TRIAL STATISTICAL ANALYSIS PLAN

c38514028-01

BI Trial No.:	1466-0001
Title:	Safety, tolerability, pharmacokinetics and pharmacodynamics of single rising subcutaneous doses of BI 3006337 in healthy male subjects (single-blind, partially randomised within dose groups, placebo-controlled, parallel (sequential) group design) (Revised Protocol including amendments 1-9 [c31412745-10])
Investigational Product:	BI 3006337
Responsible trial statistician:	[redacted] Phone: [redacted] Fax: [redacted]
Date of statistical analysis plan:	25 APR 2023 SIGNED
Version:	1

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2. LIST OF ABBREVIATIONS

See Medicine Glossary:
http://glossary

Term	Definition / description
ADA	Anti-drug Antibody
ADS	Analysis data set
ALT	Alanine transaminase
AST	Aspartate transaminase
$AUC_{0-\infty}$	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
BMI	Body mass index
[redacted]	[redacted]
BW	Body Weight
CARE	Clinical data Analysis and Reporting Environment
CI	Confidence interval
C_{max}	Maximum measured concentration of the analyte in plasma
CTX-1	Carboxy-terminal collagen crosslinks
CV	Arithmetic coefficient of variation
DG	Dose group
[redacted]	[redacted]
EDMS	Electronic documentation management system
EOT	End of Trial
gCV	Geometric coefficient of variation
gMean	Geometric mean
HMW	High Molecular Weight
λ_z	Terminal rate constant of the analyte in plasma
LLOQ	Lower limit of quantification
LOQ	Limit of quantification

Term	Definition / description
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
N	Number of non-missing observations
Nobs	Number of observations
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
P10	10th percentile
P90	90th percentile
PKS	Pharmacokinetic parameter analysis set
PT	Preferred term
PVC	Premature ventricular complex
Q1	1st quartile
Q3	3rd quartile
RAGe	Report Appendix Generator system
REP	Residual effect period
RPM	Report planning meeting
SCR	Screening
SD	Standard deviation
SOC	System organ class
SRD	Single rising dose
SV	Supraventricular
TMF	Trial master file
TS	Treated set
ULN	Upper limit of normal
ULOQ	Upper limit of quantification
WHO-DD	World Health Organization Drug Dictionary

3. INTRODUCTION

As per ICH E9 (1) the purpose of this document is to provide a more technical and detailed elaboration of the principal features of the analysis described in the protocol, and to include detailed procedures for executing the statistical analysis of the primary and secondary variables and other data.

This Trial statistical analysis plan (TSAP) assumes familiarity with the Clinical Trial Protocol (CTP), including Protocol 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 CTP for more background information on the study, e.g., on study objectives, study design and population, treatments, definition of measurements and variables, planning of sample size, randomisation.

Study data (including data entered in the RAVE EDC system and external data provided by suppliers) will be stored in a Clinical Data Repository (CDR).

Pharmacokinetic (PK) parameters will be calculated using Phoenix WinNonlin™ software (version 8.1 or higher, [redacted]).

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).

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

All analyses as planned in the CTP will be performed and are described in more detail in this TSAP. The following changes will be made as compared to the CTP:

The definition of the Treated set was changed. Instead of including all randomised and treated subjects the Treated set will include (…) *all subjects who were entered and treated with any dose of BI 3006337 or placebo.*

5. ENDPOINTS

5.1 PRIMARY ENDPOINT

Section 2.1.2 of the CTP:

The primary endpoint for assessment of safety and tolerability of BI 3006337 is the percentage of subjects with drug-related AEs occurring between first administration of trial medication (BI 3006337 or placebo) and end of trial (EOT).

5.2 SECONDARY ENDPOINTS

5.2.1 Key secondary endpoint

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

5.2.2 Secondary endpoints

Section 2.1.3 of the CTP:

The following PK parameters of BI 3006337 will be determined if feasible:

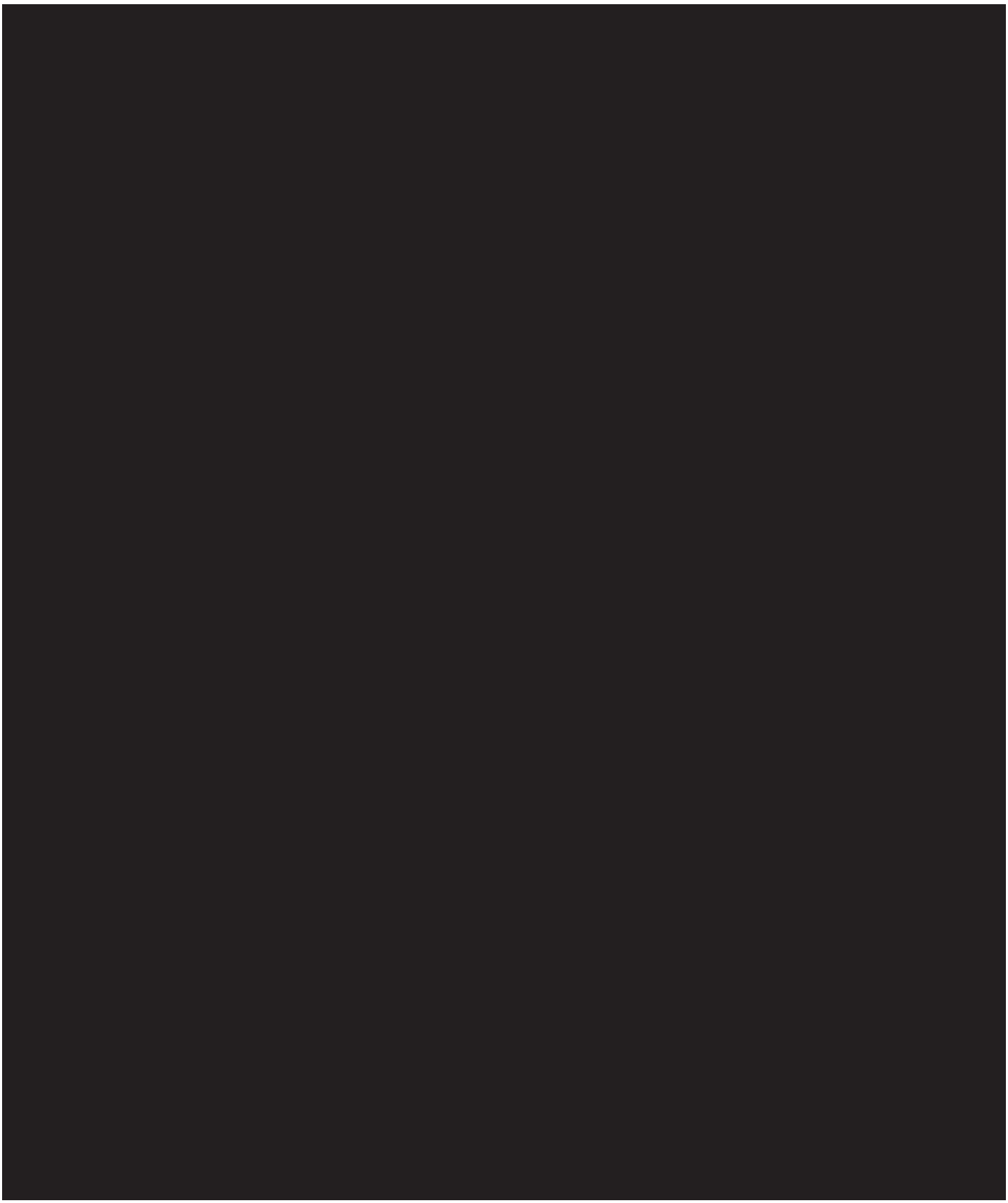
- *$AUC_{0-\infty}$ (area under the concentration-time curve of the analyte in serum over the time interval from 0 extrapolated to infinity)*
- *C_{max} (maximum measured concentration of the analyte in serum)*
- *t_{max} (time from dosing to the maximum measured concentration of the analyte in serum)*

5.3 FURTHER ENDPOINTS

Safety and tolerability endpoints

Section 2.2.2.1 of the CTP:
Safety and tolerability of BI 3006337 will be assessed during the on-treatment period, i.e. occurring between first administration of trial medication (BI 3006337 or placebo) and EOT based on:

- *AEs (including clinically relevant findings from the physical examination)*
- *Safety laboratory tests*
- *12-lead ECG*
- *Continuous (24 h) ECG monitoring*
- *Vital signs (Temperature, BP, pulse rate (PR))*



12-lead ECG endpoints:

For the definition of baseline and a summary of time points scheduled for ECG recording and central evaluation please refer to Section 6.7.1.

