who provide at least one pair of a valid drug plasma concentration and a corresponding (i.e. time-matched) ECG endpoint to be used in the exposure-response analyses. 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. For subjects treated with active drug, the decision about concentration value validity needs to be made within the Clinical Pharmacology Group

Table 6.4: 1 Subject sets analysed

Class of analysis	TS	Subject set: PKS (SRD part, MD part)	Subject set: PKS-E (Evening PK part)	Subject set: ECGPCS (SRD part, MD part)
Disposition	X			
iPDs	X			
Primary endpoint of SRD, MD part	X			
Primary endpoint(s) of Evening PK part			X	
Secondary endpoint(s) of SRD, MD part		X		
Secondary endpoint(s) of Evening PK part	X		X	
[redacted]		[redacted]	[redacted]	
Further endpoints/Safety parameters (except for exposure-response analyses of ECG data)	X			
Exposure-response analyses of ECG data (SRD, MD part)				X
Demographic/baseline characteristics, concomitant diseases, concomitant medications and concomitant procedures	X			
Treatment exposure	X			

[redacted]

6.6 HANDLING OF MISSING DATA AND OUTLIERS

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

CTP Section 7.5.1: *It is not planned to impute missing values for safety parameters.*

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

CTP Section 7.5.2: *PK parameters that cannot be reasonably calculated based on the available drug concentration-time data will not be imputed.*

Missing data and outliers of PK data are handled according to BI standards (4) and (5).

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, the handling of missing value is described in Additional Section 10.2.

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

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

SRD part:

The last non-missing value determined prior to BI 1569912 administration will be defined as baseline.

MD part:

The last non-missing value determined prior to first BI 1569912 administration will be defined as baseline.

Evening PK part:

A separate baseline will be defined for each treatment period: Baseline is the last available off-treatment value before administration of BI 1569912. Off-treatment in this context means that a value measured within an on-treatment phase concerning BI administration, as defined in Table 6.1: 3 will not be used as baseline.

Time windows are defined in Section 6.1 of the CTP. Adherence to time windows will be checked at the RPM. Data analyses by visit/time point will use the assigned visits/ time points.

Centrally evaluated 12-lead ECG time point recording are shown in Table 6.7: 1 for SRD part, Table 6.7: 2 for MD part and in Table 6.7: 3 for evening PK part.

Table 6.7: 1 Time schedule of 12-lead ECG recordings with centralised evaluation (SRD part)

Visit	Day	Planned time [hh:mm] - relative to first study drug administration	Study phase
2	1	-1:00	Baseline
		00:15, 00:30, 00:45, 01:00, 01:15, 01:30, 02:00, 02:30, 03:00, 04:00, 06:00, 08:00, 10:00, 12:00	On-treatment
	2	24:00	
		36:00	
	3	48:00[1]	
	4	72:00	Follow-up

[1] According to CTP acceptable deviation from the scheduled time point 48:00 will be ± 30 minutes, resulting in an ECG assessment within on-treatment phase or follow-up phase, depending on the actual time of the assessment.

Table 6.7: 2 Time schedule of 12-lead ECG recordings with centralised evaluation (MD part)

Visit	Day	Planned time [hh:mm] - relative to first study drug administration	Study phase
2	1	-1:00	Baseline
		00:15, 00:30, 00:45, 01:00, 01:15, 01:30, 02:00, 02:30, 03:00, 04:00, 06:00, 08:00, 10:00, 12:00	On-treatment
	2	23:00	
	3	47:00	
	4	71:00	
	14	311:00, 312:15, 312:30, 313:00, 313:15, 313:30, 314:00, 314:30, 315:00, 316:00, 318:00, 320:00, 322:00, 324:00	
	15	335:00	
	16	359:00	
	17	383:00	Follow-up

SRD and MD part:

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

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. Whether a time deviation between PK blood sampling time and corresponding ECG recording is outside a maximum acceptable time deviation for a reliable assessment and the pair has to be excluded from the analysis will be decided no later than at the RPM.

Table 6.7: 3 Time schedule of 12-lead ECG recordings with centralised evaluation (Evening PK part)

Visit	Day	Planned time [hh:mm] - relative to first study drug admin.	Study phase
2/2a	1	-1:00	Baseline
		04:00	On-treatment (Period R or Period T)
		08:00	
		12:00	
	2	24:00	
		36:00	
	3	48:00[1]	
2	4	60:00[2]	Follow-up (Period T)

[1] According to CTP acceptable deviation from the scheduled time point 48:00 will be ± 30 minutes, resulting in an ECG assessment within on-treatment phase or follow-up phase, depending on the actual time of the assessment.
[2] ECG assessment only planned if randomised to Evening PK part II.

Evening PK part:

Three triplicate ECGs will be recorded as the baseline before the first drug administration within each period, but only the first ECG of each of the 3 baseline triplicate will be transferred to the database per period. At all other time points, 1 triplicate ECG will be recorded, but only the first single ECG of the triplicate will be transferred to the database. There are two different types of baseline values for each subject. The ‘period baseline’ value of an ECG variable is defined as the mean of the ECG variable values obtained prior to drug administration per treatment period.

In general, additional (unscheduled) ECGs may be recorded for safety reasons. These ECGs are assigned to the prior scheduled time point in the sponsor’s database. Unscheduled ECGs (for safety reasons) will be transferred to the central ECG lab but will not be included into the statistical analysis of interval lengths.

7. PLANNED ANALYSIS

The format of the listings and tables will follow the BI guideline "Reporting of clinical trials and project summaries" (6).

