TRIAL STATISTICAL ANALYSIS PLAN

c38236282-01

BI Trial No.:	1445-0002
Title:	Safety, tolerability and pharmacokinetics of multiple rising oral doses of BI 1595043 (double-blind, randomised, placebo-controlled, parallel group design) in healthy male subjects Including Protocol Amendment 2 [c33929558-03]
Investigational Product:	BI 1595043
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Date of statistical analysis plan:	10-Mar-2022 SIGNED
Version:	Final

1. TABLE OF CONTENTS

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LIST OF TABLES

2. LIST OF ABBREVIATIONS

Term	Definition / description
AE	Adverse Event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
$AUC_{0-\infty}$	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity
$AUC_{0-\tau,ss}$	Area under the concentration-time curve of the analyte in plasma at steady state over a uniform dosing interval τ
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
$C_{min,ss}$	Minimum measured concentration of the analyte in plasma at steady state over a uniform dosing interval τ
$R_{A, Cmax}$	Accumulation ratio based on $C_{max,ss}$
$R_{A, AUC}$	Accumulation ratio based on $AUC_{0-\tau,ss}$
BI	Boehringer Ingelheim
C_{max}	Maximum measured concentration of the analyte in plasma
COVID	Coronavirus disease
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
CV	Arithmetic coefficient of variation
ECG	Electrocardiogram
ECGPCS	ECG plasma concentration set
gCV	geometric coefficient of variation
gMean	Geometric mean
HR	Heart rate
ICH	International Conference On Harmonisation
IPD	Important protocol deviations
LLOQ	Lower limit of quantification
MedDRA	Medical Dictionary For Regulatory Activities
PD	Pharmacodynamics

Term	Definition / description
PK	Pharmacokinetics
PKS	Pharmacokinetic parameter analysis set
PR	Pulse rate
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
QTcB	QT interval, heart rate corrected according to Bazetts formula
QTcF	QT interval, heart rate corrected according to Fridericias 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 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 CTP, and to include detailed procedures for executing the statistical analysis of the primary 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 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

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

5. ENDPOINTS

5.1 PRIMARY ENDPOINT

The primary endpoint for assessment of safety and tolerability of BI 1595043 is the percentage of subjects with drug-related adverse events.