Quantitative ECG endpoints

The following quantitative ECG endpoints will be determined for the ECG variables QTcF, HR, QT, PR, QRS, RR and QTcB, derived as described in additional Section 10.1:

- absolute values (per time point)
- changes from baseline (per time point)
- percent changes from baseline (per time point; for HR, PR, QRS)

Categorical ECG endpoints:

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

- New onset (meaning that this or a higher category was not present any time 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: 1) will be considered.
- Maximum change from baseline of QT ≤ 60 msec, or > 60 msec on treatment
- Maximum change from baseline of QTcF ≤ 30 msec, > 30 to ≤ 60 msec, or > 60 msec on treatment

The occurrence of any of the following will be considered as ‘notable findings’:

- New onset (not present any time at baseline) of uncorrected QT interval > 500 msec at any time on treatment
- New onset of QTcF interval > 500 msec at any time on treatment
- Change from baseline of QTcF > 60 msec at any time on treatment
- Percent change from baseline of HR ≥ 25%, when corresponding on treatment value of HR is > 100 beats/min, or percent change from baseline of HR ≤ - 25%, when corresponding on treatment value of HR is < 50 beats/min, at any time on treatment
- Percent change from baseline of PR ≥ 25%, when corresponding on treatment value of PR interval is > 200 msec, at any time on treatment
- Percent change from baseline of QRS ≥ 10%, when corresponding on treatment value of QRS duration is > 110 msec, at any time on treatment

For a detailed description of ‘new onset’, refer to additional Section 10.1.3.

5-lead Holter ECG endpoints

Quantitative Holter ECG endpoints are:

- Quantitative endpoints based on post-dose Holter ECGs will be assessed hourly between 0 and 70 h after administration of study drug, as well as for the overall time intervals given in Table 6.7.2: 1.

  These quantitative endpoints comprise mean, minimum and maximum HR, change from baseline in mean HR as well as time to maximum HR and time to minimum HR for the time intervals presented in Table 6.7.2: 1. Furthermore, HR and onset time (relative to drug administration) of the fastest ventricular run as well as the number of beats and onset time of the longest ventricular run will be analyzed for the overall time intervals given in Table 6.7.2: 1.

Further categorical Holter ECG endpoints:

- Findings based on 70h post-dose Holter ECG

  General remarks: Evaluations with regard to the occurrence of arrhythmia events will be performed hourly as well as for specific overall time periods (see Table 6.7.2: 1) by the central ECG lab. Furthermore, an average per hour will be calculated as the number of events observed in a time interval divided by the duration [h] of the analyzed time during that time period.

  In the following, the term "ventricular events" comprises the following findings: single ventricular escape beats, single ventricular premature extrasystoles, ventricular bigeminy, couplets, triplets, runs, and tachycardias, and the "R on T" phenomenon.

  "Single ventricular events (total)" corresponds to the sum of single ventricular escape beats and single ventricular premature extrasystoles.

  "Supraventricular events" comprises supraventricular extrasystoles and supraventricular tachycardias.

  "Other arrhythmias" includes the findings delayed normal beats, bradycardia episodes, pauses (long RR), and artifacts.

  For further details see Section 10.2.

  The following endpoints will be considered:

  - Overall Holter interpretation (normal/ abnormal clinically not relevant/ abnormal clinically relevant /not evaluable).
  - Number of subjects with ventricular events per finding; hourly and overall
  - Number of beats in the longest ventricular run; overall
  - Absolute number and change from baseline of ventricular events per finding; hourly, overall and average per hour.

- Number of single ventricular events (total); average per hour observed during 0 - 70 h post dosing, using the following categories: No events, 1 to <10, 10 to <30, 30 to <50, 50 to <100, 100 to <500, 500 to <1000, 1000 to <2000, >=2000
- Number of subjects with supraventricular events per finding; hourly and overall
- Absolute number and change from baseline of supraventricular events per finding; hourly, overall and average per hour
- Number of supraventricular extrasystoles; average per hour observed during 0 - 70 h post dosing, using the following categories: No events, 1 to <10, 10 to <30, 30 to <50, 50 to <100, 100 to <500, 500 to <1000, 1000 to <2000, >=2000
- Number of subjects with other arrhythmia events per finding; hourly and overall
- Absolute number and change from baseline of other arrhythmias per finding; hourly, overall and average per hour

6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENTS

For basic study information on treatments to be administered, assignment of treatment groups and selection of doses, please see CTP, Sections 3 and 4.

This single-rising dose (SRD) trial with 11 dose groups (DGs) is designed as a single-blind parallel group trial which is placebo-controlled and partially randomised within sequential dose groups. A total of 92 subjects will be included. For DG 1 to 10, each DG consists of 8 subjects: 6 subjects will receive BI and 2 will receive placebo. The treatments will be allocated in a pre-defined fixed order for the first four subjects (cohort 1 and 2 of each DG) and will be randomised for the latter four subjects (cohort 3 of each DG). In DG 11, a total of 12 subjects will be randomized: 9 subjects will receive BI and 3 will receive placebo.

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

Table 6.1: 1 Treatments and labels used in the analysis

Dose group	Treatment		Short label
	P*	Placebo solution, sc, qd	Placebo
DG1	K	BI 3006337, solution 0.2mg, sc, once	BI 0.2mg
DG2	A	BI 3006337, solution 0.5mg, sc, once	BI 0.5mg
DG3	B	BI 3006337, solution 1mg, sc, once	BI 1mg
DG4	C	BI 3006337, solution 2mg, sc, once	BI 2mg
DG5	D	BI 3006337, solution 4mg, sc, once	BI 4mg
DG6	E	BI 3006337, solution 8mg, sc, once	BI 8mg
DG7	F	BI 3006337, solution 15mg, sc, once	BI 15mg
DG8	G	BI 3006337, solution 30mg, sc, once	BI 30mg
DG9	H	BI 3006337, solution 50mg, sc, once	BI 50mg
DG10	I	BI 3006337, solution 100mg, sc, once	BI 100mg
DG11	L	BI 3006337, solution 150mg, sc, once	BI 150mg

* For data analysis purposes, the placebo control group will include all subjects of all DGs treated with placebo.

Section 1.2.6 of the CTP:

The Residual Effect Period (REP) of BI 3006337 in humans is not known to date. This is the period after the last dose with measurable drug levels [redacted] *still likely to be*

present. Based on the PK half-life of about [redacted] days for the GLP-1 component and 6 days for the FGF21 component, it could be determined with about 30 days.

Based on this and with a planned end-of-trial visit on Day 32-40, the following study phases will be defined for the analysis of adverse events (AEs):

- **Screening** (ranging from 0:00 h on day of informed consent until first administration of study medication (BI/Placebo))
- **On treatment** (ranging from the first time of administration of BI or Placebo until 0:00h on the day after trial termination date)

Section 7.3.4 of the CTP: *Note that AEs occurring after the last per protocol contact but entered before database lock will be reported to Pharmacovigilance only and will not be captured in the trial database.*

The following AE displays will be provided in the report:

In Section 15.3 and Appendix 16.1.13.1.8 (for ClinicalTrials.gov and EudraCT) of the CTR displays, the on treatment phase will be analysed (labelled with the short label of the study treatment). The screening phase will not be included in this analysis. In Section 15.3, a total over all on treatment phases with BI **("BI Total"**) will be provided.

