TRIAL STATISTICAL ANALYSIS PLAN

c39067821-02

BI Trial No.:	1425-0008
Title:	Safety, tolerability, and pharmacokinetics of single rising oral dose and multiple rising oral doses of BI 706321 in healthy Japanese male subjects and single oral dose of BI 706321 in healthy Chinese male subjects (double-blind, randomised, placebo-controlled, parallel group design) (Revised Protocol including amendments 1-2 [c34982691-03])
Investigational Product:	BI 706321
Responsible trial statistician:	[redacted] Phone: [redacted] Fax: [redacted]
Date of statistical analysis plan:	19 AUG 2024 SIGNED
Version:	2

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2. LIST OF ABBREVIATIONS

See Medicine Glossary:
http://glossary

Term	Definition / description
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
AUC_{0-tz}	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 to the last quantifiable data point
$AUC_{\tau,ss}$	Area under the concentration-time curve of the analyte in plasma at steady state over a uniform dosing interval τ
BMI	Body mass index
CARE	Clinical data Analysis and Reporting Environment
CI	Confidence interval
C_{max}	Maximum measured concentration of the analyte in plasma
$C_{max,ss}$	Maximum measured concentration of the analyte in plasma at steady state over a uniform dosing interval τ
$C_{min,ss}$	Minimum concentration of the analyte in plasma at steady state over a uniform dosing interval
CV	Arithmetic coefficient of variation
ECGPCS	ECG Pharmacokinetic Concentration Set
EDMS	Electronic documentation management system
EOT	End of Trial
gCV	Geometric coefficient of variation
gMean	Geometric mean
λ_z	Terminal rate constant of the analyte in plasma
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
N	Number of non-missing observations
Nobs	Number of observations
P10	10th percentile

Term	Definition / description
P90	90th percentile
PKS	Pharmacokinetic parameter analysis set
PT	Preferred term
Q1	1st quartile
Q3	3rd quartile
$R_{A,AUC}$	Accumulation ratio based on $AUC_{0-\tau}$
$R_{A,Cmax}$	Accumulation ratio based on $C_{max,ss}$
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
t_{max}	time from dosing to maximum measured concentration of the analyte in plasma
TMF	Trial master file
TS	Treated set
ULN	Upper limit of normal
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 compared to the protocol will be made:

Initiation of trial part II will be delayed and it is uncertain, if Part II will be done at all. Due to this, analysis of Part I will already be conducted and finalized directly after completion of Part I. If Part II will not be conducted, the TSAP will be amended accordingly.

By the date of this revision (TSAP version 2.0), it is known that Part II of the study will not be conducted due to termination of the development of the BI 706321 program in Crohn's Disease. It is important to note that this decision is not based on any safety finding for BI 706321. Therefore, descriptions regarding analyses for Part II of the study have been removed from all sections of the TSAP.

Linearity analysis will be adapted in line with updated BI standards. Originally, the linearity index model included a random effect for subject. This random effect will be excluded from the model as subject is already taken into account with the random error e_{ij} associated with subject j at AUC type i.

Pre-dose plasma concentrations $C_{pre,ss}$, $C_{pre,N}$ and $C_{avg,ss}$ which were defined in the CTP as further endpoints, will not be analysed as further endpoints. They will be analysed as part of the analysis of plasma concentration time data, and will be identified by their planned sampling time, e.g. concentration at planned time 431:45 h (= $C_{pre,ss}$), 120 h (= $C_{pre,1}$), 168 h ($C_{pre,3}$), 192 h ($C_{pre,4}$) etc. (Please refer the below table as reference). Instead of $C_{avg,ss}$, $C_{avg,14}$ will be calculated. However, this is not a deviation from the statistical methods described in the revised CTP.

Table 4: 1 Definition of trough concentrations data

Day	6	8	9	10	11	12	13
PTM	120:00	168:00	192:00	216:00	240:00	264:00	288:00
PK param	$C_{pre,1}$	$C_{pre,3}$	$C_{pre,4}$	$C_{pre,5}$	$C_{pre,6}$	$C_{pre,7}$	$C_{pre,8}$

Day	14	15	16	17	18	19	20
PTM	312:00	336:00	360:00	384:00	408:00	431:45	456:00
PK param	$C_{pre,9}$	$C_{pre,10}$	$C_{pre,11}$	$C_{pre,12}$	$C_{pre,13}$	$C_{pre,14}$ ($C_{pre,ss}$)	$C_{\tau,14}$

5. ENDPOINTS

5.1 PRIMARY ENDPOINT

Section 2.1.2 of the CTP:

The primary endpoint for assessment of safety and tolerability of BI 706321 is the percentage of subjects with drug-related adverse events.