The individual values of all subjects will be listed. Listings will be sorted by treatment, subject number and visit (if visit is applicable in the respective listing). AE listings will be sorted by assigned treatment (see Section 7.8.1 below for details). The listings will be contained in Appendix 16.2 (SDL) of the CTR.

The following standard descriptive statistical parameters will be displayed in summary tables of continuous variables:

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

For 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 plasma concentrations will be identical with the data format of the respective concentrations. The descriptive statistics of PK parameters will

be calculated using the individual values with the number of decimal places as provided by the evaluation program. Then the individual values as well as the descriptive statistics will be reported with three significant digits in the CTR.

Tabulations of frequencies for categorical data will include all possible categories and will display the number of observations in a category as well as the percentage (%) relative to the respective treatment group. Percentages will be rounded to integer numbers. The category missing will be displayed if and only if there actually are missing values. Percentages will be based on all subjects in the respective subject set whether they have non-missing values or not.

No formal interim analysis is planned.

In general, SRD part, MD part, and evening PK part will be analysed separately if not otherwise stated.

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

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

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. Concomitant non-drug therapies will be coded according to the most recent version of MedDRA.

A medication will be considered concomitant to a dose group, if it

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

CTP Section 7.3.4: *Previous and concomitant therapies will be presented per treatment group without consideration of time intervals and treatment periods*.

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

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 OBJECTIVE ANALYSIS

Independent of the main objectives stated in the CTP, this section describes further details of the primary endpoint analyses outlined in the CTP.

7.4.1 Main analysis

Primary endpoint analysis

SRD and MD part:

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 treatment-emergent drug related AEs, which is the primary endpoint of this trial in the SRD and MD part.

CTP Section 7.3.1: *The analysis will be based on the treated set (TS) and will be descriptive in nature.*

Evening PK part:

Relative bioavailability of BI 1566912 administered in the evening (T) compared with BI 1566912 administered in the morning (R) will be evaluated as defined in the CTP for the primary endpoints specified in Section 5.1.

CTP Section 7.3.1:

The analysis will be based on the PK evening analysis set (PKS-E).

The statistical model used for the analysis of the primary endpoints will be an analysis of variance (ANOVA) model on the logarithmic scale. That is, the PK endpoints will be log-transformed (natural logarithm) prior to fitting the ANOVA model. This model will include effects accounting for the following sources of variation: sequence, subjects within sequences, period and treatment. The effect 'subjects within sequences' will be considered as random, whereas the other effects will be considered as fixed. The model is described by the following equation:

$y_{ijkm} = \mu + \zeta_i + s_{im} + \pi_j + \tau_k + e_{ijkm}$, *where*

y_{ijkm} = *logarithm of response measured on subject m in sequence i receiving treatment k in period j,*

μ = *the overall mean,*

ζ_i = *the* i^{th} *sequence effect, i = 1, 2,*

s_{im} = *the effect associated with the* m^{th} *subject in the* i^{th} *sequence, m = 1, 2, ..., 12*

π_j = *the* j^{th} *period effect, j = 1, 2,*

τ_k = *the* k^{th} *treatment effect, k = 1, 2,*

e_{ijkm} = the random error associated with the m^{th} subject in sequence i who received treatment k in period j.

where $s_{im} \sim N(0, \sigma_B^2)$ i.i.d., $e_{ijkm} \sim N(0, \sigma_W^2)$ i.i.d. and s_{im}, e_{ijkm} are independent random variables.

Point estimates for the ratio of the geometric means (test/reference) for the primary endpoints (see Section 2.1) and their two-sided 90% confidence intervals (CIs) will be provided.

For each endpoint, the difference between the expected means for log(T)-log(R) will be estimated by the difference in the corresponding adjusted means (Least Squares Means). Additionally their two-sided 90% confidence intervals will be calculated based on the residual error from the ANOVA and quantiles from the t-distribution. These quantities will then be back-transformed to the original scale to provide the point estimate and 90% CIs for each endpoint.

The analysis of standard PK parameters is performed according to BI standards (4).

Exclusion of PK parameters

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

CTP Section 7.3: *Plasma/[redacted] 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* [descriptive summary a well as the] *statistical analyses.*

Exclusion of PK concentrations

The ADS ADPC (PK concentrations per time-point or per time-interval) contains column variables ACEX or ACEXCO indicating inclusion/exclusion (ACEX) of a concentration and an analysis flag comment (ACEXCO). Exclusion of a concentration depends on the analysis flag comment ACEXCO. For example, if ACEXCO is set to "ALL CALC", the value will be excluded for all types of analyses based on concentrations. If ACEXCO is set to "DESC STATS" the value will be excluded from descriptive evaluations per planned time point/time interval. If ACEXCO contains the addition "TIME VIOLATION" or "TIME DEVIATION", the value can be used for further analyses based on actual times. If ACEXCO is set to "HALF LIFE", the value will be excluded from half-life calculation only; the value is included for all other analyses. Excluded concentration itself will be listed in the CTR associated with an appropriate flag.

Further details are given in "Noncompartmental Pharmacokinetic / Pharmacodynamic Analyses of Clinical Studies" (4) and "Description of Analytical Transfer Files and PK/PD Data Files" (5).

