TRIAL STATISTICAL ANALYSIS PLAN

c35122034-01

BI Trial No.:	1405-0002
Title:	Safety, tolerability, pharmacokinetics, and pharmacodynamics of multiple rising oral doses of BI 1323495 versus placebo in healthy subjects, including an investigation of drug-drug interaction with microdose midazolam (double-blind, randomised, placebo-controlled [within dose groups] trial) Revised Protocol #08
Investigational Product:	BI 1323495
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Date of statistical analysis plan:	08-Apr-2021 SIGNED
Version:	Final

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2. LIST OF ABBREVIATIONS

Term	Definition / description
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC_{0-12}	Area under the concentration-time curve of the analyte in plasma over a uniform dosing interval of 12 h after administration of the first dose
AUC_{0-24}	Area under the concentration-time curve of the analyte in plasma over a uniform dosing interval of 24 h after administration of the first dose
$AUC_{0-\infty}$	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity
$AUC_{\tau,ss}$	Area under the concentration-time curve of the analyte in plasma at steady state over a uniform dosing interval τ
BI	Boehringer Ingelheim
BLQ	Below limit of quantification
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
COVID	Coronavirus disease
CTP	Clinical trial protocol
CTR	Clinical trial report
CV	Arithmetic coefficient of variation
ECG	Electrocardiogram
ECGPCS	ECG plasma concentration set
eCRF	Electronic case report form
EM	Extensive metabolizer
gCV	Geometric coefficient of variation
gMean	Geometric mean
HR	Heart rate
ICH	International Conference on Harmonisation
IPD	Important protocol deviations
IQRMP	Integrated quality and risk management plan

Term	Definition / description
LLOQ	Lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
NE	Neutrophil elastase
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PKS	Pharmacokinetic parameter analysis set
PM	Poor metabolizer
PR	Pulse rate
QRS complex	Combination of the Q, R, and S waves in an electrocardiogram
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 Bazett's formula
QTcF	QT interval, heart rate corrected according to Fridericia's formula
RAGe	Report appendix generator
RPM	Report planning meeting
RR interval	ECG interval from the peak of the R wave to the peak of the subsequent R wave
SAE	Serious adverse event
SD	Standard deviation
SOC	System organ class
TS	Treated set
TSAP	Trial statistical analysis plan
ULN	Upper limit of normal

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 trial statistical analysis plan (TSAP) assumes familiarity with the clinical trial protocol (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 Medidata Rave system.

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).

PK parameters will be calculated using Phoenix WinNonlin™ software (version Phoenix 6.3, [redacted].

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

The CTP uses the term “gender”, but means “sex” (as it is meanwhile named according to BI standards). The CTP did not mean “gender identity” (a concept that has meanwhile been developed), so “gender identity” was not collected in this trial, but “sex” was collected in the eCRF. This TSAP and the statistical analysis will use the term “sex” where the CTP uses the term “gender”.

The CTP states: “Dose proportionality may be repeated for different categories of gender and/or genotype, separately.” Since no trend for sex or genotype was seen, this analysis will not be conducted.

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

5. ENDPOINTS

5.1 PRIMARY ENDPOINT

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

5.2 SECONDARY ENDPOINTS

5.2.1 Key secondary endpoints

Not applicable.