5.2 SECONDARY ENDPOINTS

5.2.1 Key secondary endpoints

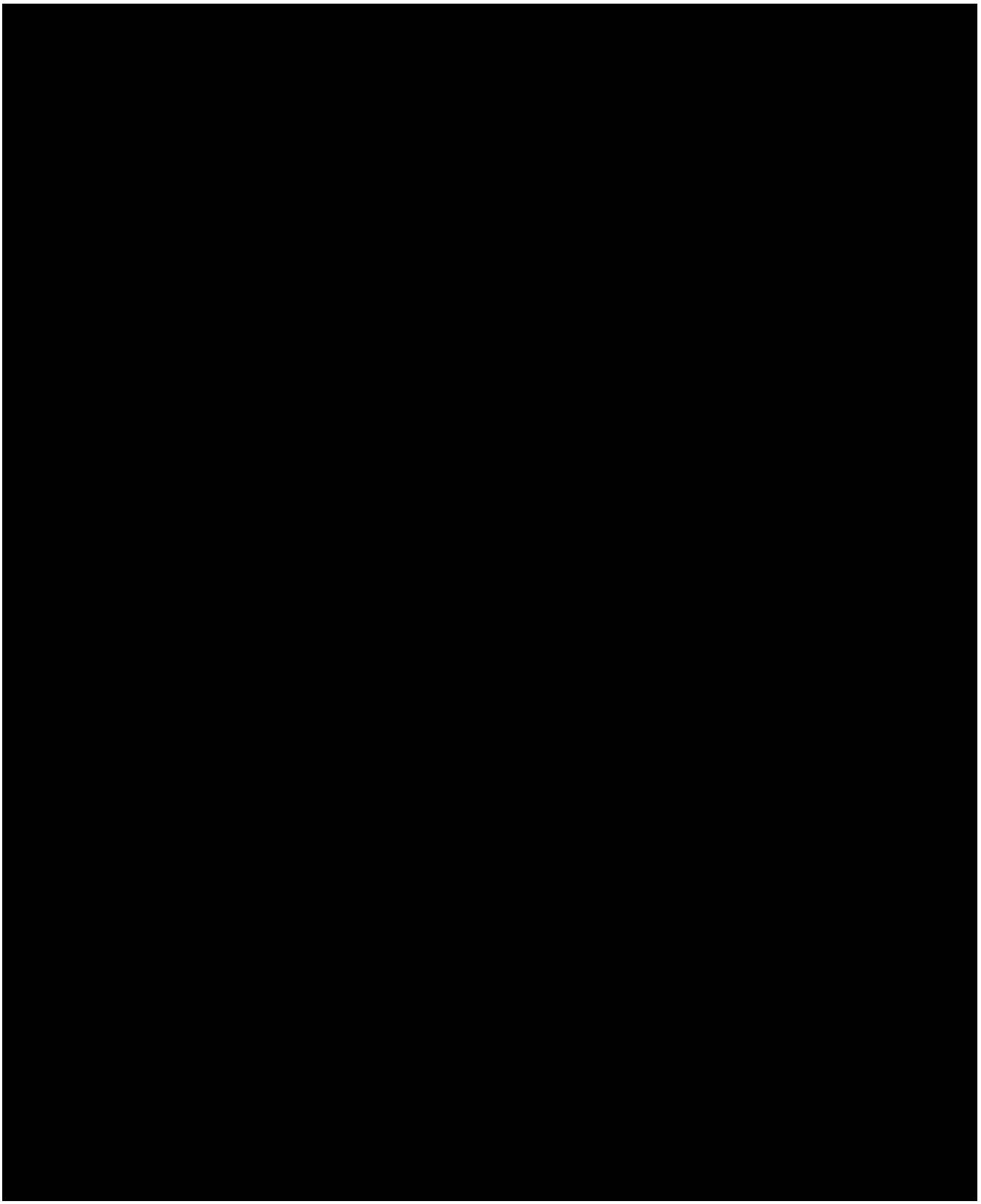
Not applicable.

5.2.2 Secondary endpoints

Secondary endpoints are PK endpoints of BI 1595043, as defined in Section 2.1.3 of the **CTP**:

After the last dose:

- *$AUC_{0-\tau,ss}$ (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)*
- *$C_{min,ss}$ (minimum measured concentration of the analyte in plasma at steady state over a uniform dosing interval τ)*
- *$R_{A,\ Cmax}$ (accumulation ratio based on $C_{max,ss}$)*
- *$R_{A,\ AUC}$ (accumulation ratio based on $AUC_{0-\tau,ss}$)*



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.

Subjects will receive tablets containing

- either 15 mg q.d, 30 mg q.d., 60 mg q.d., 120 mg q.d. or 60 mg b.i.d. of BI 1595043 (test treatments)
  or
- a matching placebo (reference treatment)

Patients of dose group 1-4 (15 mg q.d, 30 mg q.d., 60 mg q.d., 120 mg q.d.) receive treatment for 18 days, including a single dose segment on Day 1 with a washout over 4 days, and a multiple dose segment over 14 days (Days 5-18).

Patients of dose group 5 (60 mg b.i.d.) receive treatment as a multiple dose segment over 14 days, including a twice daily regimen on Days 1-13 and morning dose only on Day 14.

Additionally all patients of dose group 3-4 (60 mg q.d. and 120 mg q.d.) will receive 75 µg q.d. Midazolam for injection used as oral solution at Day -1, Day 1 and Day 18.

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 Analysis phases for statistical analysis of AEs, and actual treatment for analysis of laboratory data, vital signs and ECG

Study analysis phase	Label	Start	End
Screening[1]	**Screening**	Date of informed consent	Date/time of first administration of study drug
On treatment	**Placebo, 15 mg BI q.d., 30 mg BI q.d., 60 mg BI q.d.+Mid, 120 mg BI q.d.+Mid** or **60 mg BI b.i.d.** respectively	Date/time of first administration of study drug	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.