[redacted]

7.5 SECONDARY OBJECTIVE ANALYSIS

Independent of the main objectives stated in the CTP, this section describes further details of the secondary endpoint analyses

7.5.1 Key secondary objective analysis

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

7.5.2 Secondary objective analysis

7.5.2.1 Secondary endpoint analysis

SRD and MD part:

CTP Section 7.3.2: *The secondary endpoints (refer to Section 2.1.3) will be analysed descriptively.*

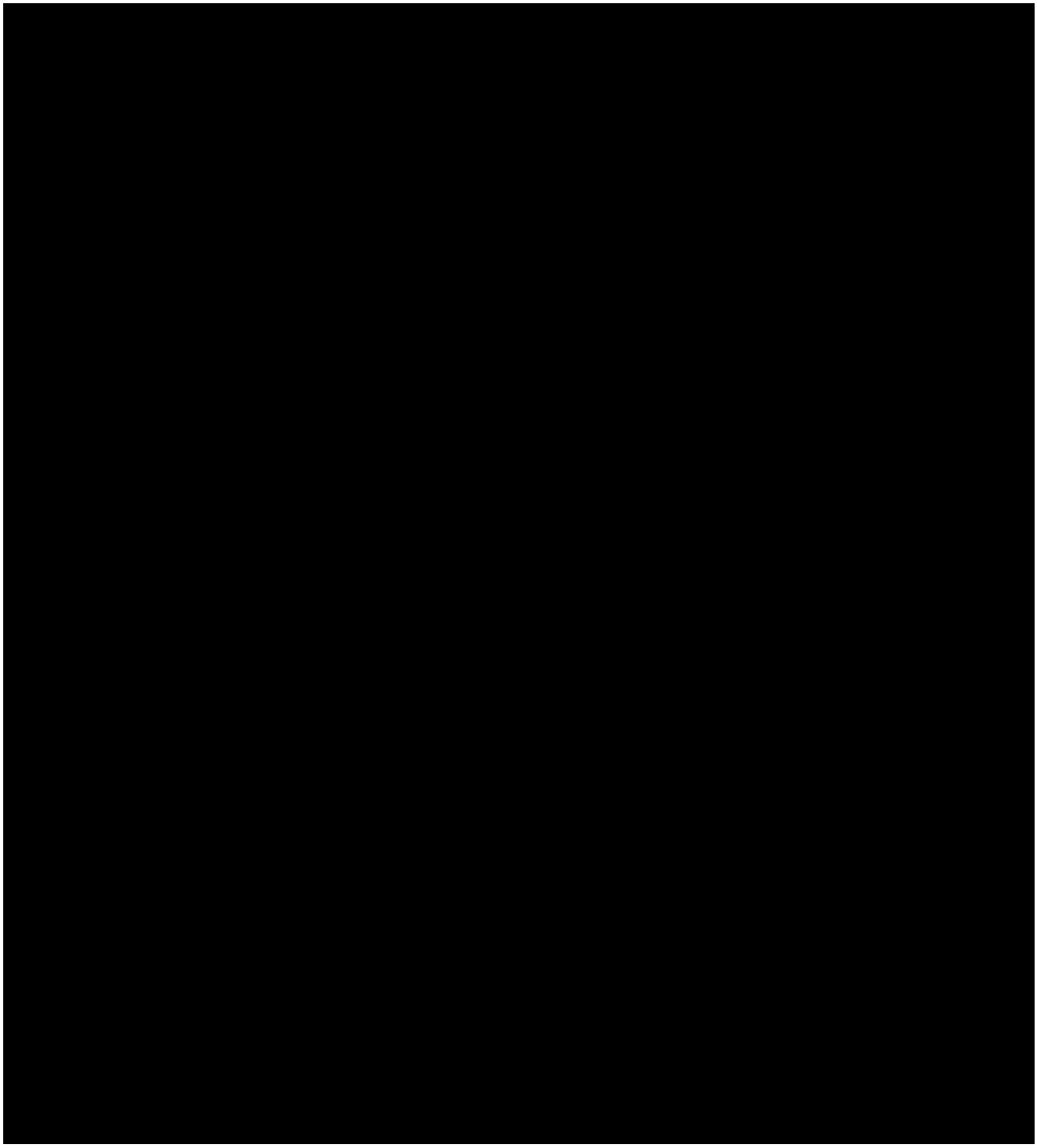
The analysis of secondary pharmacokinetic parameters will be based on the PKS.

Evening PK part:

CTP Section 7.3.2: *The secondary endpoint (refer to Section 2.1.3) will be calculated according to the relevant SOP of the Sponsor and will be assessed statistically using the same methods as described for the primary endpoints.*

The analysis will be based on the PKS-E.

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 treatment-emergent drug related AEs, which is the secondary endpoint in the evening PK part. The analysis will be based on the TS and will be descriptive in nature.