5.2.2 Secondary endpoints

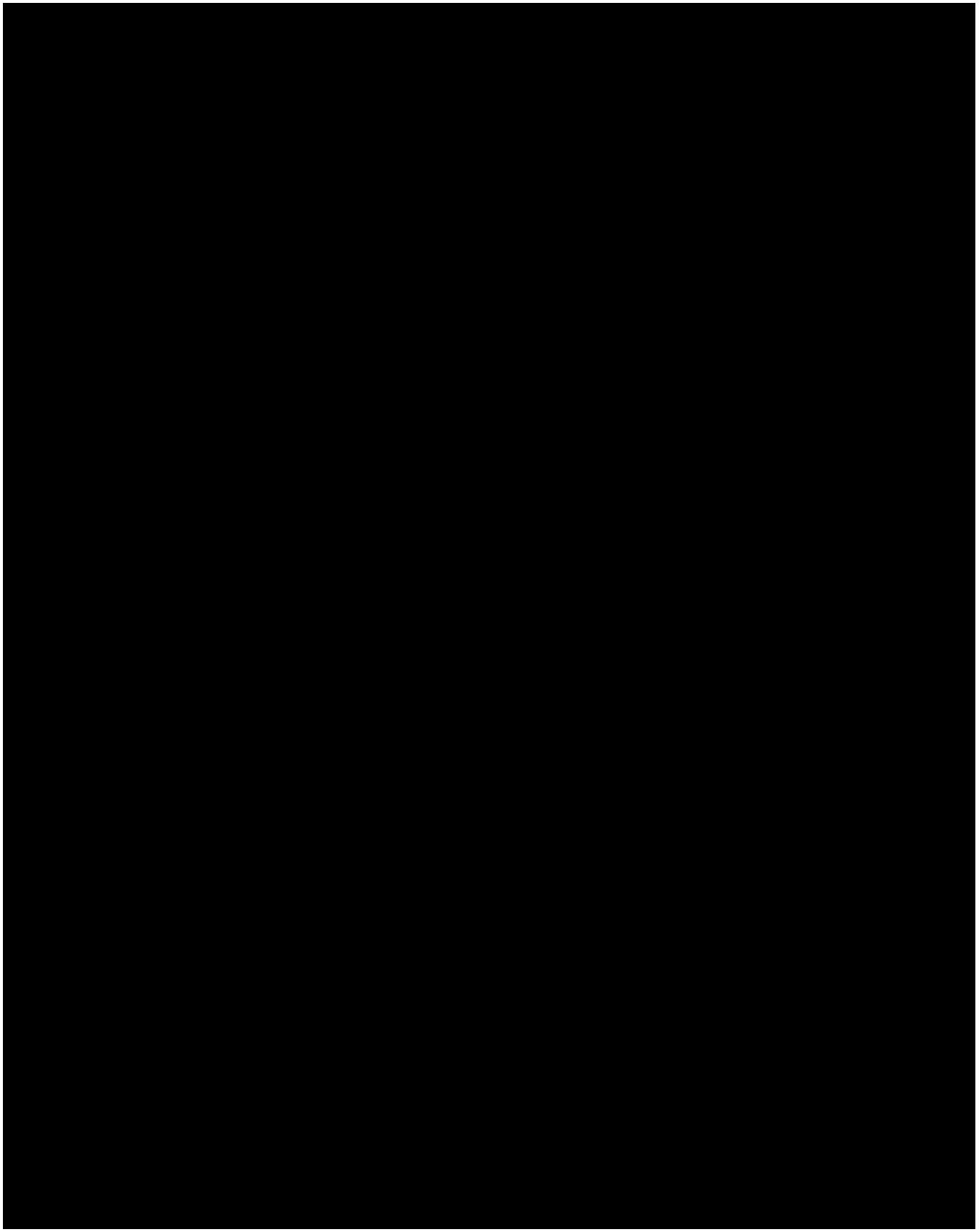
Secondary endpoints are PK endpoints of BI 1323495, as defined in Section 2.1.3 of the CTP:

After the first dose of BI 1323495:

- *AUC_{0-12} (area under the concentration-time curve of the analyte in plasma over a uniform time interval of 12 h after administration of the first dose)*
- *C_{max} (maximum measured concentration of the analyte in plasma after the first dose)*
- *Only for qd dosing: AUC_{0-24} (area under the concentration-time curve of the analyte in plasma over a uniform dosing interval of 24 h after administration of the first dose)*

[...] After the last dose of BI 1323495:

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



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.

EM subjects (Part I) were planned to be treated with

- doses of 10 mg bid, 30 mg bid, 70 mg bid, 120 mg bid, 120 mg qd, or 150 mg bid of BI 1323495 (test treatments)
  or
- matching placebo (reference treatment)

PM subjects (Part II) were planned to be treated with

- doses of 10 mg bid or 30 mg bid of BI 1323495 (test treatments)
  or
- matching placebo (reference treatment)

In the 3 highest EM bid dose groups (70 mg bid, 120 mg bid and 150 mg bid of BI 1323495), subjects were planned to receive a single dose of microdose midazolam solution on Day -1 and Day 11.

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 for each subject are provided in Table 6.1: 1.

Table 6.1: 1 Analysis phases for statistical analysis of AEs, and actual treatment for analysis of laboratory data and vital signs

Study analysis phase	Label	Start	End
Screening[1]	**Screening**	Date of informed consent	Date/time of first administration of BI drug or midazolam (whichever occurs first)
On treatment[2]	**Mid alone**	Date/time of first administration of midazolam	Date/time of first administration of BI drug
On treatment	**Placebo/Placebo+Mid, 10 mg bid EM, 10 mg bid PM, 30 mg bid EM, 30 mg bid PM, 70 mg bid+Mid EM, 120 mg bid+Mid EM, 120 mg qd EM,** or **150 mg bid+Mid EM,** respectively	Date/time of first administration of BI drug	Date/time of last administration of BI drug + residual effect period (7 days, i.e., 7 * 24 h) or 12:00 a.m. on day after last contact date (whichever occurs first)
Follow-up[3]	**F/U Placebo/Placebo+Mid, F/U 10 mg bid EM, F/U 10 mg bid PM, F/U 30 mg bid EM, F/U 30 mg bid PM, F/U 70 mg bid+Mid EM, F/U 120 mg bid+Mid EM, F/U 120 mg qd EM,** or **F/U 150 mg bid+Mid EM,** respectively	Date/time of last administration of BI drug + 7 * 24 h	12:00 a.m. on day after last contact date