In Section 15.4 and Appendix 16.2 (Listings) of the CTR displays, the screening period will additionally be included and no totals will be provided.

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

6.2 IMPORTANT PROTOCOL DEVIATIONS

Data discrepancies and deviations from the CTP will be identified for all treated subjects. Consistency check listings (for identification of deviations of time windows) and a list of protocol deviations (e.g. deviations in drug administration, in blood sampling times, etc.) will be provided to be discussed at the Report Planning Meeting (RPM). At this meeting, all manual deviations identified at the sites by the CRAs and deviations too complex to program will be reviewed by the trial team to decide which are considered important. For definition of important protocol deviations (iPD), and for the process of identification of these, refer to the Boehringer Ingelheim (BI) SOP "Identify and Manage Important Protocol Deviations (iPD)" (2).

Section 7.3 of the CTP: *IPD categories will be specified in the Domain DV. IPDs will be identified no later than in the RPM and the iPD categories will be updated as needed.*

If any iPDs are identified, they are to be summarised into categories and will be captured in the iPD specification file (DV domain) and in the decision log. The iPD specification file will be stored within the TMF in EDMS.

The iPDs will be summarized and listed in the CTR.

6.3 SUBJECT SETS ANALYSED

Section 7.3 of the CTP:

- ***Enrolled set (ES):*** *This subject set includes all subjects having signed informed consent, who were screened for inclusion into the study. The ES will be used for analyses of subject disposition.*

- ***Treated set (TS)****: The TS includes all subjects who were* entered *and treated with any dose of BI 3006337 or placebo. The TS will be used for safety analyses.*

- ***PK parameter analysis set (PKS)****: This set includes all subjects in the TS who provide at least one PK endpoint that was not excluded due to a protocol violation relevant to the evaluation of PK or due to PK non-evaluability (as specified in the following subsection 'PKs'). Thus, a subject will be included in the PKS, even if he contributes only one PK parameter value to the statistical assessment. Descriptive and model based analyses of PK parameters will be based on the PKS.*

[redacted]

[redacted]

The PKS will only include subjects who received at least one dose of the test product BI 3006337, placebo subjects will not be included.

Section 7.3 of the CTP:

Pharmacokinetics

The pharmacokinetic parameters listed in CTP *Section 2.1 for drug BI 3006337 will be calculated according to the relevant SOP of the sponsor (001-MCS-36-472).*

Serum concentration data and parameters of a subject will be included in the statistical PK analyses if they are not flagged for exclusion due to a protocol violation relevant to the evaluation of PK (to be decided no later than in the RPM) or due to PK non-evaluability (as revealed during data analysis, based on the criteria specified below). Exclusion of a subject's data will be documented in the CTR.
Relevant protocol deviations may be

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

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

- *Missing samples/concentration data at important phases of PK disposition curve.*

Serum 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.

Only concentration values within the validated concentration range and actual sampling times will be used for the calculation of PK parameters for BI 3006337. Concentrations used in the PK calculations will be in the same format as in the bioanalytical report (that is to the same number of decimal places provided in the bioanalytical report).

[redacted]

Table 6.3: 1 Subject sets analysed

	Analysis set				
Class of endpoint	ES	TS	PKS	[redacted]	[redacted]
Primary endpoint and further safety assessments (incl. Holter and central ECG)		X			
Analyses of PK endpoints			X		
[redacted]					
[redacted]					
Disposition	X				
Demographic/baseline parameters		X			
Important protocol deviations		X			
Exposure		X			

[redacted]

6.5 POOLING OF CENTRES

This section is not applicable, because the study was performed in only two centres.

6.6 HANDLING OF MISSING DATA AND OUTLIERS

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

Missing or incomplete AE dates are imputed according to BI standards (see BI-KMED-BDS-HTG-0035) (3).

Missing data and outliers of PK data are handled according to BI standards (see BI-KMED-TMCP-MAN-0012 (4) and BI-KMED-TMCP-MAN-0014 (5).

12-lead ECG and ECG-PK analysis

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

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

For the classification of the on treatment QTc/QT intervals into “no new onset” / “new onset” categories, the handling of missing value is described in Additional Section 10.1.3.

For subjects on active drug (e.g. post dose time points), missing plasma concentration values with 'BLQ' in the comment field will be replaced by ½ LLOQ for the exposure-response analysis. For placebo subjects, the missing plasma concentration values will be replaced by 0 for the exposure-response analyses.

5-lead Holter ECG

In case of a missing Holter recording at baseline, the data derived from the Holter recording at screening will be used instead.

[redacted]

[redacted]

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

The baseline value is defined as the last measurement before administration of trial medication (BI 3006337 or Placebo).

Section 6.1 of the CTP:

Exact times of measurements outside the permitted time windows will be documented. The acceptable time windows for SCR and the EOT examination are provided in the CTP *Flow Chart.*

Study measurements and assessments scheduled to occur 'before' trial medication administration on Day 1 of Visit 2 are to be performed and completed within a 1 h- or 2 h- or 3h period, respectively, prior to the trial drug administration (including blank values for PK and PD/biomarkers).

The acceptable deviation from the scheduled time for vital signs, ECG and laboratory tests will be ± 30 min for the first 72 h after trial drug. For the 24 h Holter ECG the maximum deviation will be ± 60 min for the first 72 h after trial drug. Starting from 96 h post trial drug administration a deviation from the scheduled time for all the planned trial activities of ± 120 min is acceptable.

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

Unscheduled measurements of laboratory and vital signs 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.

6.7.1 Time windows of 12-lead ECG

There will be a centralised evaluation of the 12-lead ECG recordings at the time points and for the ECG recordings specified in the following table:

Table 6.7.1: 1 Time schedule of 12-lead ECG recordings

Visit	Day	Planned time [hh:mm] (relative to drug administration)	Study phase	Central evaluation
1	-24 to -5		Screening	NA
2	-1	-26:00	Randomization	NA
	1	-02:00	Baseline	First single ECG of each of the 3 triplicate baselines
		-01:45		
		-01:30		
		00:00	On treatment	First single ECG of the triplicate
		01:00		
		02:00		
		03:00		
		07:00		
		11:00		
		15:00		
	2	23:00		
		27:00		
		31:00		
		35:00		
		39:00		
	3	47:00		
	4	72:00		
	5	96:00		
	6	120:00		
	8	168:00		
	11	240:00		
	15	336:00		
3	32 to 40		End of trial examination	NA

At screening, randomization and end of trial examination, single ECGs will be recorded and will not be transferred to the central ECG lab. Three triplicate ECGs will be recorded as the baseline before drug administration, but only the first ECG of each of the 3 baseline triplicates will be transferred to the database. At all other time points, 1 triplicate ECG will be recorded, but only the first single ECG of the triplicate will be transferred to the database. The baseline value of an ECG variable is defined as the mean of the ECG variable values prior to drug administration.

For the exposure response analyses, pairs of ECG variables and corresponding serum concentrations will be built using the same planned time points, e.g., the HR change from baseline and the serum 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 and the pair has to be excluded from the analysis will be decided no later than at the RPM. Data exclusion due to time deviations will only be applied to subjects on active study treatment. The acceptable maximum time deviations between ECG recordings and serum concentration sampling are proposed to be

- 15 minutes for up to 48 hours (including) after dosing,
- 30 minutes for time points from more than 48 hours to 192hours after dosing, and
- 60 minutes for time points at 216 hours or later after dosing,

Pairs with time deviations exceeding those specified above will be excluded from exposure-response analyses. When the sampling time of the blood sample or the ECG recording is not available, the pair will also be excluded.