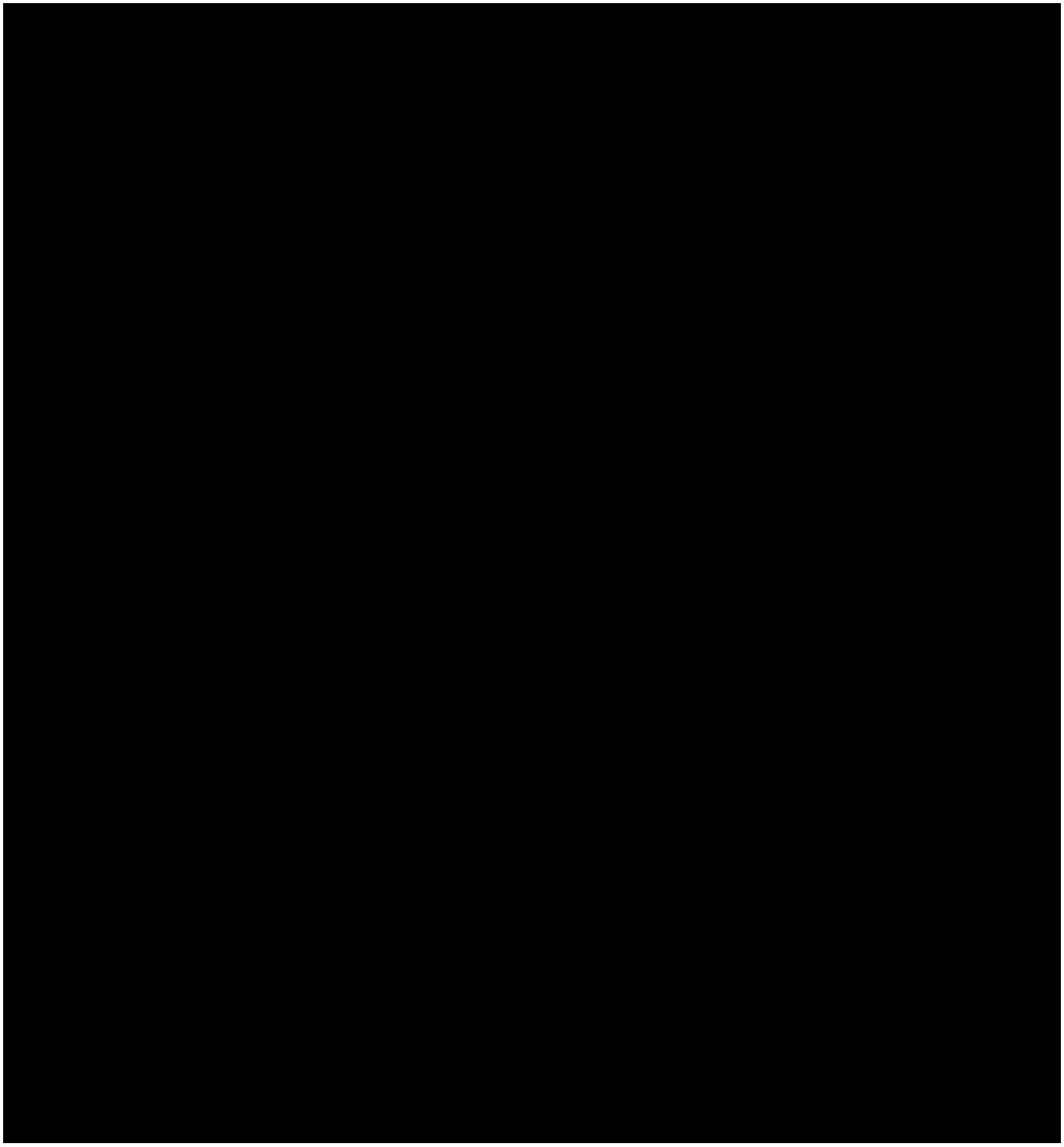


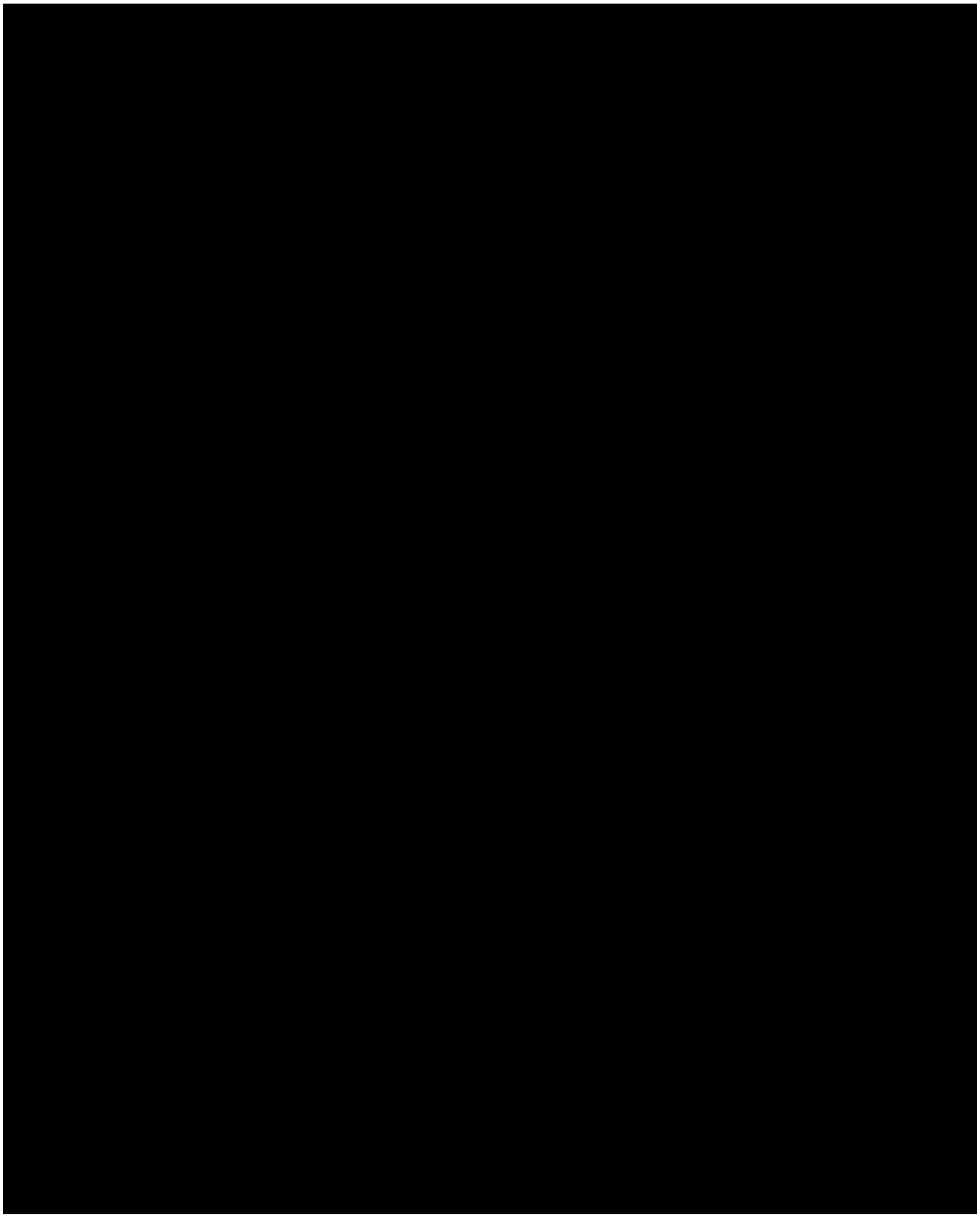
7.6 FURTHER OBJECTIVE ANALYSIS

Independent of the further objectives stated in the CTP, this section describes details of the further endpoint analyses outlined in the CTP.

7.6.1 Safety parameters

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





7.7 EXTENT OF EXPOSURE

For SRD part treatment exposure will only be listed by means of the date and time of drug administration.

For MD and evening PK part descriptive statistics are planned for this section of the report. Analysis will be based on the TS.

7.8 SAFETY ANALYSIS

All safety analyses will be performed on the TS if not otherwise stated. All parts will be analysed separately.

7.8.1 Adverse Events

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

The analyses of AEs will be descriptive in nature. All analyses of AEs will be based on the number of subjects with AEs and not on the number of AEs.

For further details on summarization of AE data, please refer to "Analysis and Presentation of Adverse Event Data from Clinical Trials" (7) and "Handling of missing and incomplete AE dates" (3).

The analysis of AEs will be based on the concept of treatment emergent AEs. That means that all AEs will be assigned to screening, on-treatment or follow-up phase as defined in Section 6.1. AEs will be analysed based on actual treatments, as defined in Table 6.1: 1, Table 6.1: 2, and Table 6.1: 3.

An overall summary of AEs will be presented. This overall summary will comprise summary statistics for the class of AESIs.

CTP Section 5.2.3.1.4: *The following are considered as AESIs:*

- *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), in addition to Deaths and Serious Adverse Events, 'other significant' AEs need to be listed in the clinical trial report. These will be any non-serious adverse event that led to an action taken with study drug (e.g. discontinuation or dose reduced or interrupted). An overall summary of adverse events will be presented.

The frequency of subjects with AEs will be summarised by treatment, primary system organ class (SOC) and preferred term (PT). Separate tables will also be provided for subjects with SAEs, AEs leading to discontinuation (MD part only), AEs which were considered by the investigator to be drug related and subjects with AESIs. AEs will also be summarized by maximum intensity.

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

7.8.2 Laboratory data

The analyses of laboratory data will be descriptive in nature and will be based on BI standards "Display and Analysis of Laboratory Data" (9).

Analyses will be based on normalised values, which means transforming to a standard unit and a standard reference range. The original values will be analysed if the transformation into standard unit is not possible for a parameter.

Descriptive statistics of laboratory values over time and for the difference from baseline (see Section 6.7) will be provided. Frequency tables of changes between baseline and last value on treatment with respect to the reference range will be presented.