AE summary tables will present results for the on-treatment phase only. All AEs will be listed.

In AE tables in CTR Section 15.3 (but not in Appendix 16.1.13.1.8.1 and Appendix 16.1.13.1.8.2 AE tables), the following total will be provided in addition:

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

Safety laboratory data, ECG, vital signs and PK parameters will be analysed based on treatment groups (Placebo, 15 mg BI q.d., 30 mg BI q.d., 60 mg BI q.d., 120 mg BI q.d. or 60 mg BI b.i.d.) 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.

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) 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 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.

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 7.3.

In addition, the following subject sets 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.

For biomarker analyses the pharmacodynamic parameter set (PDS) will be used, which is defined as following:

- This set includes all subjects in the treated set (TS) who provide at least one biomarker endpoint that was not excluded due to a protocol violation relevant to the evaluation of biomarker or due to biomarker non-evaluability. Thus, a subject will be included in the PDS, even if he/she contributes only one biomarker parameter value to the statistical assessment.

Table 6.3: 1 Subject sets analyzed

	Subject set			
Class of endpoint	TS	PKS	PDS	ECGPCS
Disposition	X			
IPDs	X			
Primary endpoint	X			
Secondary PK endpoints		X		
Further PK endpoints		X		
Further exploratory biomarker endpoints			X	
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			

[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 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).

If single cardiac cycles of an ECG are missing, the arithmetic mean for this single ECG will be computed with the reduced (1, 2 or 3) number of cardiac cycles. If replicate ECG recordings are missing, the arithmetic means per time point will be computed with the reduced number (1 or 2) of recordings.

For the classification of the on-treatment QTc/QT intervals into 'no new onset' / 'new onset' categories, the handling of missing value is described in Section 10.3.

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.

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

CTP: "*Pharmacokinetic 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

In all analyses (except for analyses of ECG variables), baseline is defined as the last available value prior to first administration of study drug.

A centralised evaluation of 12-lead ECG recordings is performed at the time points specified in Table 6.7: 1 and Table 6.7: 2.

Table 6.7: 1 Time schedule of 12-lead ECG recordings with centralised evaluation for dose groups 1-4

Visit	Day	Planned time [hh:mm] - relative to first study drug admin.	Study phase
2	1	-1:00	Baseline
		01:00	On-treatment
		02:00	
		12:00	
	2	24:00	
	5	95:45	
		97:00[1]	
	6	119:45	
		121:00[1]	
	7	143:45	
	7	145:00[1]	
	9	191:45	
		193:00[1]	
	11	239:45[1]	
		241:00[1]	
	13	287:45[1]	
		289:00[1]	
	15	335:45	
		337:00[1]	
	17	383:45[1]	
		385:00[1]	
	18	407:45	
		409:00	
		410:00	
		412:00	
		416:00	
		420:00	
	19	432:00	
	20	455:45[1]	

[1] According to CTP flow chart, there is no time-matched PK sample for several ECG measurements, i.e. measurements at planned time 97:00, 121:00, 145:00, 193:00, 239:45, 241:00, 287:45, 289:00, 337:00, 383:45, 385:00 and 455:45. This ECG measurement will not be used in the exposure-response model, which will be applied to time matched pairs of ECG measurements and PK samples.

Table 6.7: 2 Time schedule of 12-lead ECG recordings with centralised evaluation for dose group 5

Visit	Day	Planned time [hh:mm] - relative to first study drug admin.	Study phase
2	1	-1:00	Baseline
		01:00	On-treatment
		02:00	
		13:00[1]	
	2	23:45	
		25:00[1]	
		37:00[1]	
	3	47:45	
		49:00[1]	
		61:00[1]	
	5	95:45	
		97:00[1]	
		109:00[1]	
	7	143:45[1]	
		145:00[1]	
		157:00[1]	
	9	191:45[1]	
		193:00[1]	
		205:00[1]	
	11	239:45	
		241:00[1]	
		253:00[1]	
	13	287:45[1]	
		289:00[1]	
		301:00[1]	
	14	311:45	
		313:00	
		314:00	
		316:00	
		320:00	
		324:00	
	15	336:00	
	16	359:45	

