TRIAL STATISTICAL ANALYSIS PLAN

c34166601-01

BI Trial No.:	1425-0002
Title:	Safety, tolerability, and pharmacokinetics of multiple rising oral doses of BI 706321 in healthy male and female subjects (double-blind, randomised, placebo-controlled, parallel group design) Including Protocol Amendment 1 [c29586669- 02] Including Protocol Amendment 2 [c29586669- 03] Including Protocol Amendment 3 [c29586669- 04]
Investigational Product(s):	BI 706321
Responsible trial statistician(s):	[redacted] Phone: [redacted] Fax: [redacted]
Date of statistical analysis plan:	12-JAN-2021 SIGNED
Version:	1

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[redacted]

[redacted]

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2. LIST OF ABBREVIATIONS

Term	Definition / description
[redacted]	
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
$AUC_{\tau,ss}$	Area under the concentration-time curve of the analyte in plasma at steady state over a uniform dosing interval τ
$AUC_{0-\infty}$	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity
$\%AUC_{tz-\infty}$	Percentage of AUC0-∞ obtained by extrapolation
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
BI	Boehringer Ingelheim
BMS	Biomarker analysis set
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 over a uniform dosing interval τ
C_{min}	Minimum measured concentration of the analyte in plasma
CV	Arithmetic coefficient of variation
ECG	Electrocardiogram
[redacted]	
gCV	Geometric coefficient of variation
gMean	Geometric mean
ICH	International Council for Harmonisation
IPD	Important Protocol Deviation
λ_z	Terminal rate constant of the analyte in plasma
[redacted]	
MIST	Metabolites in Safety Testing
MMRM	Mixed-Effect Model for Repeated Measure
PKS	Pharmacokinetic parameter analysis set
QT	Time between start of the Q-wave and the end of the T-wave in an electrocardiogram

Term	Definition / description
QTc	QT interval corrected for heart rate using the method of Fridericia (QTcF) or Bazett (QTcB)
$R_{A,AUC}$	Accumulation ratio based on $AUC_{0-\tau}$
$R_{A,Cmax}$	Accumulation ratio based on $C_{max,ss}$
REP	Residual Effect Period
SD	Standard Deviation
ss	(At) steady state
$t_{1/2}$	Terminal half-life of the analyte in plasma
$t_{1/2,eff}$	Effective half-life
t_{max}	Time from (last) dosing to the maximum measured concentration of the analyte in plasma
$t_{max,ss}$	Time from last dosing to maximum concentration of the analyte in plasma at steady state
t_z	Time of last measurable concentration of the analyte in plasma
TS	Treated set
ULN	Upper limit of normal range
V_{ss}	Apparent volume of distribution at steady state after intravascular administration

[redacted]

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 CTP and to include detailed procedures for executing the statistical analysis of the primary and secondary variables and other data.

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

Study data will be stored in a trial database within the RAVE EDC system.

The statistical analyses will be performed within the validated working environment CARE, including SAS™ (current Version 9.4, by SAS Institute Inc., Cary, NC, USA), and a number of SAS™-based tools (e.g., macros for the analyses of AE data or laboratory data; 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 this TSAP are in accordance with the statistical methods planned in the revised CTP.

5. ENDPOINTS

5.1 PRIMARY ENDPOINT

The primary endpoint for assessment of safety and tolerability of BI 706321 is the percentage of subjects with drug-related adverse events, as defined in Section 2.1.2 of the CTP.

5.2 SECONDARY ENDPOINTS

5.2.1 Key secondary endpoint

Not applicable

5.2.2 Secondary endpoints

Secondary PK endpoints will be as defined in Section 2.1.3 of the CTP.

These endpoints are $AUC_{\tau,ss}$, $C_{max,ss}$, $C_{min,ss}$, $R_{A,Cmax}$ and $R_{A,AUC}$ of BI 706321 after the last dose of the multiple dose segment.

[redacted]

5.3.1 Safety parameters

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

- *AEs (including clinically relevant findings from the physical examination)*
- *Safety laboratory tests*
- *12-lead ECG*
- *Vital signs (blood pressure, pulse rate, body temperature)*

12-lead ECG endpoints

For the MRD part, ECG data will be analysed centrally. 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 QTcF, QT, HR, PR, QRS, RR and QTcB, derived as described in Additional Section 9.1:

- absolute values (per time point)
- changes and placebo-corrected changes from baseline (per time point)