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

Pharmacokinetic endpoints for BI 706321 are defined as secondary endpoints of the trial.

Section 2.1.3 of the CTP:

The following pharmacokinetic parameters will be determined if feasible:

Part I

Single dose part (after 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)*
- *C_{max} (maximum measured concentration of the analyte in plasma)*
- *t_{max} (time from dosing to maximum measured concentration of the analyte in plasma)*

After the last dose:

- *$AUC_{\tau,ss}$ (area under the concentration-time curve of the analyte in plasma 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 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 $AUC_{0-\tau}$)*

[redacted]

Safety and tolerability endpoints

Section 2.2.2.1 of the CTP:
Safety and tolerability of BI 706321 will be assessed based on:

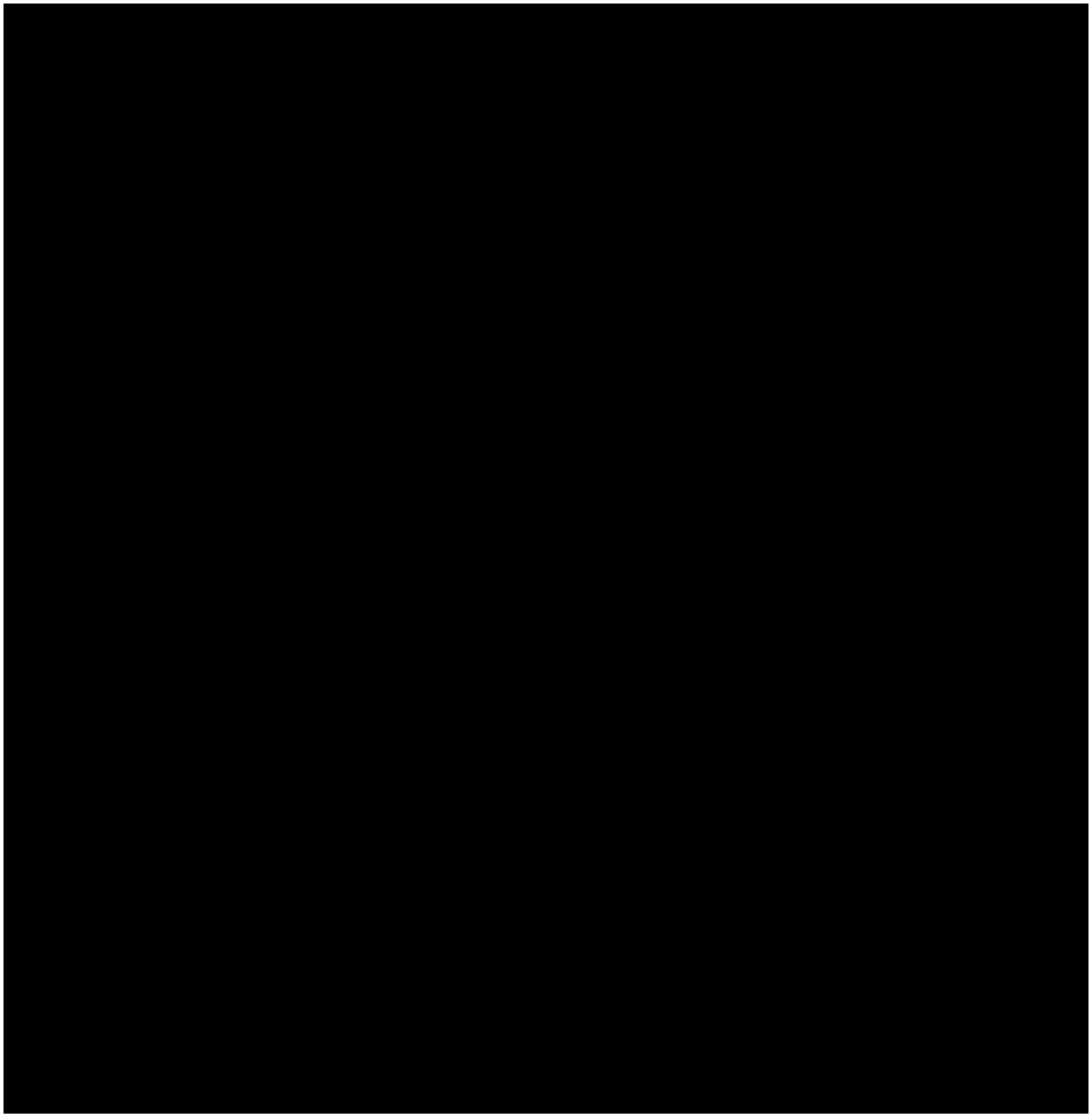
- *AEs (including clinically relevant findings from the physical examination)*
- *Safety laboratory tests*
- *12-lead ECG*
- *Vital signs (blood pressure, pulse rate, body temperature)*

[redacted]

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.