[1] According to CTP flow chart, there is no time-matched PK sample for several ECG measurements, i.e. measurements at planned time 13:00, 25:00, 37:00, 49:00, 61:00, 97:00, 109:00, 143:45, 145:00, 157:00, 191:45, 193:00, 205:00, 241:00, 253:00, 287:45, 289:00 and 301:00. This ECG measurement will not be used in the exposure-response model, which will be applied to time matched pairs of ECG measurements and PK samples.

Three triplicate ECGs will be recorded as the baseline before drug administration, but only the first ECG of each of the 3 baseline triplicate 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.

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.

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 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 or sequence 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. These will be based on the TS.

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.

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

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 analyzed 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 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.

7.5.2.1 Secondary endpoint analysis

The PK endpoints will be assessed descriptively.. The analysis of standard PK parameters is performed according to BI standards (4).

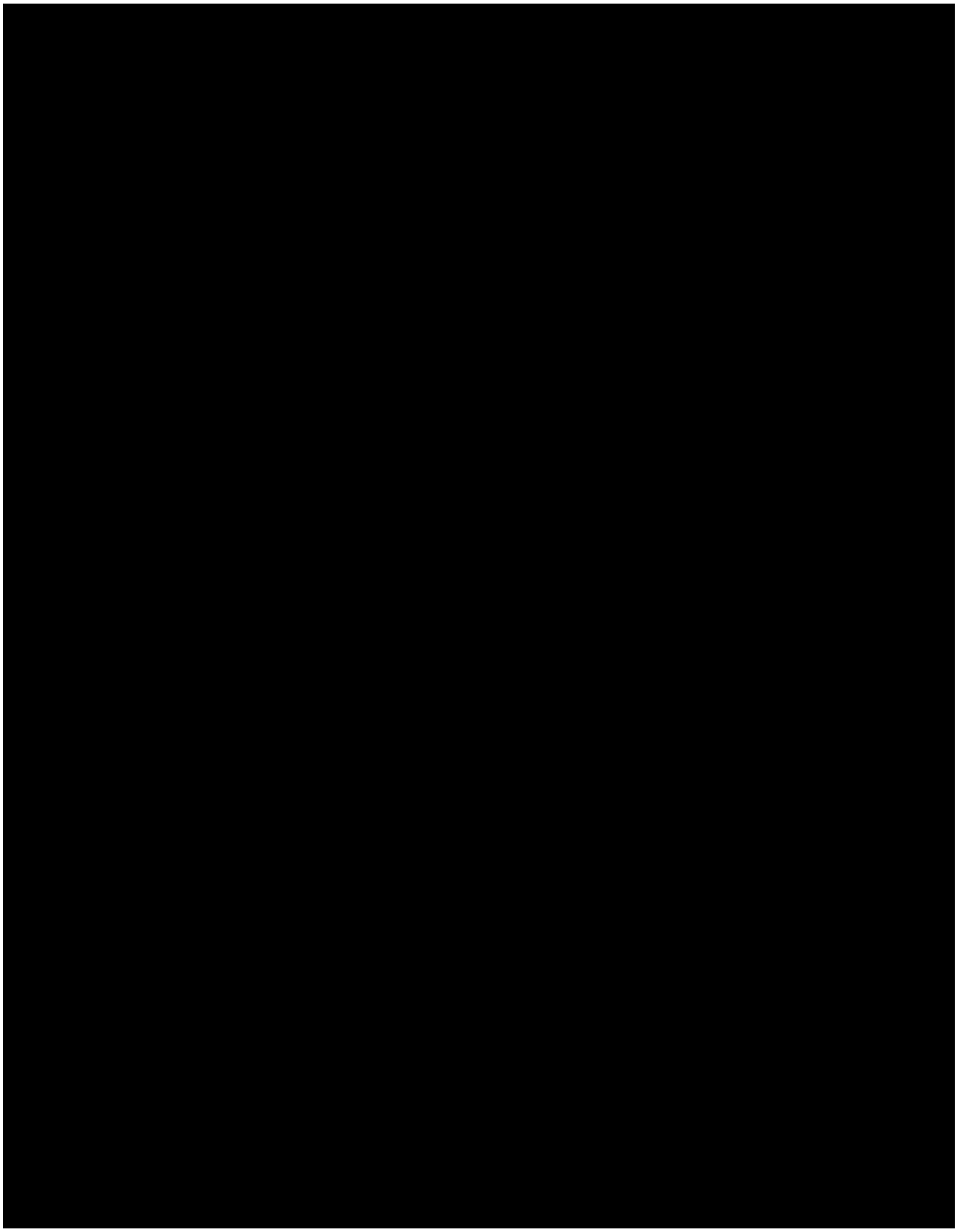
Exclusion of PK parameters

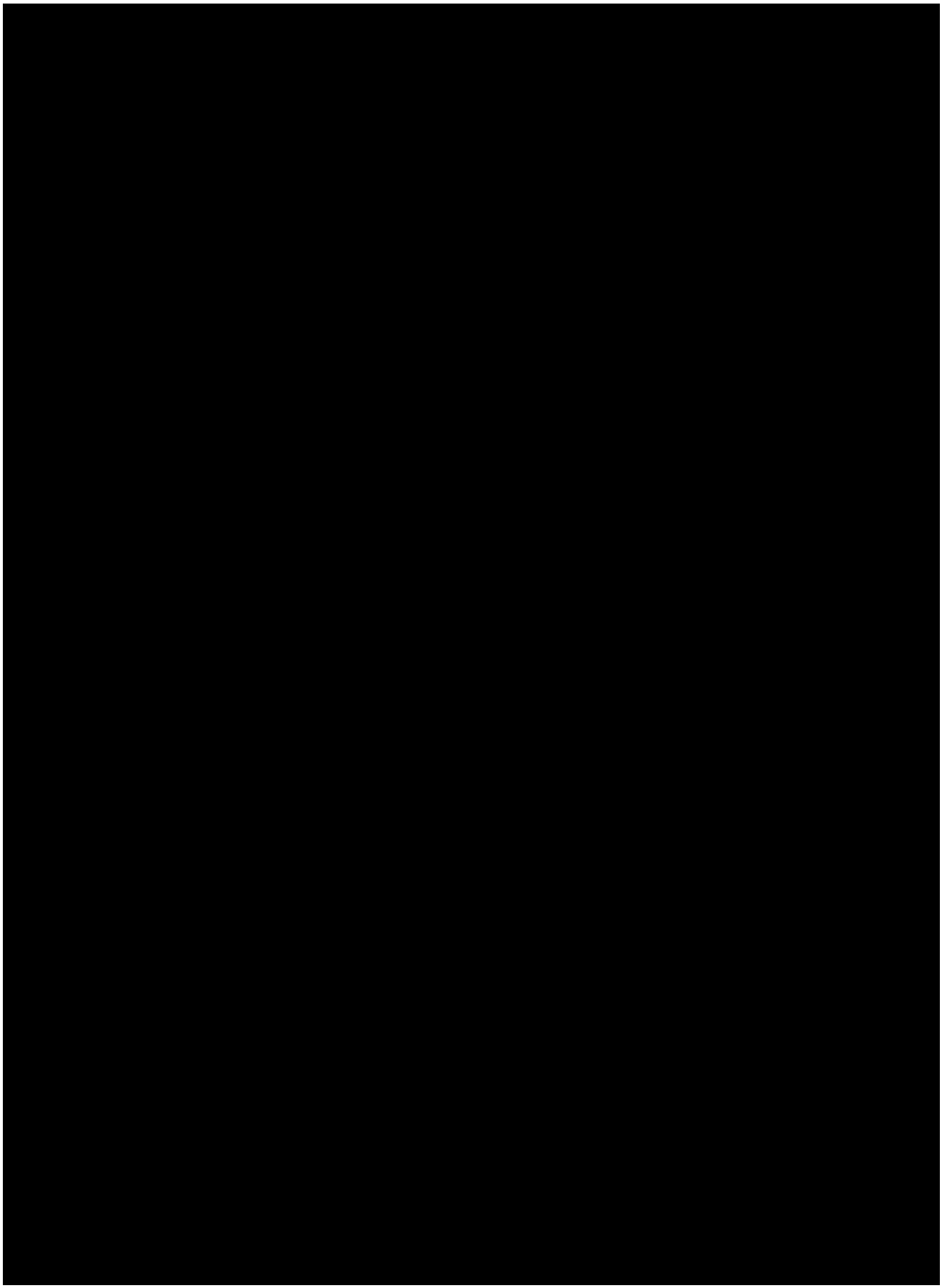
The ADS ADPP contains column variables APEXC and APEXCO indicating inclusion/exclusion (APEXC) of a PK parameter and an analysis flag comment (APEXCO). All analyses based on the PKS are based on PK parameter values which are not flagged for exclusion, i.e. with APEXC equal to "Included".