[1] See Section 6.7 for definition of baseline, which will be used in the statistical analyses of safety laboratory data, ECG and vital signs.
[2] This phase exists only in those subjects who have received Midazolam.
[3] This phase exists only in those subjects who have last contact 7 or more days after last BI drug.

AE displays in CTR Section 15.3, Appendix 16.1.13.1.8.2 and Appendix 16.1.13.1.8.3 will present results for the on-treatment phase only.

In AE tables in CTR Section 15.3 (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 presented in addition:

- "**Total BI**", defined as the total over all on-treatment phases involving BI
- "**Total BI EM**", defined as the total over all on-treatment phases in EM subjects, involving BI
- "**Total BI PM**", defined as the total over all on-treatment phases in PM subjects, involving BI
- "**Total on-trt** ", defined as the total over all on-treatment phases (involving BI, placebo and midazolam alone)

Safety laboratory data, ECG and vital signs will be statistically analysed based on dose groups (not on analysis phases defined above), with clear differentiation between baseline (cf. Section 6.7) and on-treatment measurements. Measurements will be considered on-treatment, if they were taken within the on-treatment phases as defined in Table 6.1: 1. Analysis results will be labelled with the applicable dose group, as follows:

- Placebo/Placebo+Mid
- 10 mg bid EM
- 10 mg bid PM
- 30 mg bid EM
- 30 mg bid PM
- 70 mg bid+Mid EM
- 120 mg bid+Mid EM
- 120 mg qd EM
- 150 mg bid+Mid EM

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. At this meeting, it will be decided whether a discrepant data value can be used in analyses or whether it must be corrected in the clinical database. Each protocol deviation must be assessed to determine whether it is an important PD (IPD). For 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. 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 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.

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

6.3 SUBJECT SETS ANALYSED

The treated set (TS) and pharmacokinetic parameter analysis set (PKS) will be used as defined in the CTP, Section 7.2.1.

In addition, the following subject set for a certain analysis of ECG 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.

Table 6.3: 1 Subject sets analysed

	Subject set		
Class of endpoint	TS	PKS	ECGPCS
Primary endpoint	X		
Secondary PK endpoints		X	
Further PK endpoints		X	
Further PD endpoint	X	X[1]	
Safety parameters (except for exposure-response analyses of ECG data)	X		
Exposure-response analyses of ECG data			X
Demographic/baseline characteristics	X		
Treatment exposure	X		

[1] In analysis of further PD endpoints, PKS will only be used for E_{max} model analysis

[redacted]

6.5 POOLING OF CENTRES

This section is not applicable, because the study was performed in only one centre.

6.6 HANDLING OF MISSING DATA AND OUTLIERS

CTP: *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: *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).

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 9.3.

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

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

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

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

For all parameters, except for ECG, the last non-missing value determined prior to first administration of BI 1323495 will be defined as baseline.

A centralised evaluation of 12-lead ECG recordings is performed at the time points specified in Table 6.7: 1. Three triplicate ECGs will be recorded as the baseline before the first drug administration and at planned time point 239:00, but only the first ECG of each of the 3 baseline triplicates will be transferred to the database. All other ECGs for centralized evaluation are recorded as one triplicate ECGs (i.e. three single ECGs recorded within 180

sec), but only the first single ECG of the triplicate will be transferred to the database. Central ECG lab evaluation will be performed for the first of three replicate ECGs per time point.

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 baseline value of an ECG variable is defined as the mean of the ECG variable values with centralised evaluation prior to first study drug administration.

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

Visit	Day	Planned time [hh:mm] - relative to first drug administration	Study phase
2	1	-01:00	Baseline
		01:00	On-treatment
		02:00	
		04:00	
		06:00	
		08:00	
		12:00	
	2	23:30[1]	
	5	95:30[1]	
	8	167:15[1]	
	11	239:00[1]	
		241:00	
		242:00	
		244:00	
		246:00	
		248:00	
		252:00	
	12	264:00	

[1] According to CTP flow chart, there is no time-matched PK sample for the ECG measurements at planned times 23:30, 95:30, 167:15 and 239:00 These ECG measurements will be paired with the PK measurements from planned times 24:00, 96:00, 168:00 and 240:00 respectively in the exposure-response model, which will be applied to time matched pairs of ECG measurements and PK samples.