[redacted]



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.

In Part I, a double-blind, randomised and placebo-controlled parallel-group trial in Japan is planned.

A total of 48 Japanese healthy male subjects will be treated with single and multiple doses of BI 706321. The subjects will be assigned to 4 dose groups of 12 subjects. In each dose group, 9 subjects will be randomised to active treatment and 3 subjects will be randomised to placebo. All subjects will receive a single dose on Day 1 (single dose evaluation), and further 2 weeks with daily doses of study treatment starting on Day 6 (multiple dose evaluation). For details of dosage and formulation see Table 6.1: 1.

Table 6.1: 1 Treatments and labels used in the analysis – Part I

Treatment		Short label
P*	Placebo	Placebo – Japanese
A	BI 706321, 2 mg TABLET, FILM COATED QD ORAL	BI 2mg – Japanese
B	BI 706321, 5 mg TABLET, FILM COATED QD ORAL	BI 5mg – Japanese
C	BI 706321, 8 mg TABLET, FILM COATED QD ORAL	BI 8mg – Japanese
D	BI 706321, 10 mg TABLET, FILM COATED QD ORAL	BI 10mg – Japanese

* For data analysis purposes, the placebo control group of Part I (Japan) will include all subjects of all dose groups in Part I treated with placebo.

Section 1.2.2 of the CTP:
*The Residual Effect Period (REP) of BI 706321 is 16 days and is projected based on 5*terminal $t_{1/2}$ from preliminary PK data of Trial 1425-0002. This is the period after the last dose with measurable drug levels and/or pharmacodynamic effects still likely to be present.*

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 16 days (384 hours) after the last time of administration of BI/Placebo)
- **Follow-up (F/U)** (ranging from 16 days (384 hours) after last administration of BI or Placebo until 0:00 h on day after trial termination date)

In Part I, the end-of-trial visit is planned to take place on day 27, whereas last drug administration is planned on day 19. Consequently, follow-up phase does not apply to Part I.

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.*

Displays of AEs will be stratified by treatment group as specified in Table 6.1: 1. The results will be presented separately for each trial part if not stated otherwise. The following AE displays will be provided in the report:

In Section 15.3 and Appendix 16.1.13.1.8 (for ClinicalTrials.gov) of the CTR displays, the on treatment phase will be analysed (labelled with the name of the study treatment (short label)). Screening and follow-up phases will not be included in this analysis.

The following totals will be provided for Section 15.3 (except for ECG analysis):

- a total over all on treatment phases **("Total")**
- a total over all on treatment phases with BI **("BI Total")** (for Part I only)

In Section 15.4 and Appendix 16.2 (Listings) of the CTR displays, the screening and follow-up 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: *Important protocol deviation (iPD) categories will be specified in the DV domain, iPDs will be identified no later than in the Report Planning Meeting, 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:

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

All ECG analyses are performed on the TS, except for the exposure-response analyses, which will be performed on the ECG Pharmacokinetic Concentration Set (ECGPCS) defined below.

- **ECG PK 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 database lock. The ECGPCS will be used for the exposure-response analyses.

Section 7.3 of the CTP:

The pharmacokinetic parameters listed in CTP *Section 2.1.3 and 2.2 for drug BI 706321 and BI 706062 will be calculated according to BI Standards.*

Plasma and urine concentration data and parameters of a subject will be included in the statistical pharmacokinetic (PK) analyses if they are not flagged for exclusion due to a protocol deviation *relevant to the evaluation of PK (to be decided no later than in the Report Planning Meeting) 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*

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

- *The subject experienced emesis that occurred at or before two times median t_{max} of the respective treatment (Median t_{max} is to be determined excluding the subjects experiencing emesis),*
- *Missing samples/concentration data at important phases of PK disposition curve.*

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.

Table 6.3: 1 Subject sets analysed

	Analysis sets		
Class of endpoint	TS	PKS	ECGPCS
Primary endpoint and further safety assessments (incl. central ECG)	X		
Analyses of PK endpoints		X	
ECG exposure response analysis			X
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 trial was performed in only one centre.