Categorical ECG endpoints

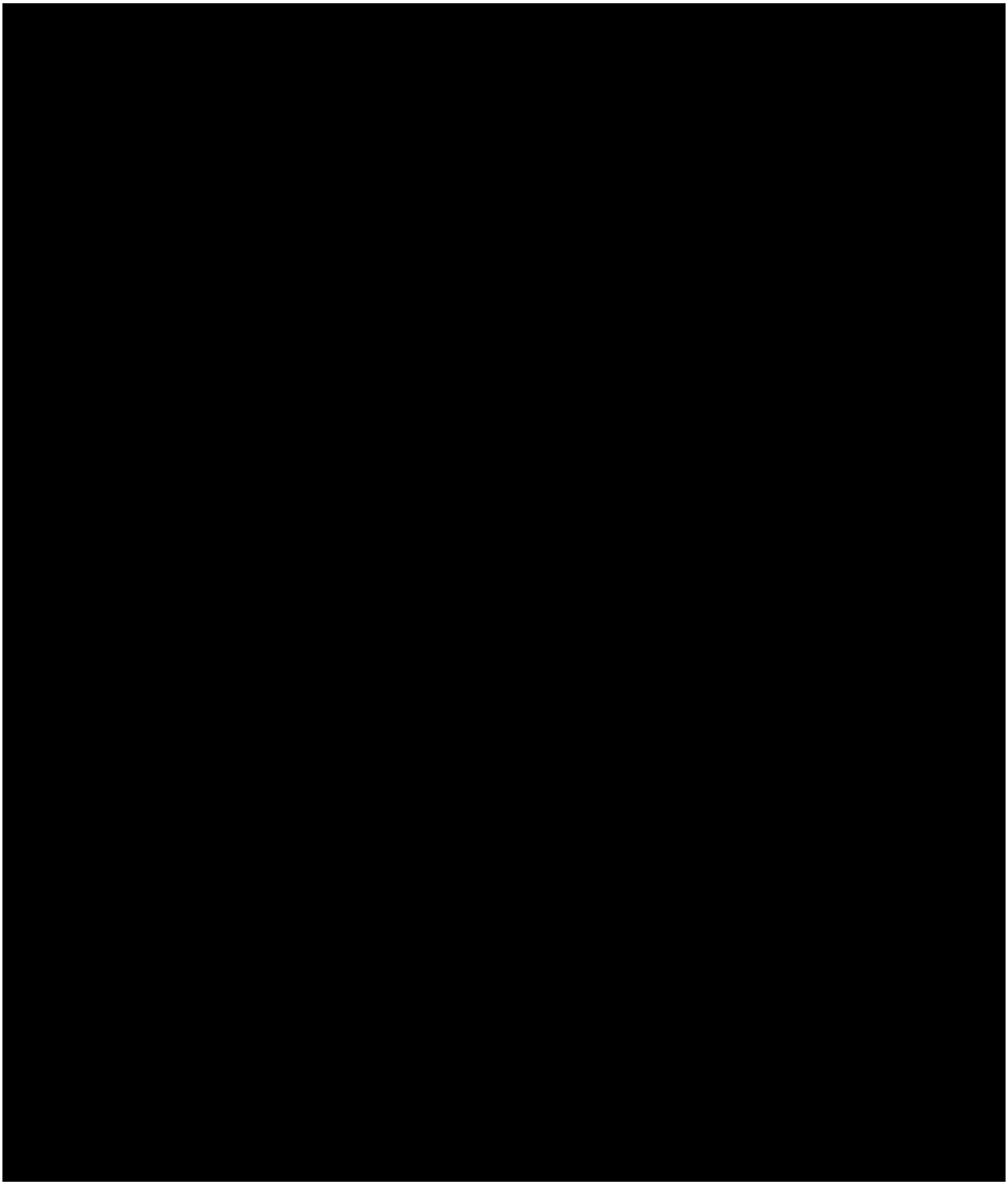
The following categorical ECG endpoints will be determined based on the quantitative ECG endpoints:

- New onset (meaning that this or a higher category was not present at baseline) of maximum QTcF interval > 450 to 480 msec, > 480 to 500 msec, or > 500 msec on treatment.
  For assignment of a particular subject to one of the above categories, all time points on-treatment (refer to Table 6.7: 1) will be considered. If baseline is missing, but the maximum absolute QTcF interval falls in a category other than normal (i.e. when QTcF > 450 msec), then this is categorized as a new onset in the respective category. If baseline is missing, but the maximum absolute QTcF interval is normal, then it is categorized as "No new onset".
- Maximum change from baseline in QT interval ≤ 60 msec, or > 60 msec on treatment
- Maximum change from baseline in QTcF interval ≤ 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 any time at baseline) of uncorrected QT interval > 500 msec at any time on treatment
  If baseline is missing, any occurrence of QT interval > 500 msec at any time on treatment will be a notable finding
- New onset of QTcF interval > 500 msec at any time on treatment
  If baseline is missing, any occurrence of QTcF interval > 500 msec at any time on treatment will be a notable finding
- Change from baseline of QTcF > 60 msec at any time on treatment
- Percent change from baseline of HR ≥ 25%, when corresponding on-treatment value of HR is > 100 beats/min, or percent change from baseline of HR ≤ - 25%, when corresponding on-treatment value of HR is < 50 beats/min, at any time on treatment
- Percent change from baseline of PR ≥ 25%, when corresponding on-treatment value of PR interval is > 200 msec, at any time on treatment
- Percent change from baseline of QRS ≥ 10%, when corresponding on-treatment value of QRS complex is > 110 msec, at any time on treatment

For a detailed description of ‘new onset’, refer to Additional Section 9.4.



6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENTS

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

In this study, subjects will receive a single dose of 2 mg, 5 mg, 8 mg or 10 mg of BI 706321 or placebo (orally as capsules) on Day 1 followed by 14 days with once daily multiple doses from Day 6 to Day 19. [redacted] no separate phases will be defined for the safety analysis of dose groups 3 and 4.

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

For statistical analysis of AEs, the following analysis phases are defined for each subject:

Table 6.1: 1 Flow chart of analysis phases for statistical analyses of AEs for dose groups 1 to 4

Study analysis phase	Label	Start (inclusive)	End (exclusive)
Screening	**Screening**	Date of informed consent	Date/time of first administration of BI 706321 /Placebo
On-treatment	**Placebo,** **2 mg BI**, **5 mg BI**, **8 mg BI,** or **10 mg BI**, respectively	Date/time of first administration of BI 706321 /Placebo	8 days after last administration of BI 706321 /Placebo
Follow-up *	**F/U Placebo,** **F/U 2 mg BI**, **F/U 5 mg BI**, **F/U 8 mg BI,** or **F/U 10 mg BI**, respectively	8 days after last administration of BI 706321 /Placebo	12:00 a.m. on day after subject's trial completion date

* If a subject completes the study in accordance with the CTP, no follow-up (F/U) phase exists for this subject.

Analysis phases for statistical analysis of AEs are defined for each subject as described in the Table 6.1: 1 for dose groups 1,2, 3 and 4.

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

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

- "**Total BI**", defined as the total over all on-treatment phases involving BI (this includes BI plus [redacted])
- "**Total on-trt**", defined as the total over all on-treatment phases, involving BI (this includes BI plus [redacted]) and placebo

Safety laboratory data, vital signs and ECG will be analysed based on dose groups (Placebo, 2 mg, 5 mg, 8 mg and 10 mg of BI 706321). ECG measurements are considered to be on-treatment if they were measured between the first administration of BI 706321 /Placebo and 8 days after the last administration of BI 706321 /Placebo.