6.7.2 Time windows of 5-lead Holter ECG

The following Table 6.7.2: 1 summarizes the planned time intervals for Holter evaluations with regard to cardiac arrhythmia events. For screening as well as for all other time intervals with planned Holter ECG, hourly evaluations at each hour are planned.

Subject data from a time interval will only be used in summary tables if the analyzed time slots extended over 90% or more of the originally planned time interval (except for the table on descriptive statistics of the analyzed time slots, providing an overview of the duration of the actually analyzed Holters). For example, if a subject has an analyzed time slot of only 45 min (instead of 60 min, i.e. 75%) in the time interval >= 1:00 to 2:00, the data of this time interval will be excluded from the analyses.

At Visit 2 Day 1, only the 22 hours of the 24-hours ECG recorded after intake of trial medication will be used in the analysis of the overall time intervals, i.e. the first 2 hours of this recording (prior to trial medication) will not be included.

The overall baseline for Holter events is defined as the 24-hours Holter recording at Visit 2 Day -1. It serves as baseline for the subsequent 24-hours recordings post-dose at Visit 2 Day 2 and Visit 2 Day 3 and for the 22-hours post-dose recording (0:00 to 22:00) at Visit 2 Day 1. For the evaluation of the hourly time intervals, the baseline will be each hour of the 24-hours Holter recording at Visit 2 Day -1. It serves as time-matched baseline for all subsequent 24-hour recordings at Visit 2 Day 1, Visit 2 Day 2 and Visit 2 Day 3.

Table 6.7.2: 1 Time intervals of Holter evaluations, overall and hourly

		Overall evaluations		Hourly evaluations		
Study phase	**Visit Day [Vx Dx]**	**Planned time[1] [hh:mm]**	**Time interval**	**Planned time[1] [hh:mm]**	**Time interval**	
Screening	V1 D-24 to -5		min. 24 hours	Hourly evaluations at each hour		
Pre-dose	V2 D-1	-26:00	>= -26:00 to -2:00	-26:00	>= -26:00 to -25:00	Baseline
				-25:00	>= -25:00 to -24:00	
				(…)	(…)	
	V2 D1	-2:00	>= -2:00 to 0:00	-2:00	>= -2:00 to -1:00	24 hours Day 1
				-1:00	>= -1:00 to 0:00	
Post-dose / on treatment	V2 D1	0:00	>= 0:00 to 22:00	0:00	>= 0:00 to 1:00	
				1:00	>= 1:00 to 2:00	
				(…)	(…)	
	V2 D2	22:00	>= 22:00 to 46:00	22:00	>= 22:00 to 23:00	24 hours Day 2
				23:00	>= 23:00 to 24:00	
				(…)	(…)	
	V2 D3	46:00	>= 46:00 to 70:00	46:00	>= 46:00 to 47:00	24 hours Day 3
				(…)	(…)	
				69:00	>= 69:00 to 70:00	

1: Time relative to administration of study drug

7. PLANNED ANALYSIS

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

Statistical model-based analysis of PK [redacted] will be performed by [redacted] and will be presented in Section 15.5 of the CTR and Appendix 16.1.13.3 for PK endpoints and in Section 15.7 and Appendix 16.1.13.6 for [redacted].

Descriptive data analysis of PK [redacted] analysis will be performed by the [redacted]. The results will be presented in Section 15.6 of the CTR and Appendix 16.1.13.5 for PK endpoints, in Section 15.7 of the CTR and Appendix 16.1.13.6 [redacted].

The format of the listings and tables will follow the BI standards (see BI-KMED-BDS-HTG-0045 (6)) with the exception of those generated for PK-calculations following BI standards for PK/[redacted] (7).

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

No inferential statistical interim analysis is planned.

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

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

For analyte concentrations and PK parameters, the following descriptive statistics will additionally be calculated:

Nobs	number of observations
CV	arithmetic coefficient of variation
gMean	geometric mean
gCV	geometric coefficient of variation
P10	10th percentile
Q1	1st quartile
Q3	3rd quartile
P90	90th percentile

The data format for descriptive statistics of concentrations will be identical to the data format of the respective concentrations. The descriptive statistics of PK [redacted] 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 available in the CRF and will display the number of observations in a category, as well as the percentage (%). Percentages will be rounded to one decimal place and will be based on all subjects in the respective subject set whether they have non-missing values or not. The category 'missing' will be displayed only if there are actually missing values.

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

Exclusion of PK [redacted] parameters

The ADS "ADPP" (PK parameters) [redacted] contain column variables APEX and APEXCO indicating inclusion/exclusion (APEX) of a PK [redacted] parameter and an analysis flag comment (APEXCO). All analyses based on the PKS, [redacted] respectively, will include parameters only if they are not flagged for exclusion, that is APEX is equal to "Included".

Exclusion of PK [redacted] concentrations

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

Further details are given in *BI-KMED-TMCP-MAN-0014* "Noncompartmental Pharmacokinetic [redacted] Analyses of Clinical Studies" (5) and *BI-KMED-TMCP-MAN-0010*: "Description of Analytical Transfer Files and PK [redacted] Data Files" (8).

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Only descriptive statistics are planned for this section of the report, based on the TS.
The data will be summarised by treatment group and in total.

7.2 CONCOMITANT DISEASES AND MEDICATION

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

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

The diagnoses and medications will be listed. Subjects without any concomitant diagnoses or concomitant therapies will be marked with a "No" in the respective column.

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

7.3 TREATMENT COMPLIANCE

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

It is not intended to list the compliance separately. Any deviations from complete intake will be addressed in the RPM (cf. TSAP Section 6.2) and described in the CTR.

7.4 PRIMARY ENDPOINT

Refer to TSAP Section 7.8 for a description of the analysis of the primary endpoint.