Unscheduled measurements of laboratory data will be assumed to be repeat measurements of the most recent scheduled measurement (e.g. for follow-up or confirmation of a particular value). Therefore, unscheduled measurements will be assigned to the planned time point of the previous scheduled measurement. Descriptive statistics will be calculated by planned time

point based on the worst value of the subject at that planned time point (or assigned to that planned time point).

Clinically significant abnormal laboratory values are only those identified either in the Investigator's comments or at the Report Planning Meeting at the latest. It is the Investigator's responsibility to decide whether a lab value is clinically significant abnormal or not.

Laboratory data will be compared to their reference ranges. Values outside the reference range as well as possibly clinically significant values (according to standard BI criteria defining possibly clinically significant abnormalities) will be highlighted in the listings. Possibly clinically significant laboratory values will be listed in Section 15.4.1.

Clinically relevant findings in laboratory data will be reported as baseline conditions (prior to first administration of study treatment) or as AEs (after first administration of study treatment) if judged clinically relevant by the investigator, and will be analysed as such.

7.8.3 Vital signs

The analyses of vital signs (blood pressure, pulse rate and body temperature) will be descriptive in nature. Descriptive statistics of vital signs over time and for the difference from baseline (see Section 6.7) will be provided.

Unscheduled measurements of vital signs will be assigned to planned time points in the same way as described above for laboratory data. However, for vital signs, descriptive statistics will be calculated by planned post-baseline time point based on the last value of the subject at that planned time point (or assigned to that planned time point). If the time of measurement is missing for a scheduled post-baseline measurement the scheduled measurement will be used in calculation of descriptive statistics (as time difference between scheduled and unscheduled cannot be assessed). If the time of measurement is missing for an unscheduled post-baseline measurement, this measurement will be listed but will be ignored for the calculation of descriptive statistics.

In descriptive statistic of the Screening visit the planned time point will be used. However, if an unscheduled measurement on the same day as the screening visit exists then the unscheduled assessment will be used in descriptive statistics of the Screening visit.

Clinically relevant findings in vital signs data will be reported as baseline conditions (prior to first administration of study treatment) or as AEs (after first administration of study treatment) if judged clinically relevant by the investigator, and will be analysed as such.

7.8.4 ECG

All evaluations of ECG data will be based on the TS except for the exposure-response analysis, which will be based on the ECGPCS.

Abnormal findings, irrespective of whether they originate from central or local evaluation, will be reported as baseline conditions (prior to first administration of study treatment) or as AEs (after first administration of study treatment) if judged clinically relevant by the investigator.