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 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 decision log. Categories which are considered to be IPDs in this trial are defined in the integrated quality and risk management plan (IQRMP). If the data show other IPDs, the definition in the IQRMP will be supplemented accordingly by the time of the Report Planning Meeting.

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 Report Planning Meeting, 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 Report Planning Meeting.

Important and non-important Covid-19 related PDs will only be listed (12).

Table 6.2: 1 Handling of iPDs

iPD code	iPD Category & Brief Description	Excluded from which analysis set
A1	Inclusion Criteria Not Met	PKS, BMS
A2	Exclusion Criteria Violated	PKS, BMS
B1	Informed consent not available/not done	TS, PKS, BMS
B2	Informed consent too late	None
C1	Non-compliance	PKS, BMS
C2	Incorrect intake of trial medication	PKS, BMS
C3	Randomization not followed	PKS, BMS
C4	Accidental Unblinding	PKS, BMS
D1	Prohibited medication use	PKS, BMS
D2	Improper washout of concomitant medication	PKS, BMS
E1	Certain violations of procedures used to measure primary or secondary data	PKS
F1	Certain violations of time schedule used to measure primary or secondary data	PKS
G1	Intake of meal not according to CTP	PKS

6.3 SUBJECT SETS ANALYSED

Subject sets will be used as defined in the **Section 7.3 of the CTP**:

- *Treated set (TS): The treated set includes all subjects who were randomized and treated with at least one dose of study drug. The treatment assignment will be determined based on the first treatment the subjects received. The treated set will be used for safety analyses.*
- *Pharmacokinetic parameter analysis set (PKS): This set includes all subjects in the treated set (TS) who provide at least one PK endpoint that was not excluded due to a protocol deviation relevant to the evaluation of PK or due to PK non-evaluability (as specified in the following subsection 'Pharmacokinetics'). Thus, a subject will be included in the PKS, even if he/she contributes only one PK parameter value for one period to the statistical assessment. Descriptive and model based analyses of PK parameters will be based on the PKS.*

In addition, the following subject sets for a certain analysis of ECG and biomarker data will be used.

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

- ECG plasma 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.

[redacted]

Table 6.3: 1 Subject sets analysed

	Subject set			
Class of endpoint	TS	PKS	ECGPCS	[redacted]
Disposition	X			
IPDs	X			
Primary endpoint	X			
Secondary endpoints		X		
[redacted]				
Safety parameters	X			
Demographic/baseline conditions	X			
Exposure	X			
Exposure-response analyses of ECG data			X	
ECG except from exposure-response analyses	X			

[redacted]

6.5 POOLING OF CENTRES

This section is not applicable because the trial is performed in only one center.

6.6 HANDLING OF MISSING DATA AND OUTLIERS

Data of subjects who received the first administration of trial medication but failed to complete all periods of the study (dropouts or withdrawals) will be reported in the CTR as far as their data are available. Subjects who removed or withdraw from trial prior to the first administration of BI 706321 will not be entered in the CRF and thus will not be reported in the CTR. All withdrawals will be documented and the reason for withdrawal 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 are AE dates. Missing or incomplete AE dates are imputed according to BI standards (3).

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

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, the handling of missing value is described in Additional Section 9.4. For subjects on active drug, missing plasma concentration values with ‘BLQ’ in the comment field will be replaced by ½ LLOQ.

For placebo subjects, the missing plasma concentration values will be replaced by 0 for the exposure-response analyses.

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

For all parameters, except for ECG, the last non-missing value determined prior to first dosing of BI 706321 or placebo will be defined as baseline.

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

Three triplicate ECGs will be recorded as the baseline before the first drug administration. Triple ECGs (3 single ECGs recorded within 180 sec) will be recorded on on-treatment time points defined in the protocol with centralised ECG evaluation.

The baseline value of an ECG variable is defined as the mean of the 3 single ECGs of the first of the 3 triplicates prior to first study drug administration. For all on-treatment assessments, only the first of the three replicate ECG at a single assessment time will be centrally evaluated.

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

Visit	Day	Planned time [hh:mm] - relative to respective drug administration	Study phase	Central evaluation
2	1	-1:00	Baseline	Mean of the 3 single ECGs of the first of the 3 triplicates prior to first study drug administration
		1:00	On-treatment	First single ECG of the triplicate
		2:00		
		4:00		
		8:00		
		12:00		
	2	24:00		
		36:00		
	3	48:00		
	19	431:45		
		433:00		
		434:00		
		436:00		
		440:00		
		444:00		
	20	456:00		
	21	480:00		

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 01:00 will build one pair. Whether a time deviation between PK blood sampling time and corresponding ECG recording is too big for a reliable assessment and the pair has to be excluded from the analysis will be decided no later than at the RPM.

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

7. PLANNED ANALYSIS

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

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

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

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

For plasma concentrations as well as for all PK parameters the following descriptive statistics will additionally be calculated:

CV	arithmetic coefficient of variation
gMean	geometric mean
gCV	geometric coefficient of variation

For PK parameters the following descriptive statistics will additionally be calculated:

P10	10^{th} percentile
Q1	1^{st} quartile
Q3	3^{rd} quartile
P90	90^{th} percentile

The data format for descriptive statistics of 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 one decimal place. 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 subjects set whether they have non-missing values or not.