7.5 SECONDARY ENDPOINTS

7.5.1 Key secondary endpoint

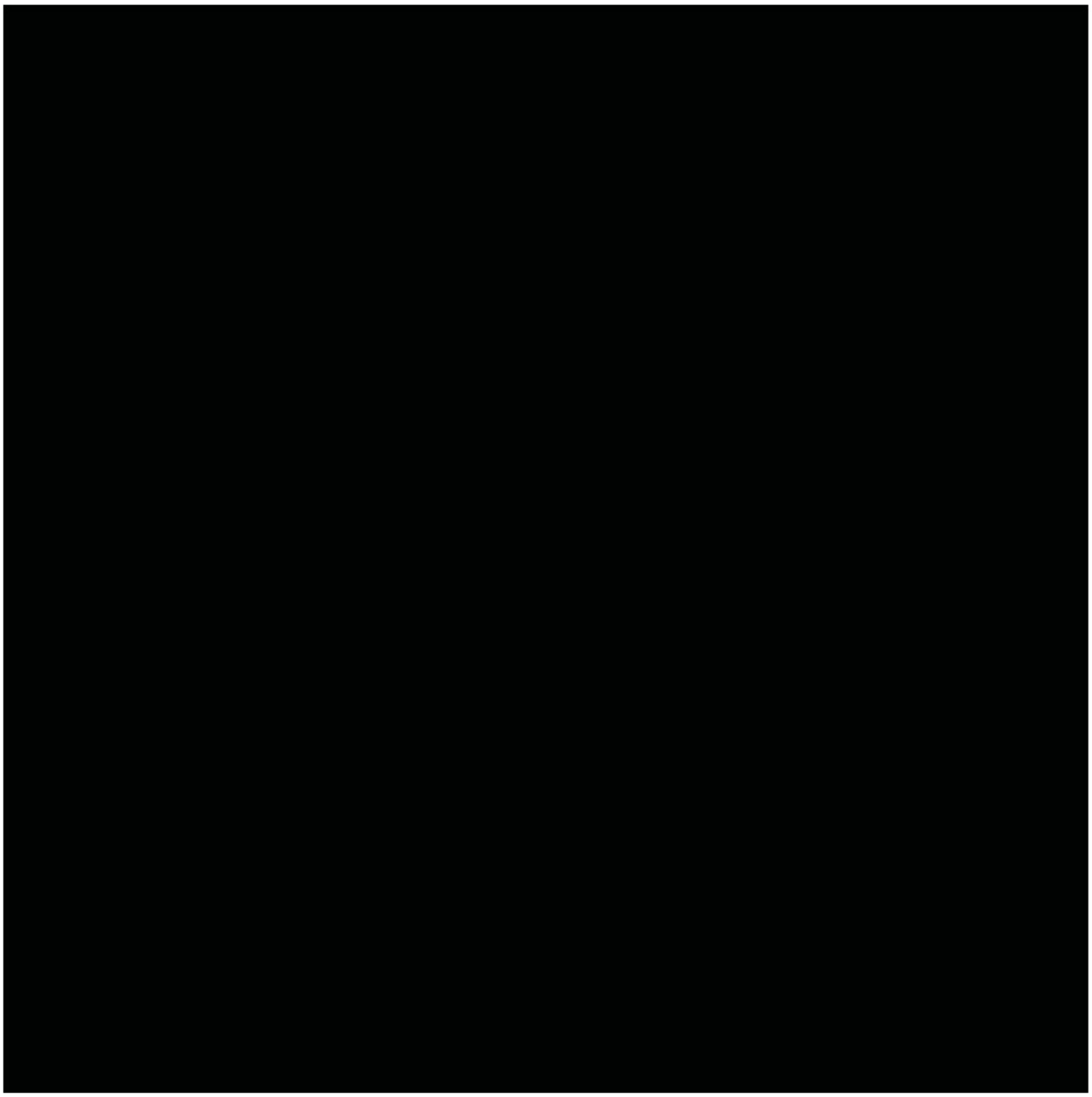
This section is not applicable as no key secondary endpoint has been specified in the protocol.

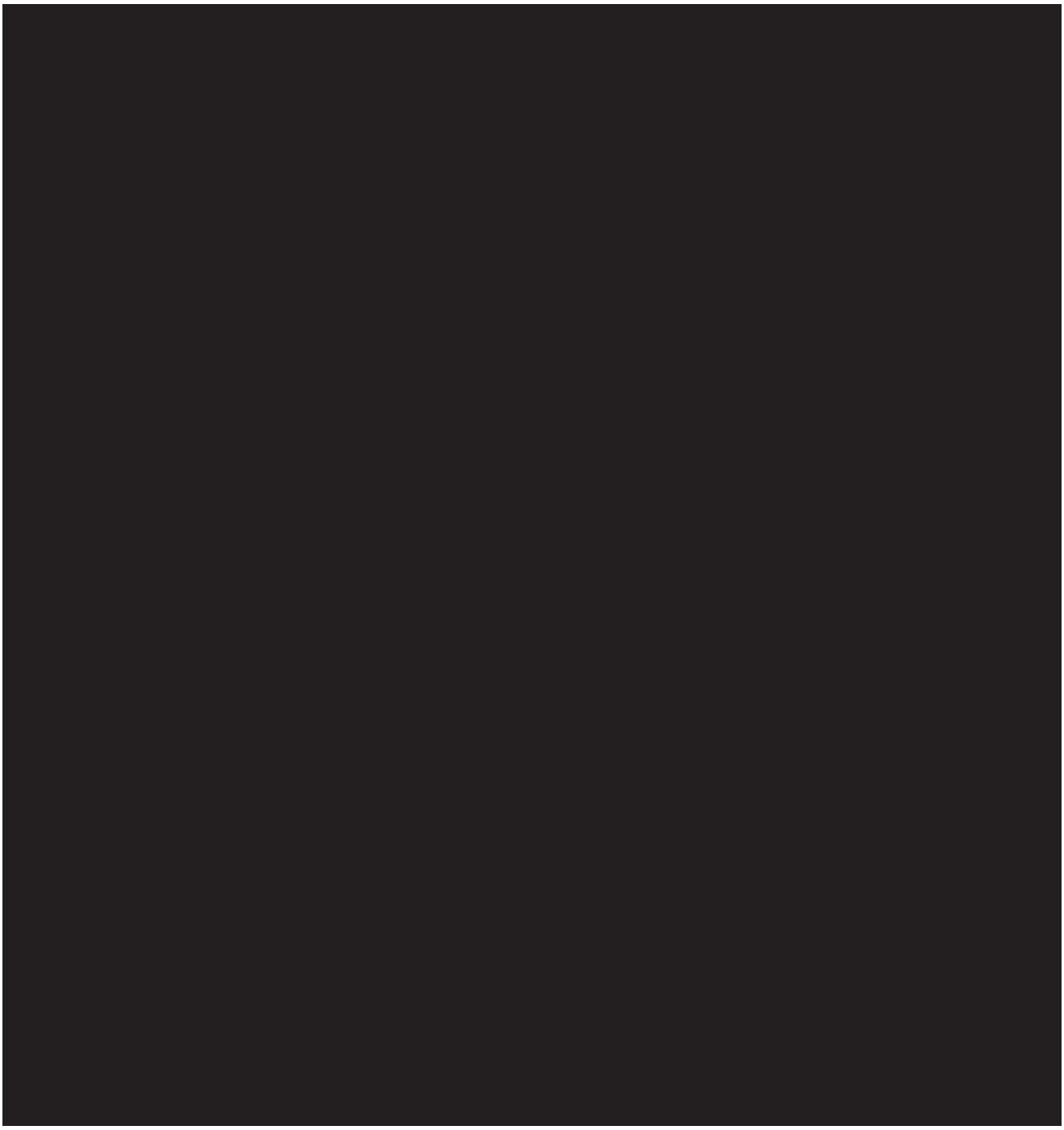
7.5.2 (Other) Secondary endpoints

Section 7.3.2 of the CTP:

Primary analyses

The secondary endpoints (refer to CTP *Section 2.1.3) will be analysed descriptively. Analyses will be performed for BI 3006337, separately for each DG.*





7.7 EXTENT OF EXPOSURE

Descriptive statistics are planned for this section of the report based on the TS. The date and time of drug administration will be listed for each subject.

7.8 SAFETY ANALYSIS

All safety analyses will be performed on the TS [redacted].

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

7.8.1 Adverse Events

AEs will be coded using MedDRA. The coding version number will be displayed as a footnote in the respective output.

Unless otherwise specified, 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. BI standards as presented in "Analysis and Presentation of Adverse Event Data from Clinical Trials – Display Template" [BI-KMED-BDS-HTG-0041] (9) and [BI-KMED-BDS-HTG-0066] (10) will be applied.

The analysis of AEs will be based on the concept of treatment emergent AEs. That means that all AEs will be assigned to 'screening' and 'on treatment' phases as defined in Section 6.1. AEs will be analysed based on actual treatments, as defined in Table 6.1: 1.

According to the clinical study protocol, adverse events of special interest (AESI) will be analysed:

Section 5.2.6.1.4 of the 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 T-BIL* (total bilirubin) ≥*2-fold ULN measured in the same blood sample, and/or*
  - *Aminotransferase (ALT and/or AST) elevations ≥10 fold ULN*

According to ICH E3 (11), in addition to Deaths and Serious Adverse Events, 'other significant' AEs need to be listed in the clinical trial report. These will be any non-serious adverse event that led to an action taken with study drug (e.g. discontinuation or dose reduced or interrupted).

An overall summary of AEs will be presented.