No separate listing or analysis of continuous ECG monitoring (by investigator) will be prepared.

12-lead ECG

ECG measurements will not be included in the statistical analysis if one of the following applies:

- No date or time available for ECG measurement
- Pre-dose measurement done after first drug administration
- On-treatment measurement done before first drug administration
- Measurement is a repeated measurement
- More than 3 single ECGs (i.e., measurements from 4th single ECG onwards will not be included)
- Unscheduled measurements

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.

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 presented in figures.

For more details to categorical endpoint definition refer to Additional Section 10.2.

Quantitative endpoints

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

Exposure-response analysis

This analysis will be done separately for SRD and MD part.

SRD part:

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 the Statistical Appendix of the CTR), as well as for means per dose group (presented in the End-of-Text part of the CTR).

The relationship between BI 1569912 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 1569912 and placebo and its 90% confidence interval at the geometric mean of C_{max} (after single dose) for each dose group. 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, centered baseline QTcF and plasma concentration as continuous covariates, treatment, time and day as fixed categorical effects, and a random intercept and slope for each subject. Restricted maximum likelihood estimation will be performed, and the Kenward-Roger method will be applied to adjust standard errors and estimate denominator degrees of freedom. For more details refer to Additional Section 10.3.

For visualization, a scatterplot of the BI 1569912 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.

The goodness of fit of the above model will be checked. The visual checks will include the inspection of concentration-QTcF quantile plots (see [R18-0143] (10)) and residual plots.

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.

MD part:

For MD part the number of pairs of ECG variables and corresponding plasma concentrations is insufficient to fit a random coefficient model. Furthermore, the planned number of Placebo subjects (n=3) is low and only one active dose group will be investigated in this part. 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 dose group (presented in the End-of-Text part of the CTR). These figures will also be presented for HR.

Appropriateness of heart rate correction methods of QT interval

This analyses will be done separately for all parts.

To evaluate the appropriateness of the heart rate correction methods, the slope of the relationship of QTcF interval versus RR interval will be estimated separately for off-drug values and active treatment, by applying the random coefficient model described in Additional Section 10.4 using the QTcF and RR variable values per time point. A scatterplot of QTcF vs RR including the overall regression lines 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 Other

7.8.5.1 Physical findings

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

7.8.5.2 Mental and neurological examination

Clinically relevant findings of the mental and neurological examination will be reported as adverse events (during the trial) or as baseline conditions (at screening) and will be summarized as such. No separate listing or analysis of mental and neurological examination findings will be prepared.

7.8.5.3 Assessment of suicidal ideation and behavior (SIB) based on C-SSRS

Suicidality monitoring will be performed as described in **Section 5.2.4.2 of the CTP**, results will be listed.

Findings may also be reported as AEs as described in the CTP.

7.8.5.4 Assessment of dissociative symptoms

Frequency of subjects categorized by CADSS total score ‘0’ or ‘>=1’ will be presented by treatment (or treatment sequence) and time point.

7.8.5.5 Electroencephalography

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

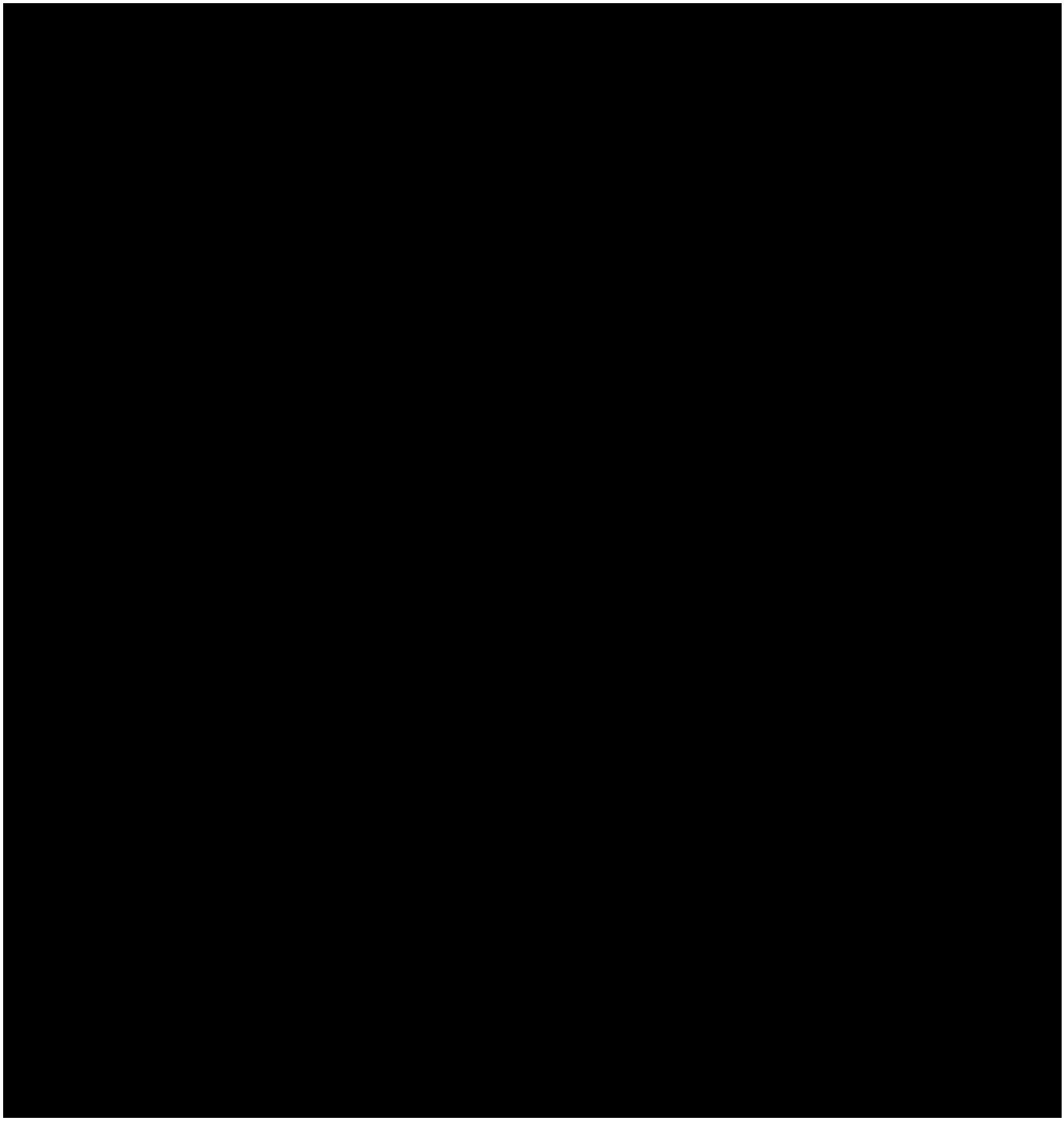
Frequency of patients categorized by EEG abnormalities will be presented by treatment and time point.