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Only descriptive statistics are planned for this section of the 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, if it

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

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

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

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

7.3 TREATMENT COMPLIANCE

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

7.4 PRIMARY ENDPOINT

7.4.1 Primary analysis of the primary endpoint

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

[redacted]

7.5 SECONDARY ENDPOINTS

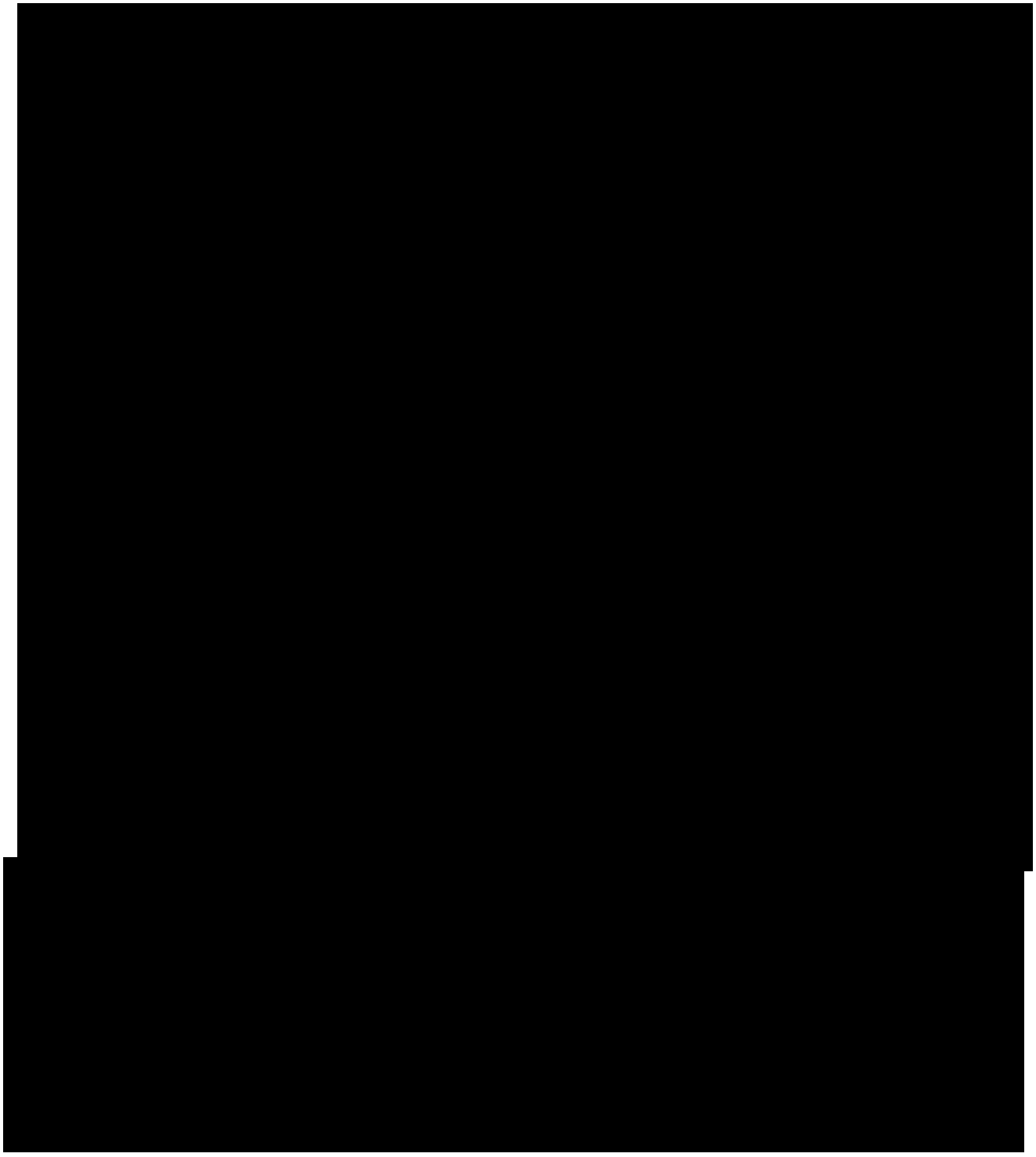
7.5.1 Key secondary endpoint

Not applicable.

7.5.2 Secondary endpoints

Primary analyses

The secondary endpoints will be analysed descriptively based on the PKS and will be performed for the parent drug. The analysis of standard PK parameters is performed according to BI standards (4).