The frequency of subjects with AEs will be summarised by treatment, primary system organ class (SOC) and preferred term (PT).). Separate tables will be provided for subjects with serious AEs, for subjects with drug-related AEs, for subjects with drug-related serious adverse events and for subjects with AESIs. In addition, the frequency of subjects with AEs will be

summarised by treatment, worst intensity, primary system organ class (SOC) and preferred term (PT).

The system organ classes will be sorted alphabetically, PTs will be sorted by frequency (within SOC). The MedDRA version number will be displayed as a footnote in the respective output.
In addition, frequencies of subjects with non-serious AEs that had an incidence of > 5% for at least one treatment will be summarised by treatment, primary SOC and PT.

For disclosure of adverse events on EudraCT, additional information not included in a standard AE analysis will be performed. The following three entries will be created:

- Adverse Events per arm for disclosure on EudraCT
- Non-serious Adverse Events for disclosure on EudraCT
- Serious Adverse Events for disclosure on EudraCT

7.8.2 Laboratory data

The analyses of laboratory data will be descriptive in nature and will be based on BI standards [BI-KMED-BDS-HTG-0042] (12). Analyses will be based on normalised values.

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

Clinically relevant findings in laboratory data will be reported as baseline conditions (at screening) or as AEs (during the trial) if judged clinically relevant by the investigator, and will be analysed as such.
It is the investigator's responsibility to decide whether a lab value is clinically significantly abnormal or not (at the RPM at the latest).

Descriptive statistics of laboratory data including change from baseline 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).

7.8.3 Vital signs

Descriptive statistics over time including change from baseline will be performed for vital signs (blood pressure, pulse rate, body temperature). In the listing the difference from baseline will also be displayed.

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

7.8.4 ECG

Continuous safety ECG monitoring (by investigator)

Clinically relevant abnormal findings will be reported as adverse events.

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

7.8.4.1 12-lead ECG

Abnormal findings will be reported as baseline conditions (at screening) or as AEs (during the trial) if judged clinically relevant by the investigator. All evaluations of ECG data will be based on the TS, except the exposure-response analyses, which are based on the ECGPCS.

Listing of individual data

For all quantitative endpoints, listings of individual data will be shown in Appendix 16.2. For QTcB and RR, only listings will be provided. Occurrences of notable findings will be flagged.

Comments regarding the ECGs will be listed.

Categorical endpoints

For the categorical endpoints, frequency tables will be provided.

For all subjects with any notable finding in ECG intervals, a separate listing will be created as end-of-text display (based on the same display template as in Appendix 16.2), and the corresponding time profiles will be shown.

Quantitative endpoints

Descriptive statistics (N, mean, SD, min, median, max) will be provided for the absolute values and changes from baseline over time of QTcF, QT, HR, PR and QRS. The time profiles of mean and SD for the changes from baseline on treatment will be displayed graphically by treatment. No totals will be provided.

For QTcF and HR changes from baseline, the relationship to the corresponding serum 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 serum 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 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 serum 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 treatment group (presented in the End-of-Text part of the CTR).

The relationship between BI 3006337 serum concentrations and QTcF changes from baseline will be investigated in an exploratory manner using a random coefficient model to estimate the difference in means between BI 3006337 and placebo of QTcF change from baseline and its 90% confidence interval at the geometric mean of C_{max} after single dose. Additionally, the estimated overall slope with its 90% confidence interval will be provided. The used random coefficient model is based on a white paper from Garnett et al. (13) with ΔQTcF as response variable, centered baseline QTc and plasma concentration as continuous covariates and treatment 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 10.1.4.

For visualization, a scatterplot of the BI 3006337 serum concentration against the following individual QTcF values will be provided: For each subject on active treatment and each time point, subtract the mean value of all individual observed ΔQTcF values from the placebo group for this time point from the individual observed ΔQTcF value for this subject and time point. This results in estimates for "individual ΔΔQTcF" values, which should only be used for plotting purposes. The corresponding regression line and its pointwise confidence bands as well as and the geometric mean of C_{max} for each dose will additionally be displayed in the plot.

The goodness of fit of the above model will be checked. The visual checks will include the inspection of concentration-QTcF quantile plots (13) and residual plots. 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.

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

Appropriateness of heart rate correction methods of QT interval

To evaluate the appropriateness of the heart rate correction methods, the slope of the relationship of QTcF interval versus RR interval will be estimated separately for off-drug values and active treatment, by applying the random coefficient model described in Section 10.1.2 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.

Additionally, the slope of the relationship of log-transformed QT interval versus log-transformed RR interval will be estimated separately for off-drug values and active treatment, by applying a random coefficient model per single ECG.

7.8.4.2 5-lead Holter ECG

Frequencies of the changes in the overall Holter interpretation between baseline and on treatment values will be displayed in two-way shift-tables for the overall time intervals.

The following analyses will be performed for the overall time intervals (presented in the end-of-text part of the CTR) as well as for the hourly time intervals (presented in the statistical appendix of the CTR):

- summary statistics for the minimum, mean and maximum heart rate as well as for the change from baseline in mean heart rate
- frequency tables displaying the number of subjects with specific ventricular, supraventricular and other arrhythmia events per treatment group
- summary statistics (only N, Min, Median, Max) for the absolute number of events as well as for the changes from baseline in number of events

Additionally, the time profiles of mean and SD regarding the mean heart rate will be displayed graphically by treatment based on the hourly intervals. This plot will be presented in the end-of-text part of the CTR.

Based on the overall time intervals, summary statistics (only N, Min, Median, Max) for the average number of events per analyzed hours will be shown per treatment group. Furthermore, shift tables displaying the changes of the average number of events between baseline and on treatment values will be generated using the categories for numbers of single ventricular events (total) and supraventricular extrasystoles as defined in Section 5.3.

The Holter analyzed time will be also analyzed descriptively and presented in the Statistical Appendix of the CTR.

7.8.5 Others

Local tolerability

Section 5.2.5.1 of the CTP: *Local tolerability will be assessed by the investigator or authorised designee according to 'swelling', 'induration', 'heat', 'redness', 'pain', or 'other findings'.*
Injection site reactions of clinical relevance will be recorded as AE and will be summarised as such.