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 1:00 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 Report Planning Meeting.

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 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 subject set whether they have non-missing values or not.

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Only descriptive statistics are planned for this section of the 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.

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

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).

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. Any deviations from complete intake will be addressed in the Report Planning Meeting (cf. Section 6.2) and described in the CTR.

7.4 PRIMARY ENDPOINTS

7.4.1 Primary analysis of the primary endpoints

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.

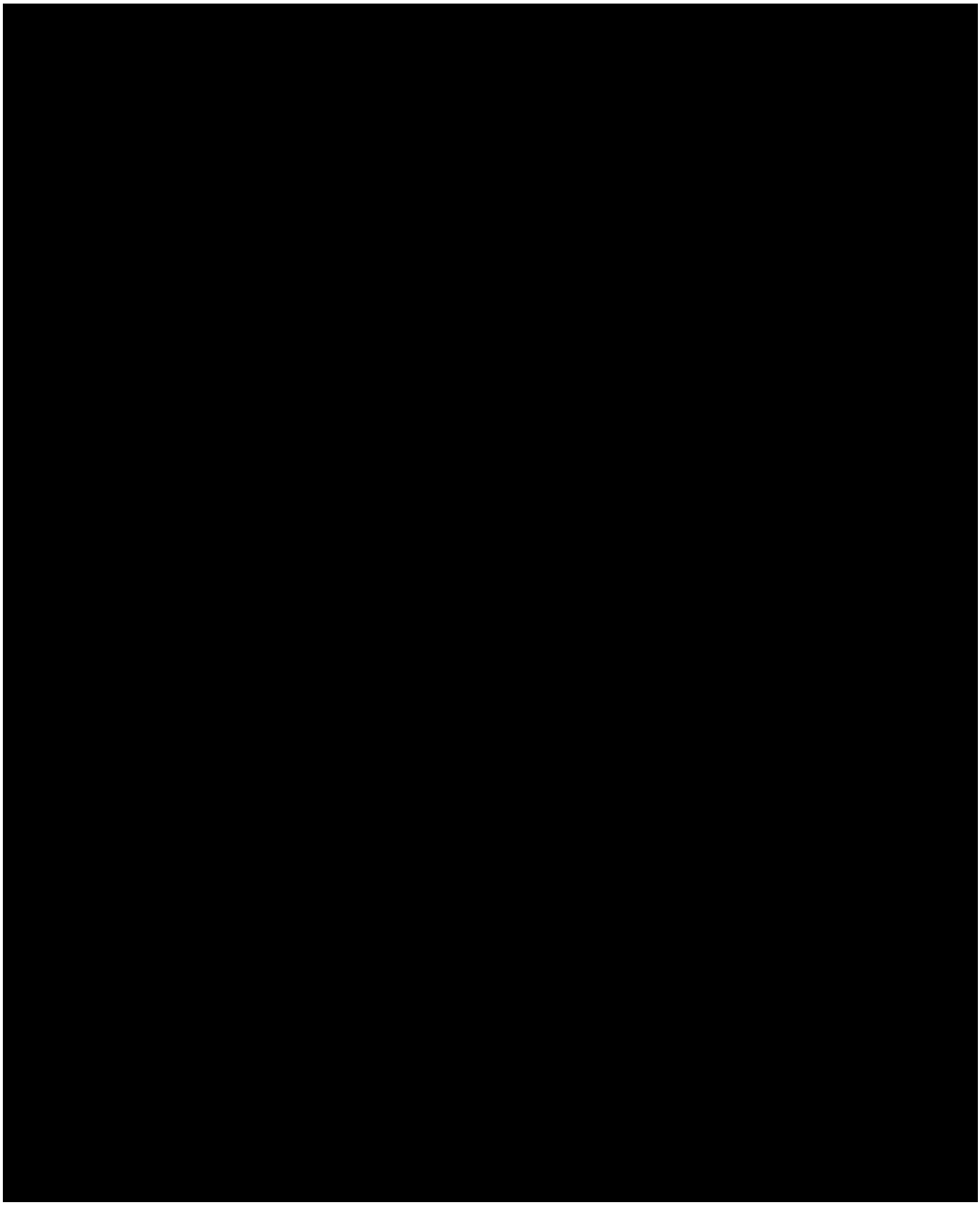
7.5 SECONDARY ENDPOINTS

7.5.1 Key secondary endpoints

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

7.5.2 Secondary endpoints

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



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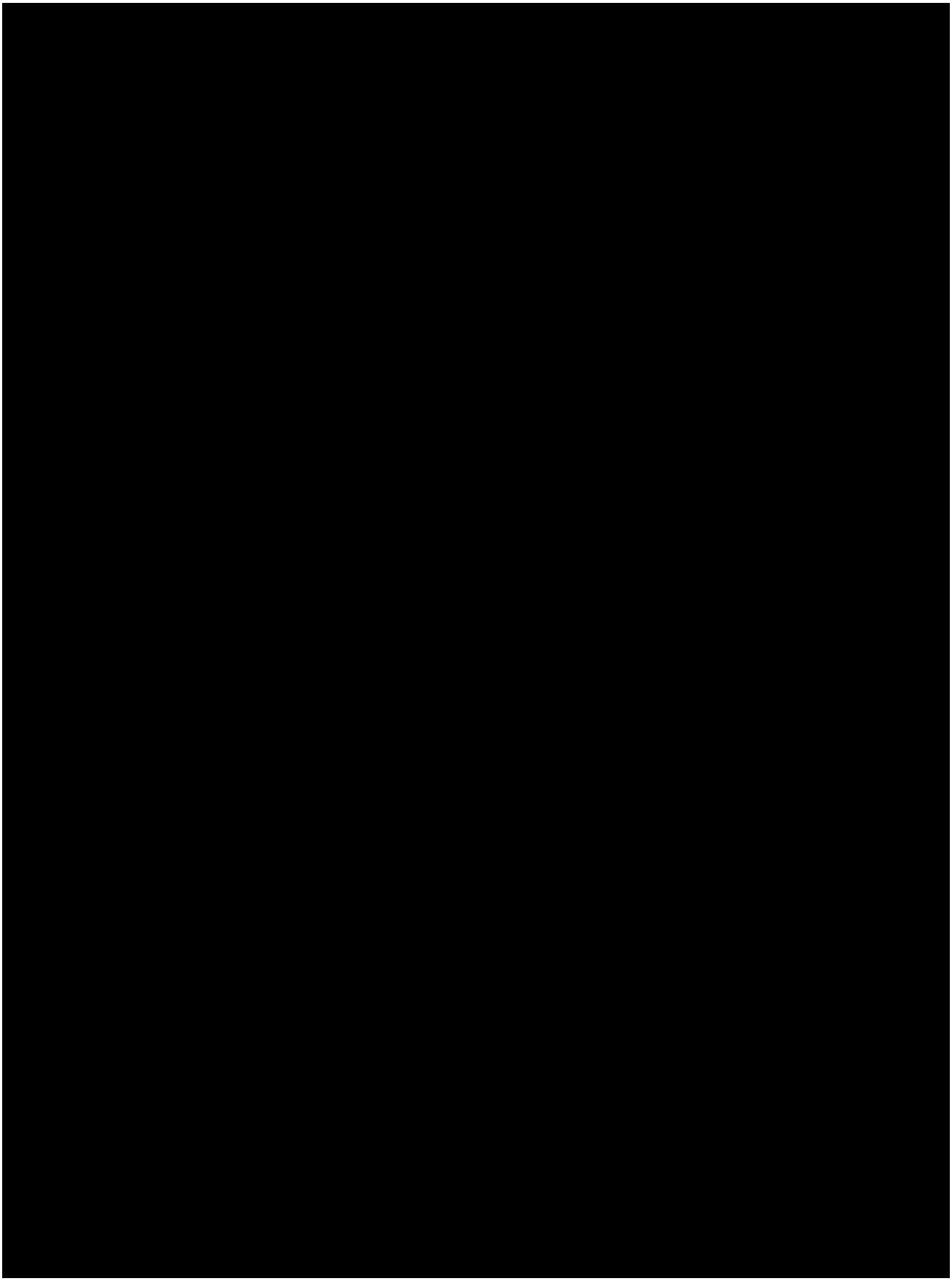
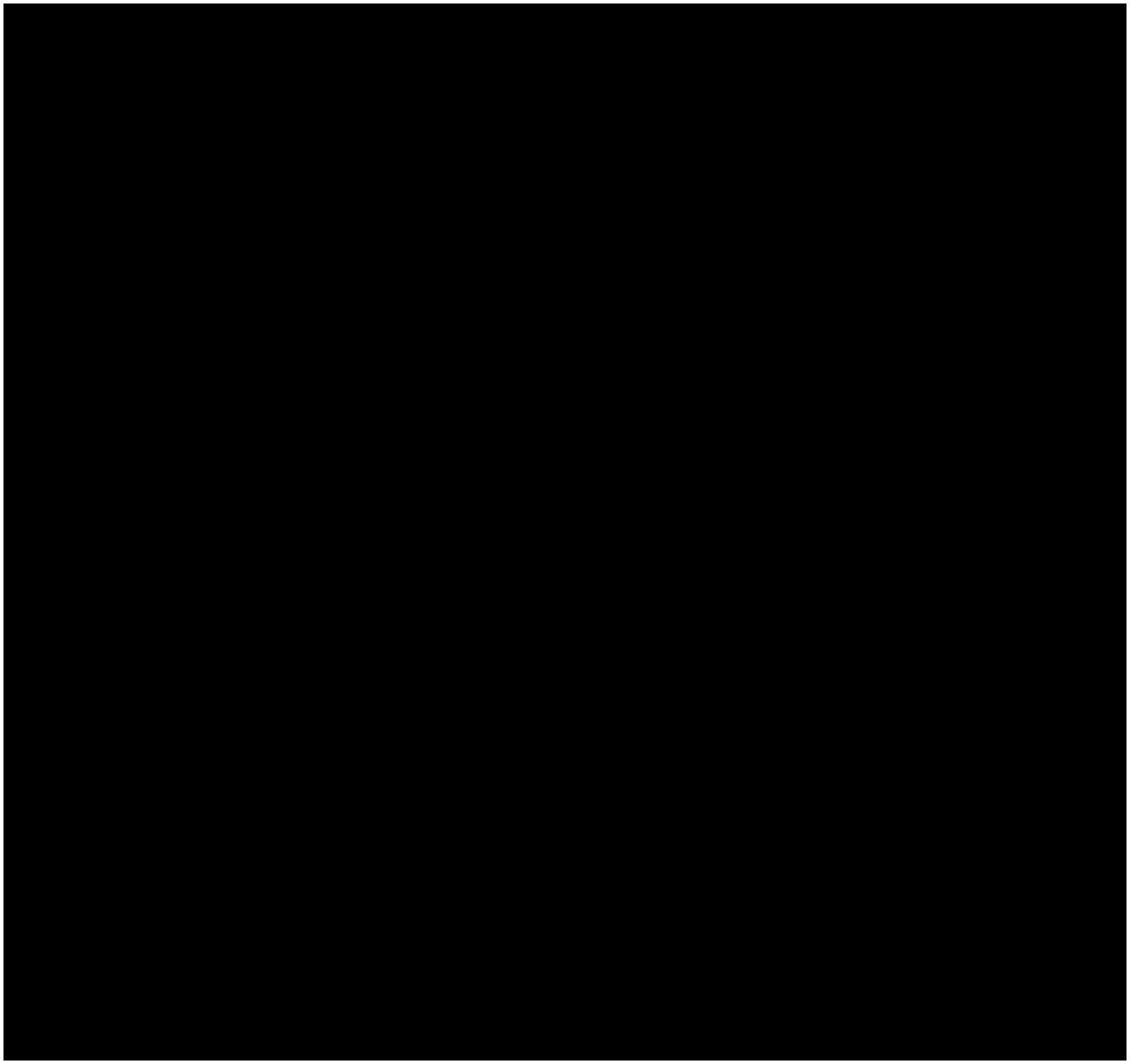