Exclusion of PK parameters

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

Exclusion of plasma and urine concentrations

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

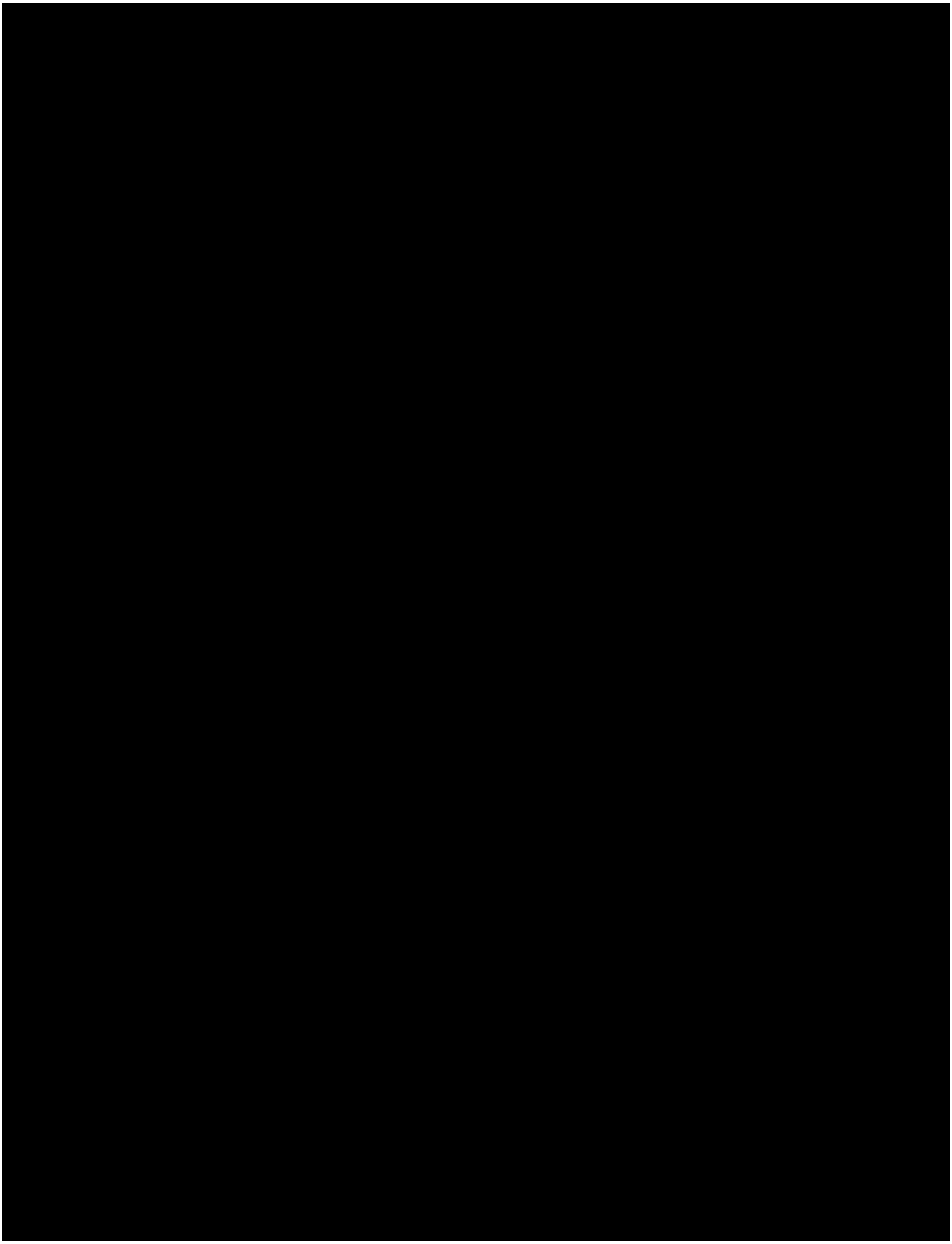
Further details are given in "Noncompartmental Pharmacokinetic / Pharmacodynamic Analyses of Clinical Studies"(4) and "Description of Analytical Transfer Files and PK/PD Data Files" (5).

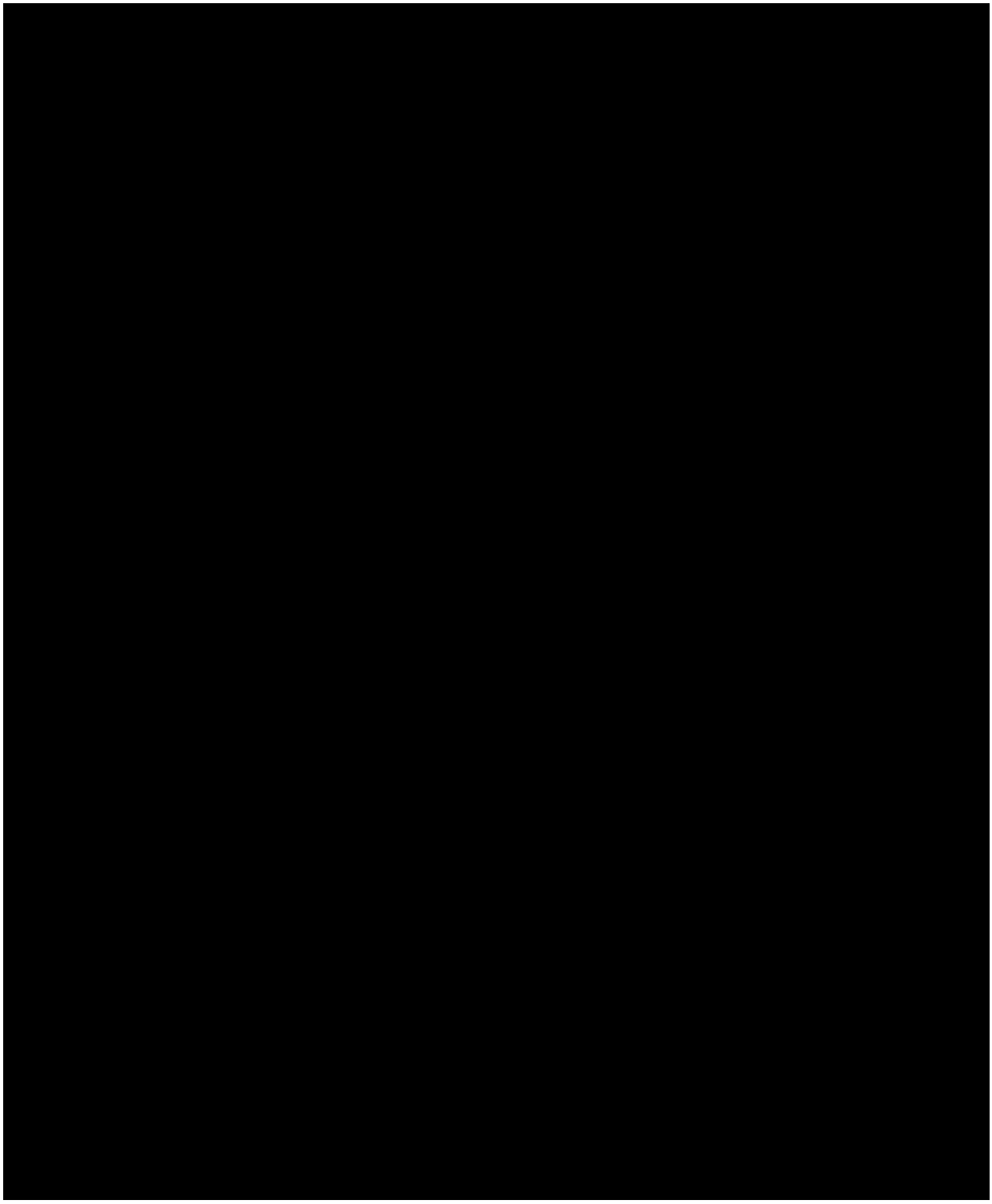
[redacted]

7.6.1 Safety parameters

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

[redacted]





7.7 EXTENT OF EXPOSURE

Descriptive statistics are planned for this section of the report.