8. TIMEPOINT OF RELEASE OF TREATMENT INFORMATION

For SRD part, the treatment information will be loaded into the trial database at trial initiation. For MD and evening PK part the treatment information will be loaded into the trial database before start of the part.

9. REFERENCES

1	*CPMP/ICH/363/96*: "Statistical Principles for Clinical Trials", ICH Guideline Topic E9; Note For Guidance on Design, Conduct, Analysis and Evaluation of Clinical Trials, current version
[redacted]	
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
[redacted]	
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]



10.2 DETAILS FOR THE DERIVATION OF CATEGORICAL ECG ENDPOINTS

New onsets for categorical endpoints are derived based on the table below:

Table 10.2: 1 New onsets of notable QTc/QT findings

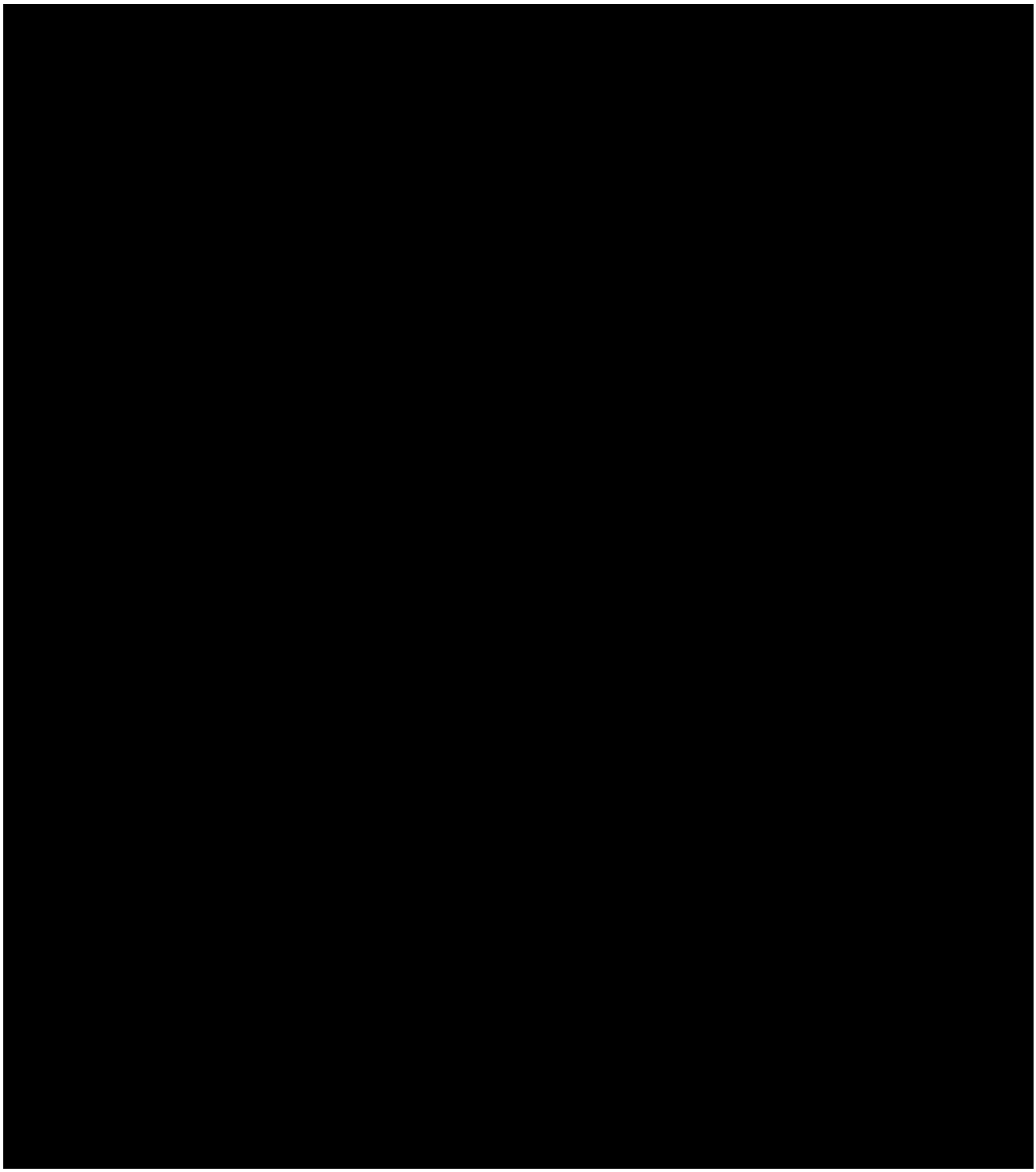
"New onset"/"no new onset" of a notable QTc/QT finding (aggregated result presented in Table)	**At baseline**	**On treatment**
No new onset	Any value	≤ 500 msec (all time points)
No new onset	> 500 msec (at least one time point[1])	Any value
New onset	≤ 500 msec or missing	> 500 msec (at least one time point)
Missing	≤ 500 msec or missing	Missing (at least one time point), ≤ 500 msec (all other time points)