7.7 EXTENT OF EXPOSURE

Descriptive statistics are planned for this section of the report.

7.8 SAFETY ANALYSIS

All safety analyses will be performed on the TS.

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 phases as defined in Section 6.1. AEs will be analysed based on actual treatments, as defined in Table 6.1: 1.

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

CTP: *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 draw 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).

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 once overall and, additionally, stratified by sex only for EM dose groups. Separate tables will also be provided for subjects with SAEs and subjects with AESIs. AEs will also be 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 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.

Results from the pregnancy tests will only be listed.

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).

Laboratory data will be compared to their reference ranges. Values outside the reference range as well as possibly clinically significant values will be highlighted in the listings.

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 and pulse rate) 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.

Body weight and aural body temperature will be listed, including its change from baseline.

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 analysed as such.

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.

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.

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.

Comments regarding the ECGs will be listed.

Categorical endpoints

For the categorical endpoints, frequency tables will be provided.

For all subjects with any notable finding in 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.

Exposure-response analysis

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 1323495 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 1323495 and placebo and its 90% confidence interval at the geometric mean of C_{max} 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. For more details refer to Additional Section 9.4.

For visualization, a scatterplot of the BI 1323495 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]) 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 for the exposure-response analysis will be also performed for HR in place of QTcF.

Appropriateness of heart rate correction methods of QT interval

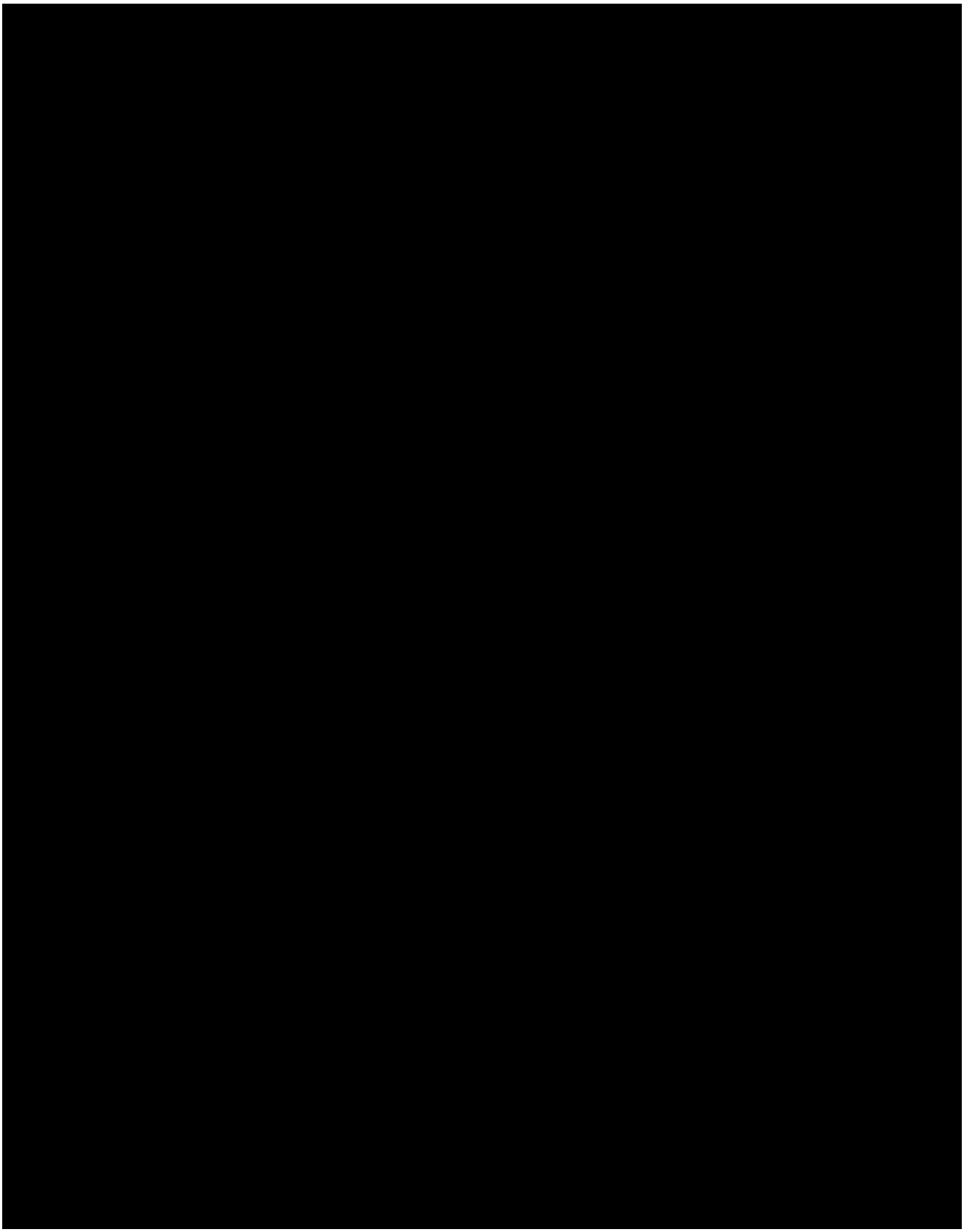
To evaluate the appropriateness of the heart rate correction methods, the slope of the relationship of QTcF interval versus RR interval will be estimated separately for off-drug values and active treatment, by applying the random coefficient model described in Additional Section 9.2 using the QTcF and 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.