7.8 SAFETY ANALYSIS

All safety analyses will be performed on the TS.

CTP Section 7.3.5: *Treatments will be compared in a descriptive way. The placebo group in the safety evaluation will consist of all subjects treated with placebo, regardless of the DG in which they were treated. The test treatment groups will be compared to the placebo group in a descriptive way. Tabulations of frequencies/proportions will be used for the evaluation of categorical (qualitative) data, and tabulations of descriptive statistics will be used to analyse continuous (quantitative) data.*

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 or on-treatment phases as defined in Section 6.1.

AEs will be analysed based on actual treatments, as defined in Table 6.1: 1.
AEs occurring after the REP but prior to trial termination date will be assigned to 'follow-up'.

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

CTP Section 5.2.5.1.4: *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), meaning AEs
(i) which are marked hematological or other lab abnormalities, or
(ii) which were reported with "action taken = discontinuation" or "action taken = reduced", or
(iii) which lead to significant concomitant therapy as identified by the Clinical Monitor/Investigator at a Medical Quality Review Meeting.

The frequency of subjects with AEs will be summarised by treatment, primary SOC and preferred term. AEs which were considered by the investigator to be drug related will be summarised separately. Separate tables will also be provided for subjects with SAEs and subjects with AESIs (according to ICH E3 (8)). AEs will be additionally summarized by maximum intensity.

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

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

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

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

7.8.2 Laboratory data

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

Analyses will be based on normalised values, which mean 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 absolute values and change from baseline from laboratory parameters over time (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).

Possibly clinically significant abnormal laboratory values are only those identified either in the Investigator's comments or at the Report Planning Meeting (RPM) at the latest. It is the Investigator's responsibility to decide whether a lab value is clinically significant abnormal or not. Standard or project-specific rules for flagging clinically significant values in an automated manner will not be applied in this study.

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 analyzed as such.

Line plots presenting individual values and means of c-reactive protein by treatment group over time as well as a scatter plot including $AUC_{\tau,ss}$ and maximum c-reactive protein (during multiple dosing period) by treatment group will be displayed.

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 absolute values and (possible on-treatment relevant) changes from baseline from vital signs over time (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 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 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 analyzed as such.

A graph of body temperature by actual time will also be presented.

7.8.4 ECG

Abnormal findings will be reported as baseline conditions (prior to first study drug administration) or as AEs (from first study drug administration onwards) if judged clinically relevant by the investigator (applies to all post-baseline ECG measurements). No separate listing or analysis of safety ECG findings will be prepared.

Centralized ECG

Descriptive analysis of ECG endpoints will be based on the TS.

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

Generally, 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 as well as measurements which are excluded from the statistical analysis will be flagged. In case of excluded measurements the reason for exclusion will be displayed.

CTP Section 5.2.4.1: *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.*

The above mentioned unscheduled ECGs will be listed separately.

Additionally comments regarding the ECGs will be listed.

Categorical endpoints

CTP Section 7.3.4: *The ECG variables QT, HR, QTcF, QTcB, PR, QRS, and RR obtained from the centralised evaluation of 12-lead ECG recordings will be the basis for the derivation of quantitative and categorical ECG endpoints.*

For the categorical endpoints, frequency tables will be provided.

For all subjects with any notable finding in 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.

For subjects with notable findings, the individual time courses of QTcF, QT, HR, PR and QRS of these subjects will be presented in figures. Additionally a corresponding listing will be provided.

Quantitative endpoints

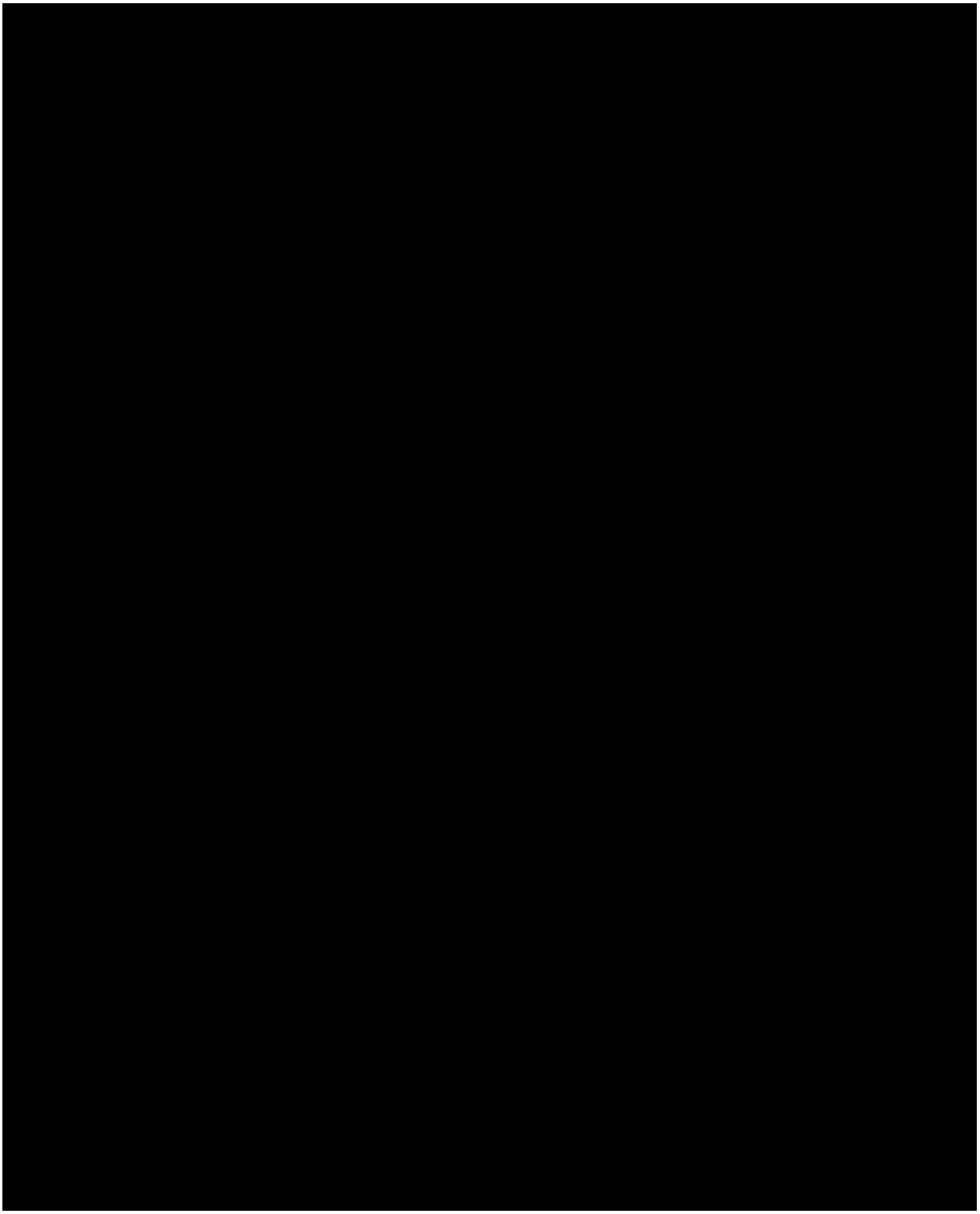
Descriptive statistics (N, mean, SD, min, median, max) will be provided for the absolute values and changes from baseline over time of QTcF, HR, QT, PR and QRS. The time profiles of mean and SD for the changes from baseline on treatment will be displayed graphically by treatment for PR, QT and QRS. Similar plots (not showing SD) are defined for QTcF and HR below, in context of the exposure-response analysis.