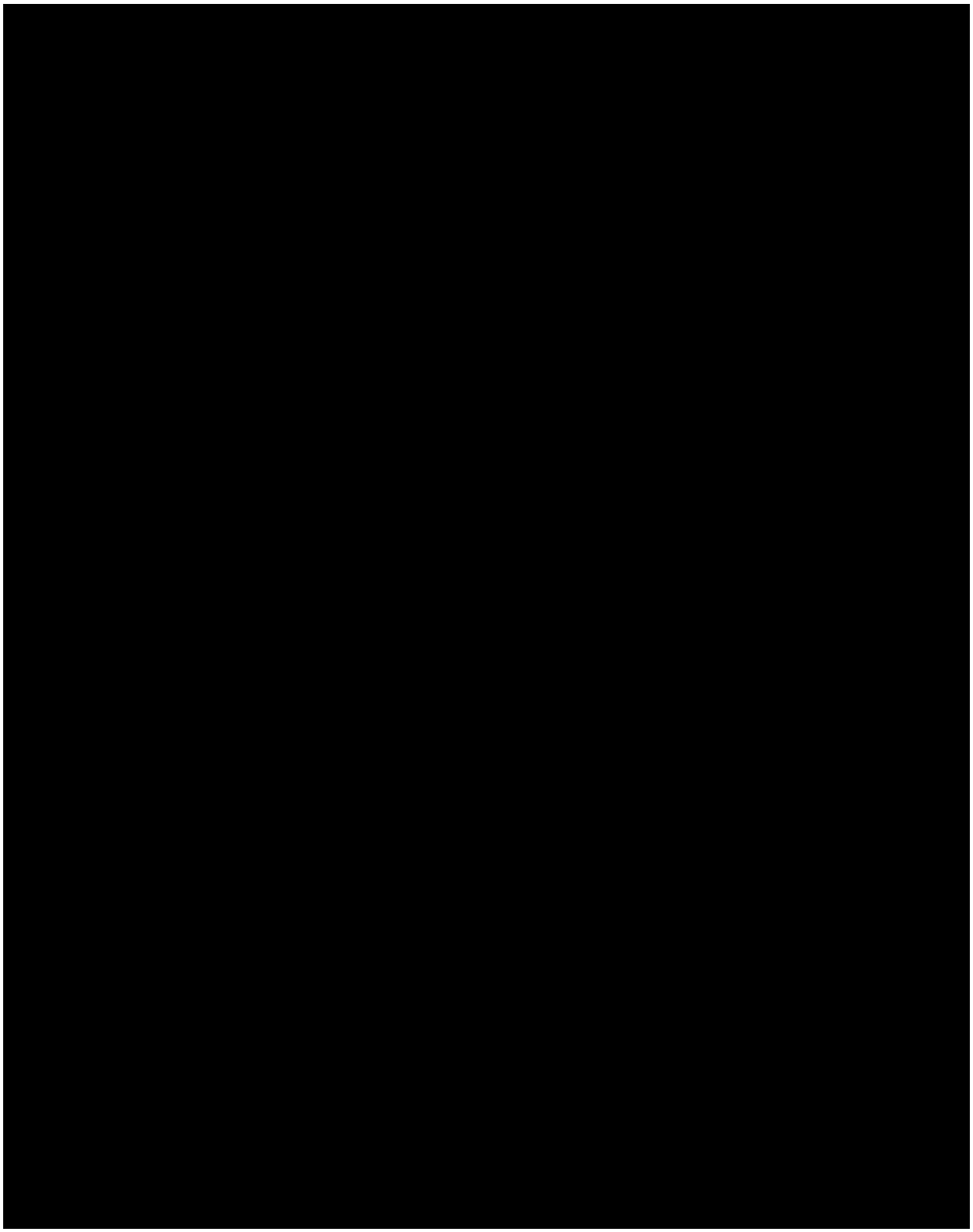
[1]: E.g., in case of a time-matched baseline, the baseline consists of several time points.

Table 10.2: 2 New onsets of values above thresholds

"New onset of values above thresholds" (aggregated result presented in Table)	**At baseline**	**On treatment**
No new onset	Any value	≤ 450 msec (all time points)
No new onset	> 500 msec (at least one time point[1])	Any value
New onset > 450 msec	≤ 450 msec or missing	> 450 msec (at least one time point), ≤ 480 msec (all time points)
New onset > 480 msec	≤ 480 msec or missing	> 480 msec (at least one time point), ≤ 500 msec (all time points)
New onset > 500 msec	≤ 500 msec or missing	> 500 msec (at least one time point)
Missing	≤ 500 msec or missing	Missing (at least one time point), ≤ 500 msec (all other time points)

[1]: E.g., in case of a time-matched baseline, the baseline consists of several time points.





11. HISTORY TABLE

Table 11: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
1.0	**15-NOV-23**	[redacted]	None	This is the final TSAP.