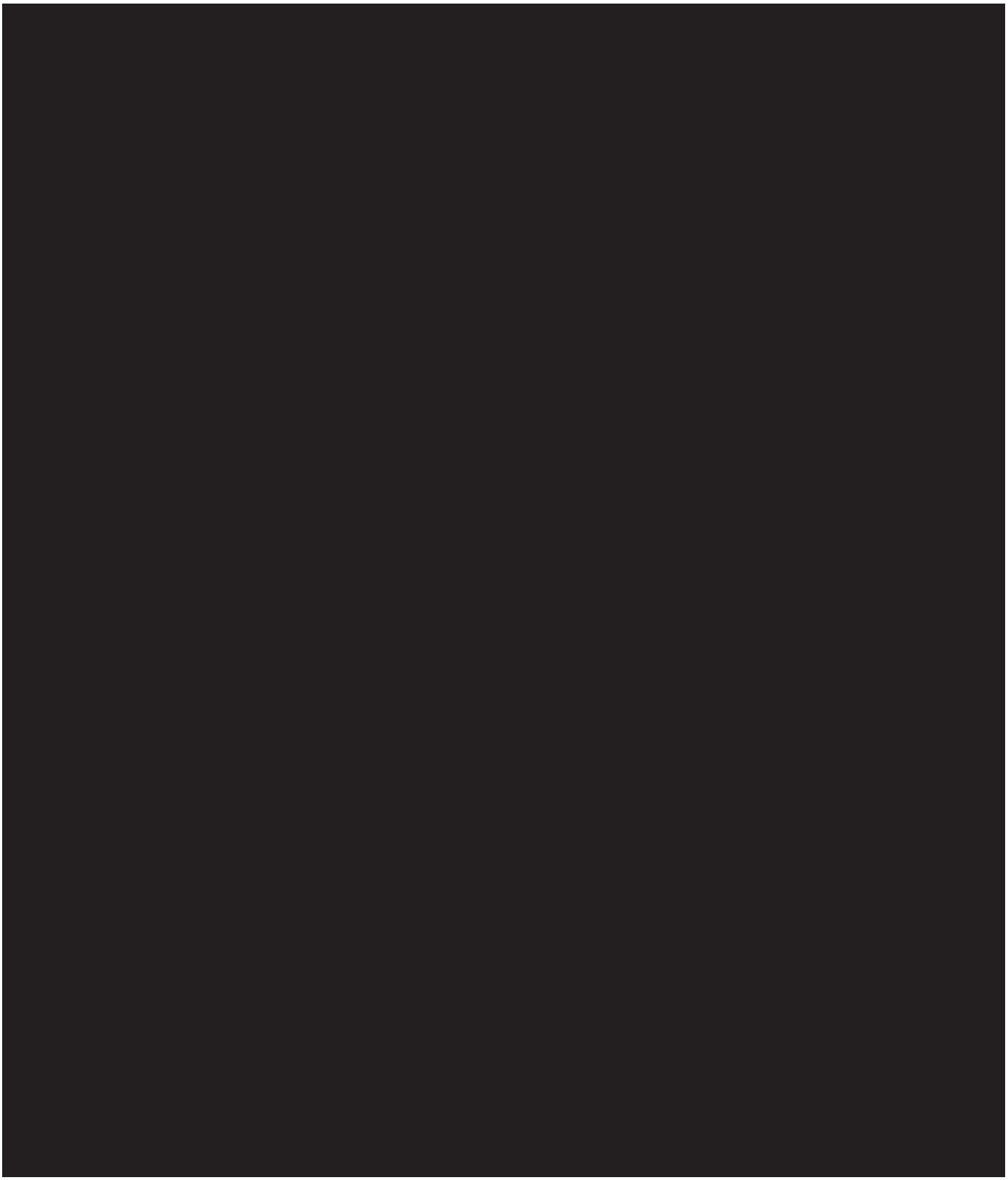
[redacted]