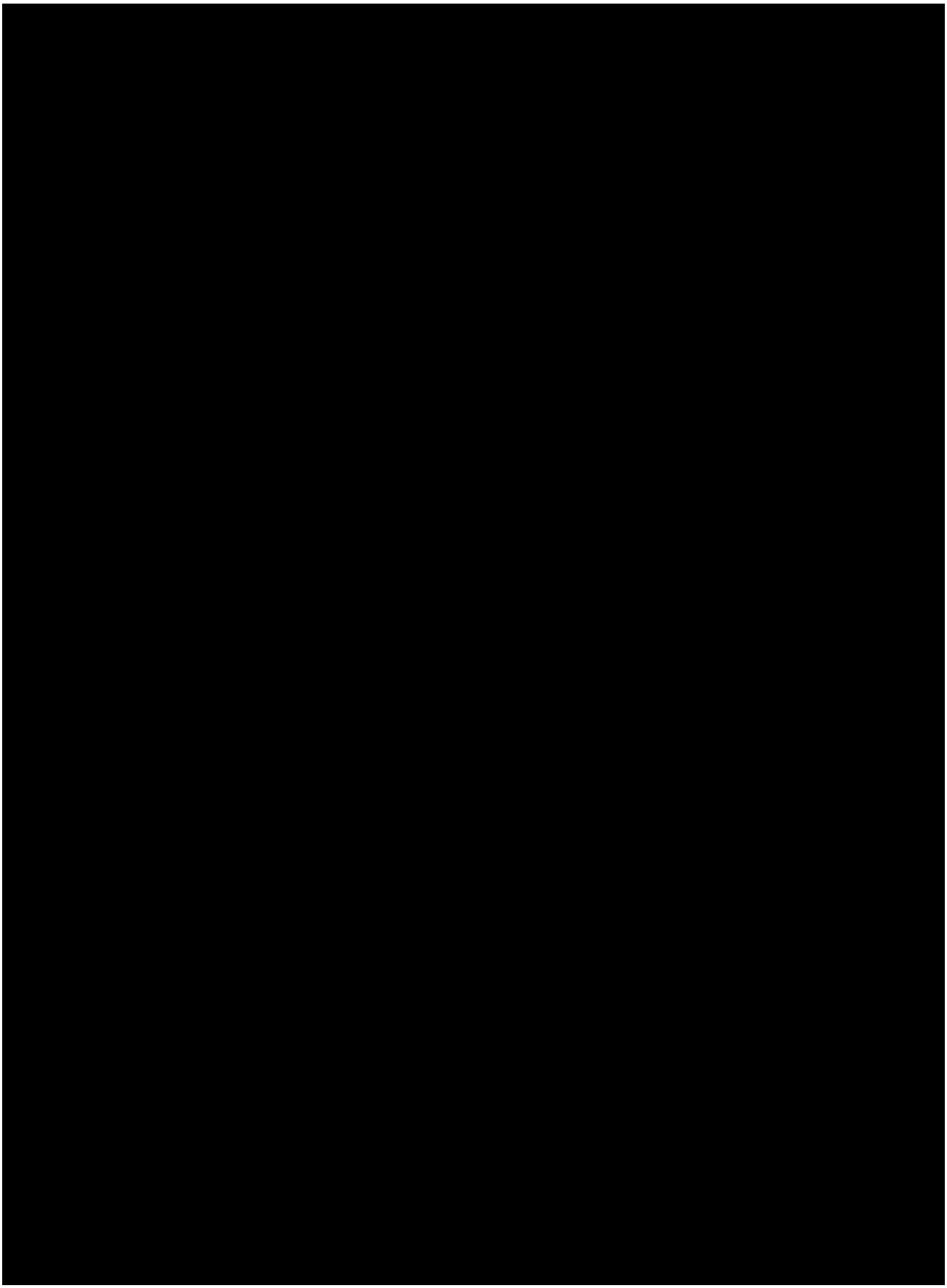
7.8.5 Others

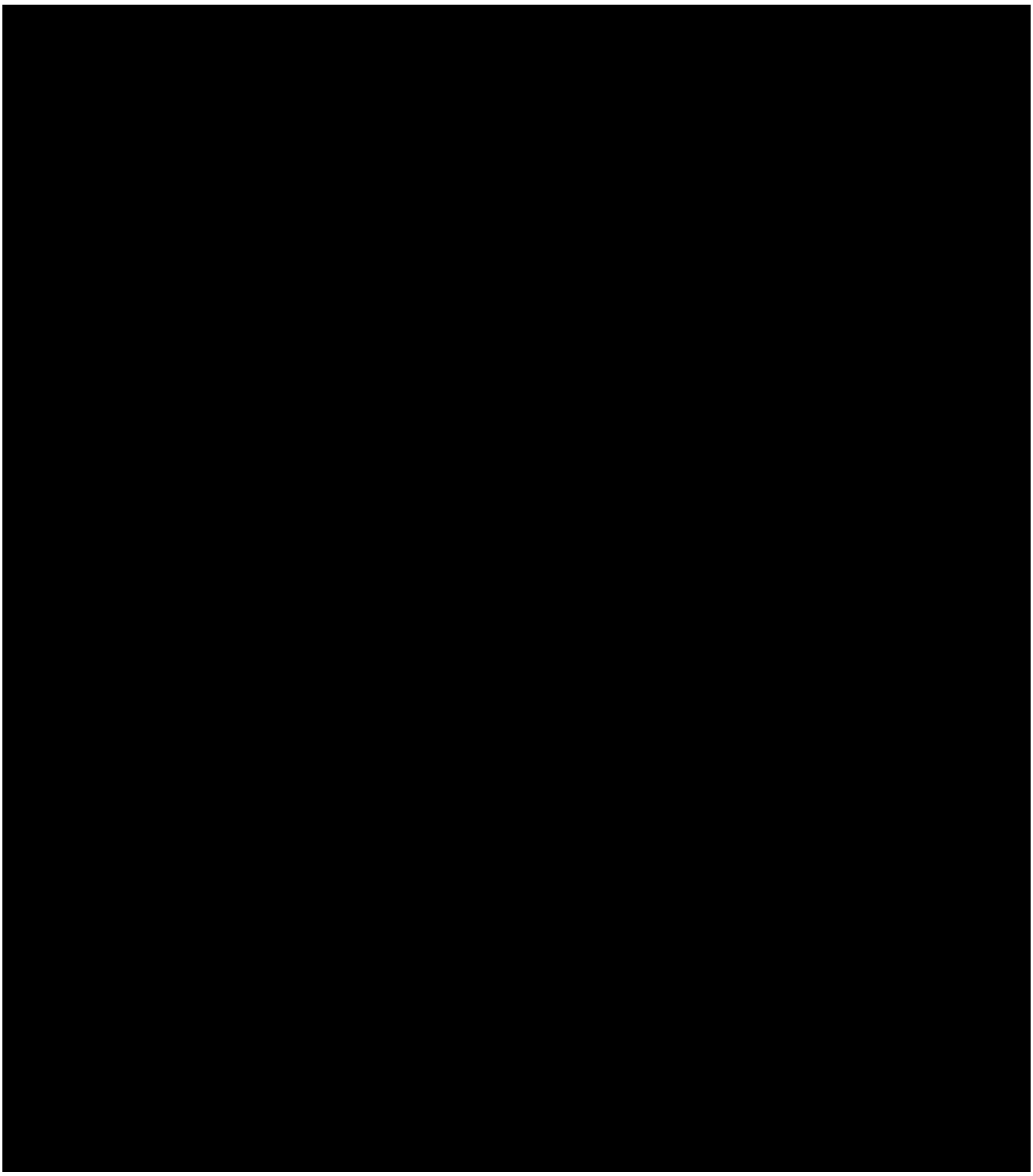
Physical examination findings will be reported as relevant medical history/baseline condition (if a condition already exists before first administration of study treatment) or as AE (if condition emerges after first administration of study treatment) and will be summarized as such. No separate listing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

8. REFERENCES

1	*CPMP/ICH/363/96*: "Statistical Principles for Clinical Trials", ICH Guideline Topic E9; Note For Guidance on Design, Conduct, Analysis and Evaluation of Clinical Trials, current version
2	*001-MCS-40-413_2.0:* "Identify and Manage Important Protocol Deviations (iPD)", current version; IDEA for CON
3	*KM Asset BI-KMED-BDS-HTG-0035:* "Handling of missing and incomplete AE dates", current version; KMED
4	*001-MCS-36-472_RD-01*: "Noncompartmental Pharmacokinetic / Pharmacodynamic Analyses of Clinical Studies", current version; IDEA for CON
5	*001-MCS-36-472_RD-03*: "Description of Analytical Transfer Files and PK/PD Data Files", current version; IDEA for CON
6	*KM Asset BI-KMED-BDS-HTG-0045:* "Standards for Reporting of Clinical Trials and Project Summaries", current version; KMED
7	*KM Asset BI-KMED-BDS-HTG-0066:* "Analysis and Presentation of Adverse Event Data from Clinical Trials", current version; KMED
8	*CPMP/ICH/137/95*: "Structure and Content of Clinical Study Reports", ICH Guideline Topic E3; Note For Guidance on Structure and Content of Clinical Study Reports, current version
9	*KM Asset BI-KMED-BDS-HTG-0042:* "Display and Analysis of Laboratory Data", current version; KMED
10	Garnett C, Bonate PL, Dang Q, Ferber G, Huang D, Liu J, et al. Scientific white paper on concentration-QTc modeling. J Pharmacokinet Pharmacodyn. 2018;45(3):383-397 [R18-0143]
11	*BI Statistical Position Paper*: "Statistical Methods for PK", current version; KMED
12	*KM Asset BI-KMED-COPS-HTG-0141:* "CTR writing guidance for trial impacted by the COVID-19 pandemic", current version; KMED







10. HISTORY TABLE

Table 10: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
1	**12-JAN-21**	[redacted]	None	This is the final TSAP