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

Exclusion of plasma 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).





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 or on-treatment phase 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: *Hepatic injury is considered an AESI in this trial. 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).

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. 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.

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 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 analyzed as such.

Urinary creatinine (from spot samples) was measured as part of routine safety lab, but will not be analysed or listed. This is a technical parameter and is not useful for safety evaluation.

7.8.3 Vital signs

The analyses of vital signs (blood pressure, pulse rate, oral 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 as follows:

- Unscheduled measurements prior to the first scheduled measurement within a visit will be assigned to the planned time point of the first scheduled measurement of that visit.
- Other unscheduled measurements will be assigned to the planned time point of the previous, most recent scheduled measurement.

Unscheduled measurements of vital signs will be used in calculation of descriptive statistics by planned time point as follows:

- If an unscheduled measurement is the last available off-treatment value before study drug administration, this unscheduled measurement will be used in the statistical analysis as baseline (as this is in accordance with the definition of baseline, cf. Section 6.7).
- At post-baseline time points, descriptive statistics by planned time point will be calculated based on the last value of the subject within 20 minutes of the scheduled measurement of that planned time point. The rationale for this rule is that these measurements are interpreted to be repeat measurements of the scheduled measurement (e.g. for confirmation of a particular value).

  An unscheduled measurement more than 20 minutes after the time of the scheduled measurement of that planned time point will be listed, but will not be used in calculation of descriptive statistics. These measurements are interpreted as off-schedule vital signs measurements, taken for other reasons.

If an unscheduled measurement is taken at exactly the same time as the scheduled measurement, this unscheduled measurement will be considered to be done after the scheduled measurement, and will potentially qualify to be the "last value of the subject within 20 minutes of the scheduled measurement of that planned time point".

If the time of measurement is missing for a scheduled 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 measurement, this measurement will be listed but will be ignored for the calculation of descriptive statistics.

If a scheduled measurement is "not done", and the unscheduled measurement is within 20 minutes of the "not done" assessment, the unscheduled will be used in calculation of descriptive statistics at the respective 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.

7.8.4 ECG

Abnormal findings 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.

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.

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.

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.

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 1595043 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 1595043 and placebo and its 90% confidence interval at the geometric mean of C_{max} (after single dose) and of $C_{max,ss}$ 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 Section 10.4.

For visualization, a scatterplot of the BI 1595043 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 for the exposure-reponse 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 Section 10.2 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

7.8.5.1 Physical examination

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.

7.8.5.2 Body weight

Body weight will only be listed.