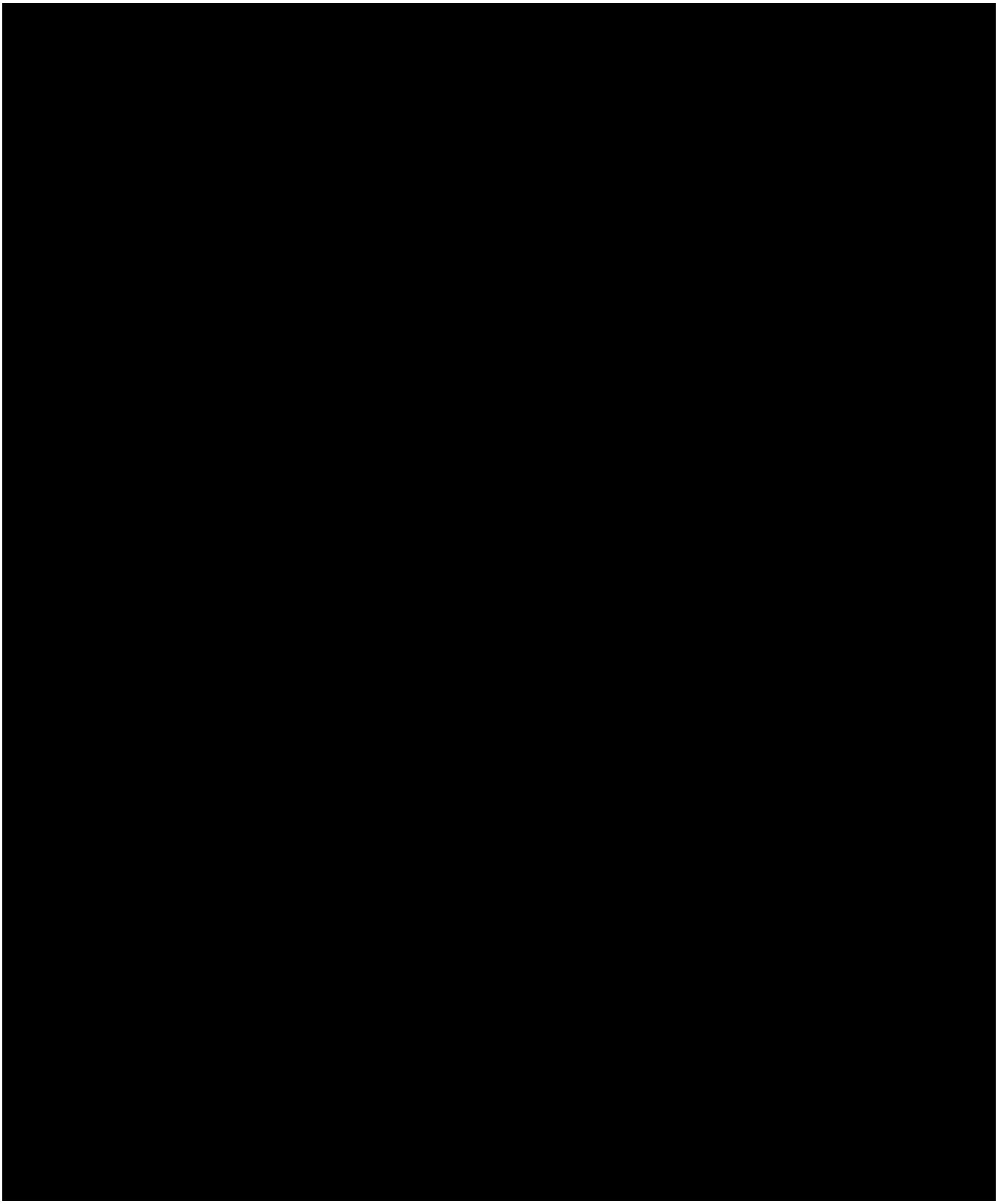
7.8.5 Others

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_1.0:* "Identify and Manage Important Protocol Deviations (iPD)", current version; IDEA for CON
3	*KM Asset BI-KMED-BDS-HTG-0035:* "Handling of missing and incomplete AE dates", current version; KMED
4	*KM Asset BI-KMED-TMCP-MAN-0014*: "Noncompartmental PK/PD Analyses of Clinical Studies", current version; KMED
5	*KM Asset BI-KMED-TMCP-MAN-0010: "Description of Analytical Transfer Files, PK/PD Data files and ADA files", current version; KMED*
6	*KM Asset BI-KMED-BDS-HTG-0045:* "Reporting of Clinical Trials and Project Summaries", current version; KMED
7	*KM Asset BI-KMED-BDS-HTG-0041:* "Analysis and Presentation of Adverse Event Data from Clinical Trials", current version; KMED
8	*CPMP/ICH/137/95*: "Structure and Content of Clinical Study Reports", ICH Guideline Topic E3; Note For Guidance on Structure and Content of Clinical Study Reports, current version
9	*KM Asset BI-KMED-BDS-HTG-0042:* "Display and Analysis of Laboratory Data", current version; KMED
10	Garnett C, Bonate PL, Dang Q, Ferber G, Huang D, Liu J, et al. Scientific white paper on concentration-QTc modeling. J Pharmacokinet Pharmacodyn. 2018. 45(3): 383-397. [R18-0143]





10. HISTORY TABLE

Table 10: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
Final	**08-APR-2021**	[redacted]	None	This is the final TSAP