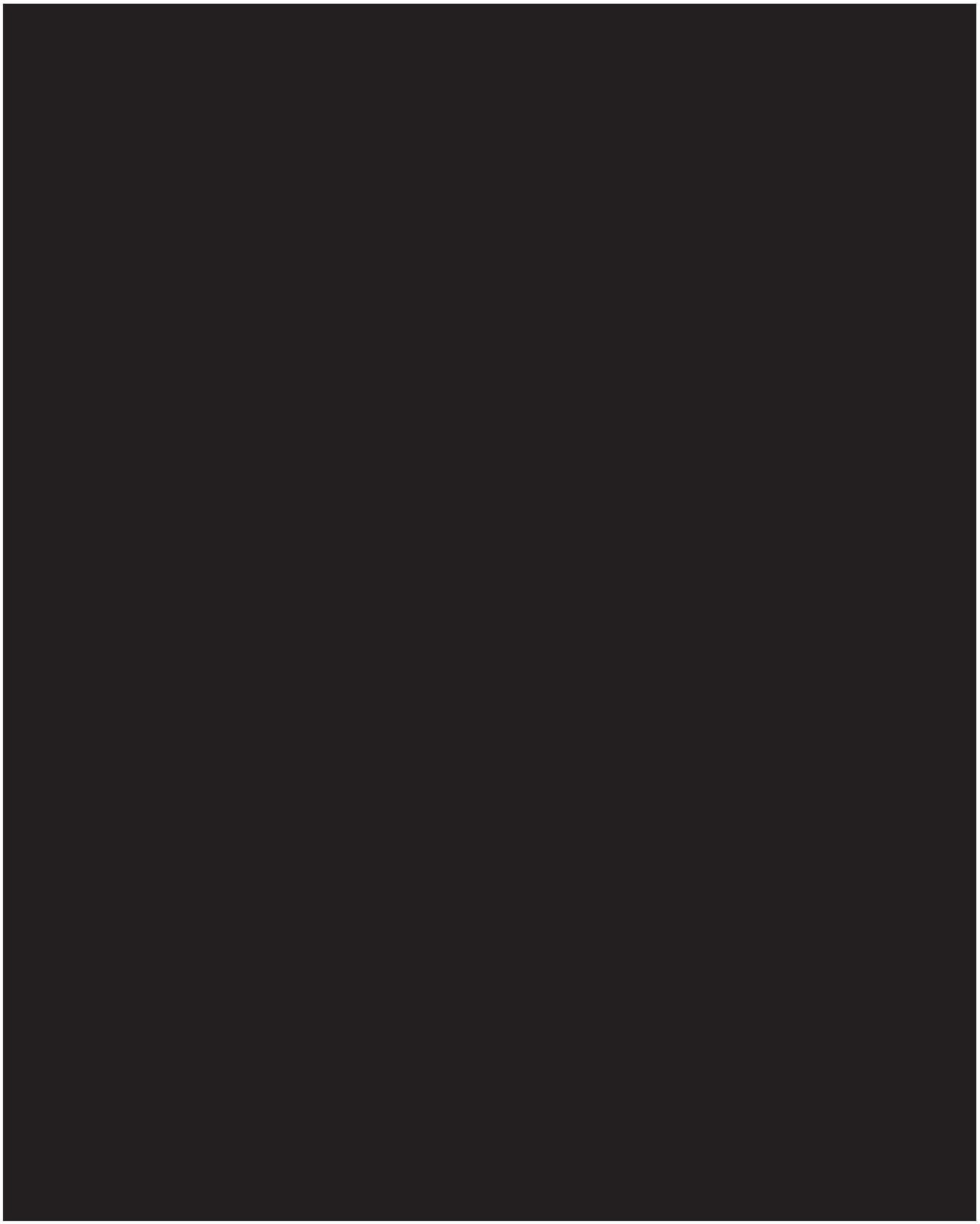
8. TIMEPOINT OF RELEASE OF TREATMENT INFORMATION

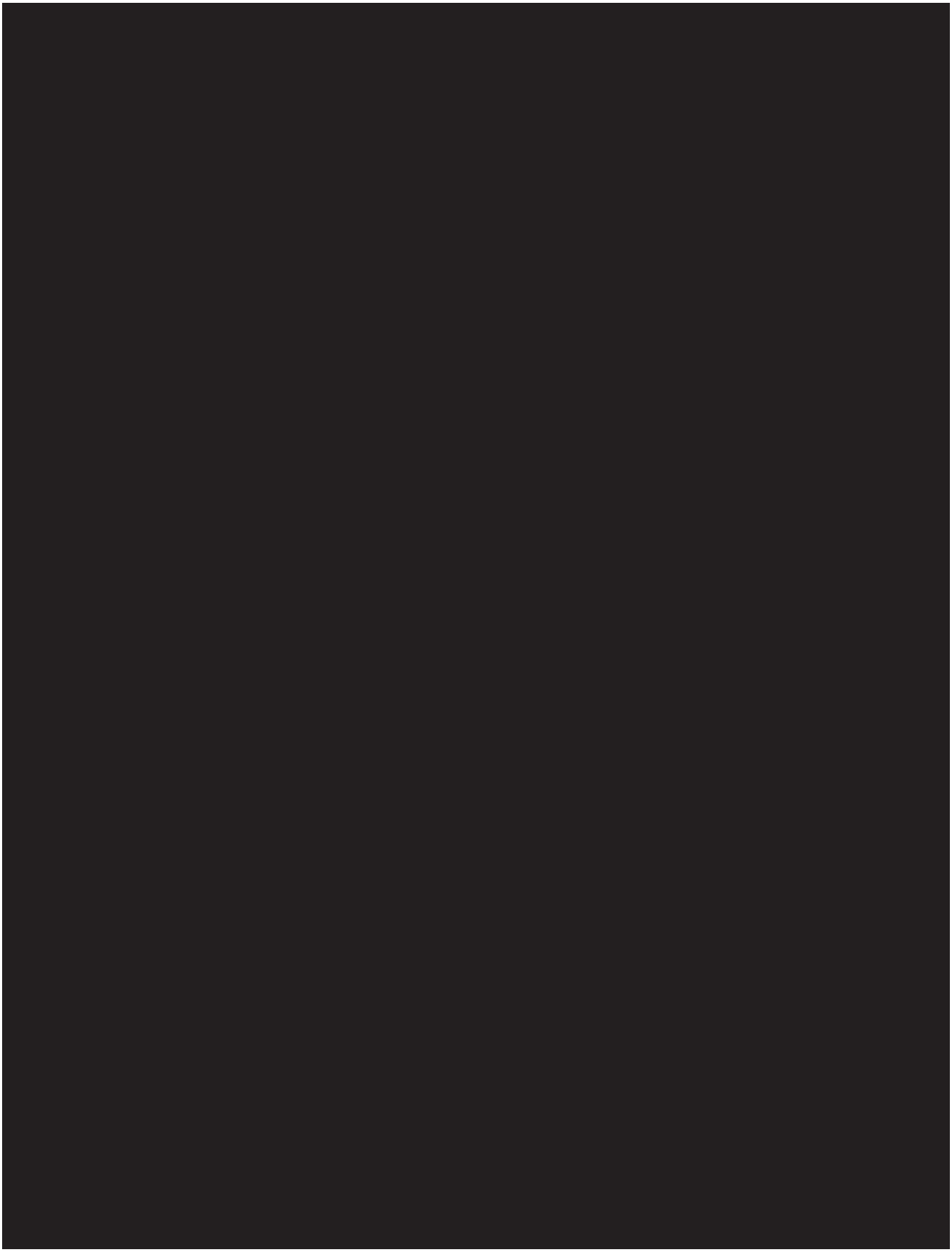
Not applicable due to open label handling of the trial as described in the CTP section 4.1.6.1.

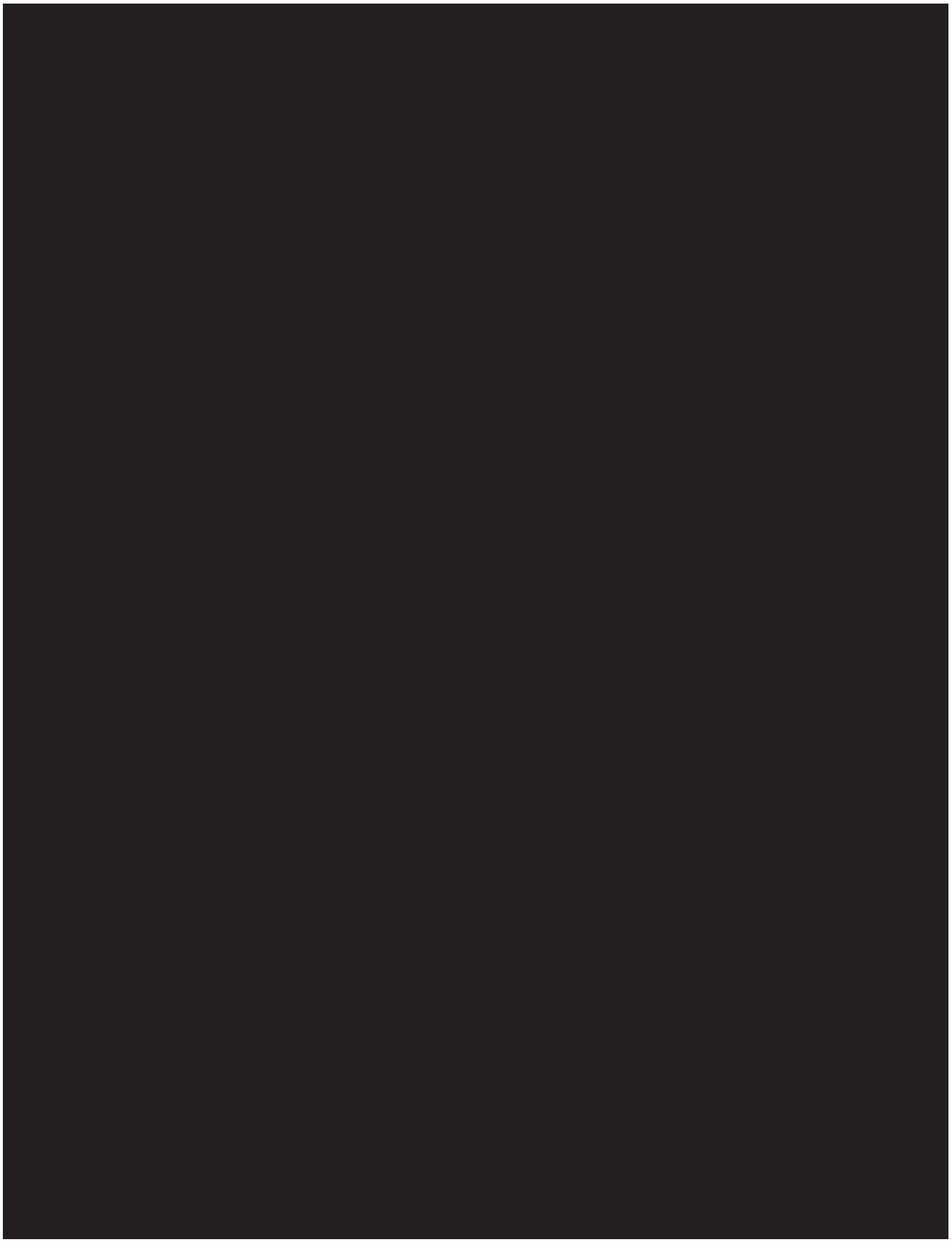
9. REFERENCES

1.	*CPMP/ICH/363/96:* "Statistical Principles for Clinical Trials", ICH Guideline Topic E9, Note For Guidance on Statistical Principles for Clinical Trials, current version.
2.	*001-MCS-40-413:* "Identify and Manage Important Protocol Deviations (iPD) ", current version, IDEA for CON.
3.	*BI-KMED-BDS-HTG-0035*: "Handling of Missing and Incomplete AE Dates", current version; KMED.
4.	*BI-KMED-TMCP-MAN-0012*: "Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics", current version; KMED.
5.	*BI-KMED-TMCP-MAN-0014*: "Noncompartmental Pharmacokinetic / Pharmacodynamic Analyses of Clinical Studies", current version; KMED.
6.	*BI-KMED-BDS-HTG-0045*: "Standards for Reporting of Clinical Trials and Project Summaries", current version; KMED.
7.	*BI*-KMED-TMCP-OTH-0003: "Graphs and Tables for Clinical Pharmacokinetics and Pharmacodynamic Noncompartmental Analyses", current version, KMED.
8.	*BI-KMED-TMCP-MAN-0010*: "Description of Analytical Transfer Files and PK/PD Data Files", current version; KMED.
9.	*BI-KMED-BDS-HTG-0041*: "Analysis and Presentation of Adverse Event Data from Clinical Trials – Display Template", current version; KMED.
10.	*BI-KMED-BDS-HTG-0066*: "Analysis and Presentation of AE data from clinical trials", current version, KMED.
11.	*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.
12.	*BI-KMED-BDS-HTG-0042*: "Handling, Display and Analysis of Laboratory Data", current version; KMED.
13.	Garnett C, Bonate PL, Dang Q, Ferber G, Huang D, Liu J, et al; Scientific white paper on concentration-QTc modeling. J Pharmacokin Pharmacodyn (2017).









11. HISTORY TABLE

Table 11: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
1	**25-APR-22**	[redacted]	None	This is the final TSAP