7.8.5.3 Ophthalmological examination

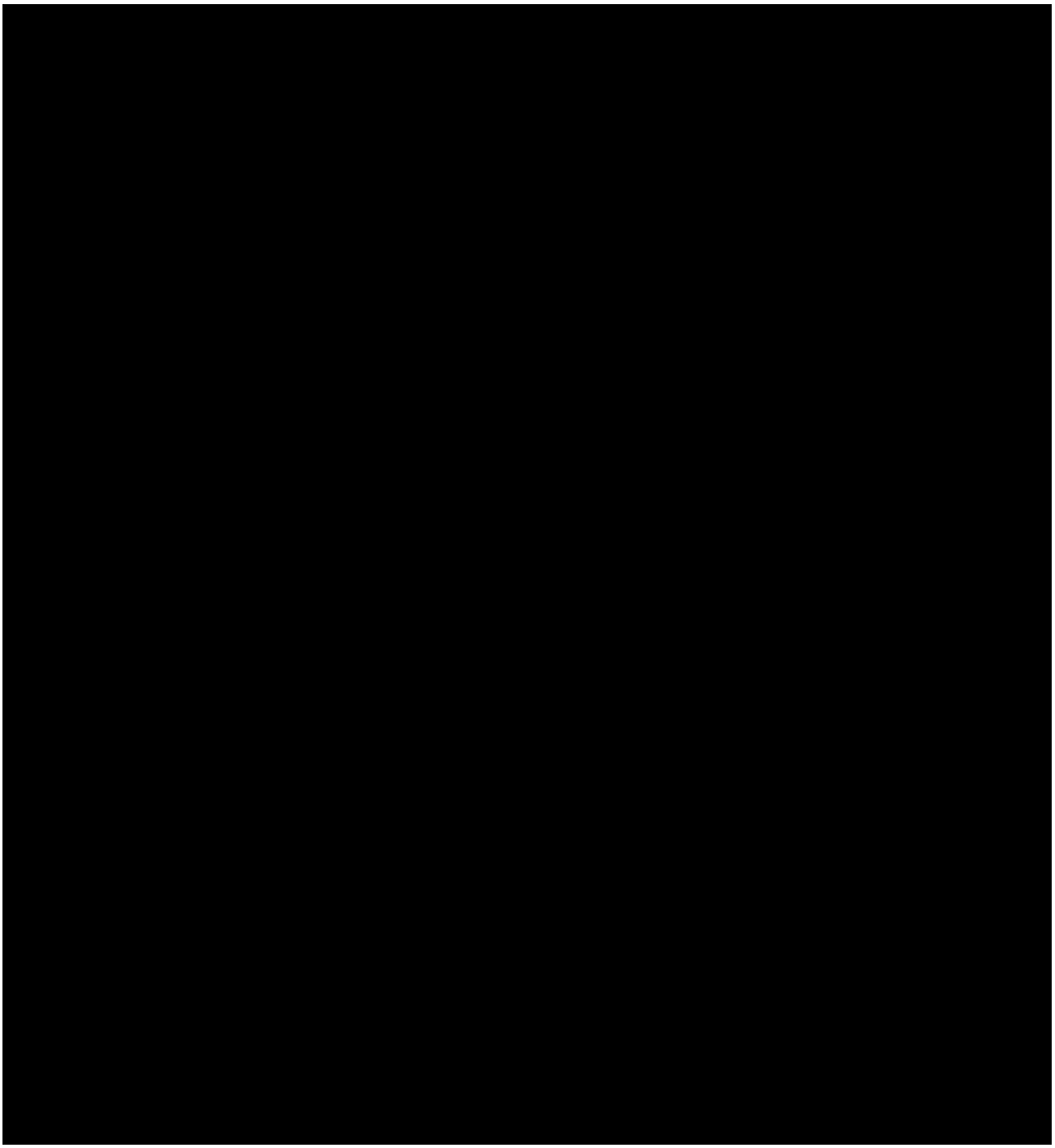
A slit lamp examination will be conducted by an ophthalmologist at Screening and EoT. Abnormal findings will be recorded as AEs if judged clinically relevant by the Investigator. No separate listing or analysis of ophthalmological examination will be prepared.

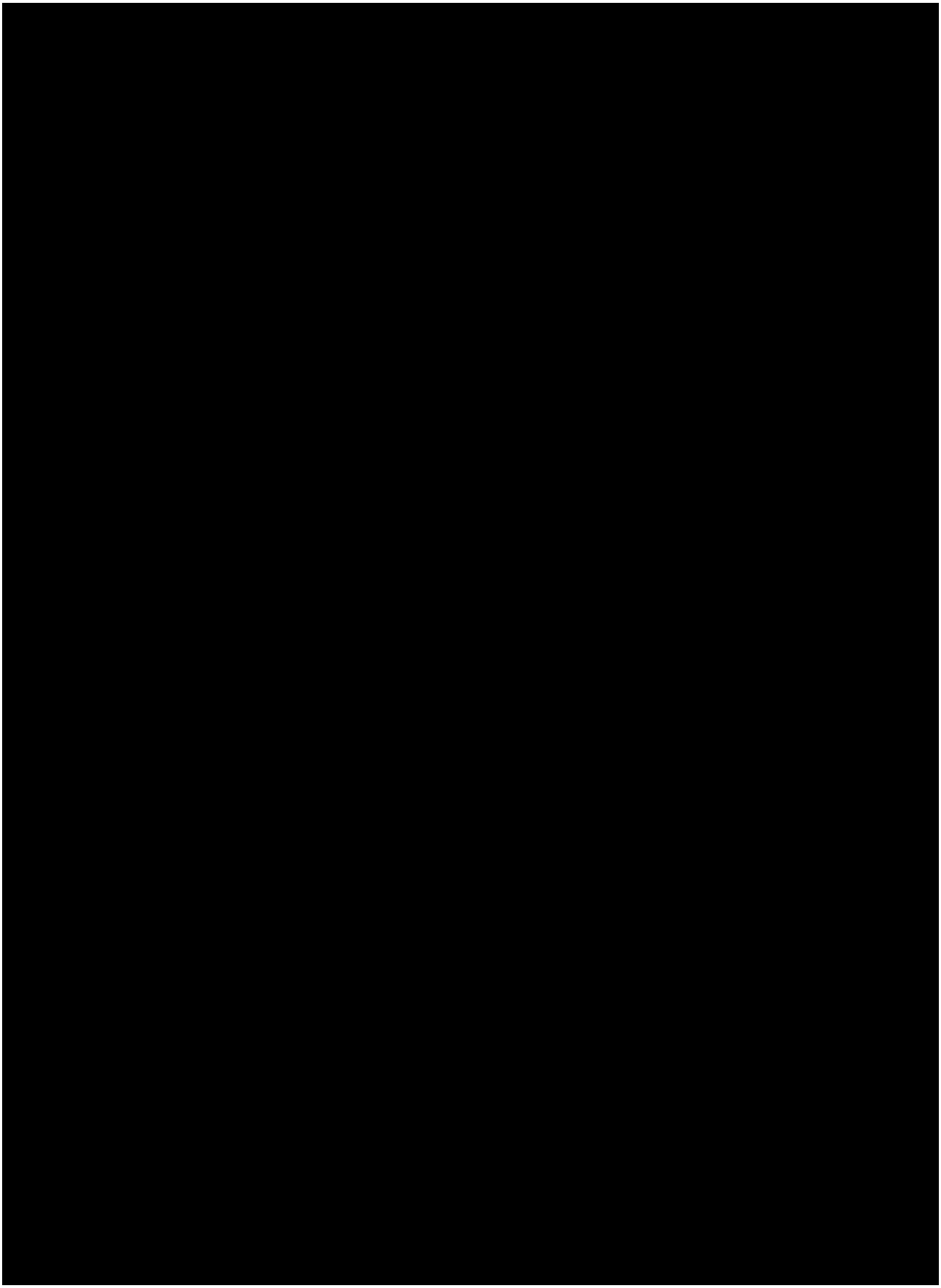
8. TIMEPOINT OF RELEASE OF TREATMENT INFORMATION

The treatment information in each dose group will be released based on a treatment-information-request when all subjects of the respective dose group have been randomized.

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
2	*BI-VQD-12045_40-413:* "Identify and Manage Important Protocol Deviations (iPD)", current version; KMED
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-TCMP-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:* "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:* "Handling, 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





11. HISTORY TABLE

Table 11: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
Final	**10-MAR-2022**	[redacted]	None	This is the final TSAP