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).

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 values 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.

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

The baseline value is defined as the last measurement before administration of trial medication (BI 706321 or Placebo).

Section 6.1 of the CTP:

Study measurements and assessments scheduled to occur ‘before’ trial medication administration on Day 1 are to be performed and completed within a 3 h-period prior to the trial drug administration (including blank values for PK).

The acceptable deviation from the scheduled time for vital signs, ECG, and laboratory tests will be ± 15 min for the first 4 h after trial drug administration, ± 30 min thereafter on Day 1, ± 60 min on Day 2 (except for urinalysis which can performed between wake-up time to the scheduled time), and ± 120 min from 48 h post administration onwards.

The tolerance for drug administration will be ± 1 min on Days 1, 12, 19 and ± 10 min on all other treatment days.

The tolerance for PK blood sampling will be ± 5 minutes for up to 6 hours (including) after dosing, 15 minutes for time points from more than 8 hour to 12 hours after dosing, 60 minutes for time points from more than 24 hour to 48 hours after dosing, and 120 minutes for time points at 72 hours or later after dosing.

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.

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

At screening and end of trial examination, single ECGs will be recorded and will not be transferred to the central ECG lab.

Section 5.2.4.1 of the CTP: *Central ECG lab evaluation will be performed for all time points with triplicate ECGs. For some time points* (…) *three triplicate ECGs are recorded (i.e. on days 1 and 19 in Part I and on day 1 in Part II). Always, only the first single ECG per triplicate will be evaluated.*

The baseline value of an ECG variable is defined as the mean of the ECG variable values prior to drug administration.

For the exposure response analyses, pairs of ECG variables and corresponding plasma concentrations will be built using the same planned time points, e.g., the HR change from baseline and the plasma concentration measured at planned time 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 plasma concentration sampling are proposed to be

- 30 minutes for up to (and including) 12 hours after dosing,
- 60 minutes for time points from 24 hours up to (and including) 36 hours after dosing,
- 90 minutes for time points at 48 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.

Table 6.7: 1 Time schedule of 12-lead ECG recordings in Part I

Visit	**Day**	**Planned time [hh:mm] (relative to drug administration)**	**Study phase**	**Central evaluation**
1	-28 to -1		Screening	NA
2	**1**	**-01:30**	**Baseline**	**First single ECG of each triplicate**
		-01:15		
		-01:00		
		01:00	**On treatment**	
		02:00		
		04:00		
		08:00		
		12:00		
	2	**24:00**		
		36:00		
	3	**48:00**		
	5	96:00	On treatment	NA
	6	120:00		
	7	144:00		
	9	192:00		
	11	240:00		
	13	288:00		
	15	336:00		
	17	384:00		
	19	**431:15**	**On treatment**	**First single ECG of each triplicate**
		431:30		
		431:45		
		433:00		
		434:00		
		436:00		
		440:00		
		444:00		
	20	**456:00**		
	21	**480:00**		
	22	504:00	On treatment	NA
	24	552:00		
3	27	624:00	End of trial examination	

7. PLANNED ANALYSIS

If not stated otherwise, the trial parts will be evaluated separately.

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 will be performed by [redacted] and will be presented in Section 15.5 of the CTR and Appendix 16.1.13.3.

Descriptive data analysis of PK will be performed by the department [redacted] at [redacted] The results will be presented in Section 15.6 of the CTR and Appendix 16.1.13.5.

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/PD analysis (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 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 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 parameters

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

Exclusion of PK concentrations

The ADS "ADPC" (PK concentrations per time-point or per time-interval) contains column variables ACEX and ACEXC indicating inclusion/exclusion (ACEX) of a concentration and an analysis flag comment (ACEXC). Exclusion of a concentration depends on the analysis flag comment ACEXC. For example, if ACEXC is set to 'ALL CALC', the value will be excluded for all types of analyses based on concentrations. If ACEXC is set to 'DESC STATS' the value will be excluded from descriptive evaluations per planned time point/time interval. If ACEXC contains the addition 'TIME VIOLATION' or 'TIME DEVIATION' the value can be used for further analyses based on actual times. If ACEXC 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 / Pharmacodynamic Analyses of Clinical Studies" (5) and *BI-KMED-TMCP-MAN-0010*: "Description of Analytical Transfer Files and PK/PD 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 plasma concentrations and/or urinary excretion 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

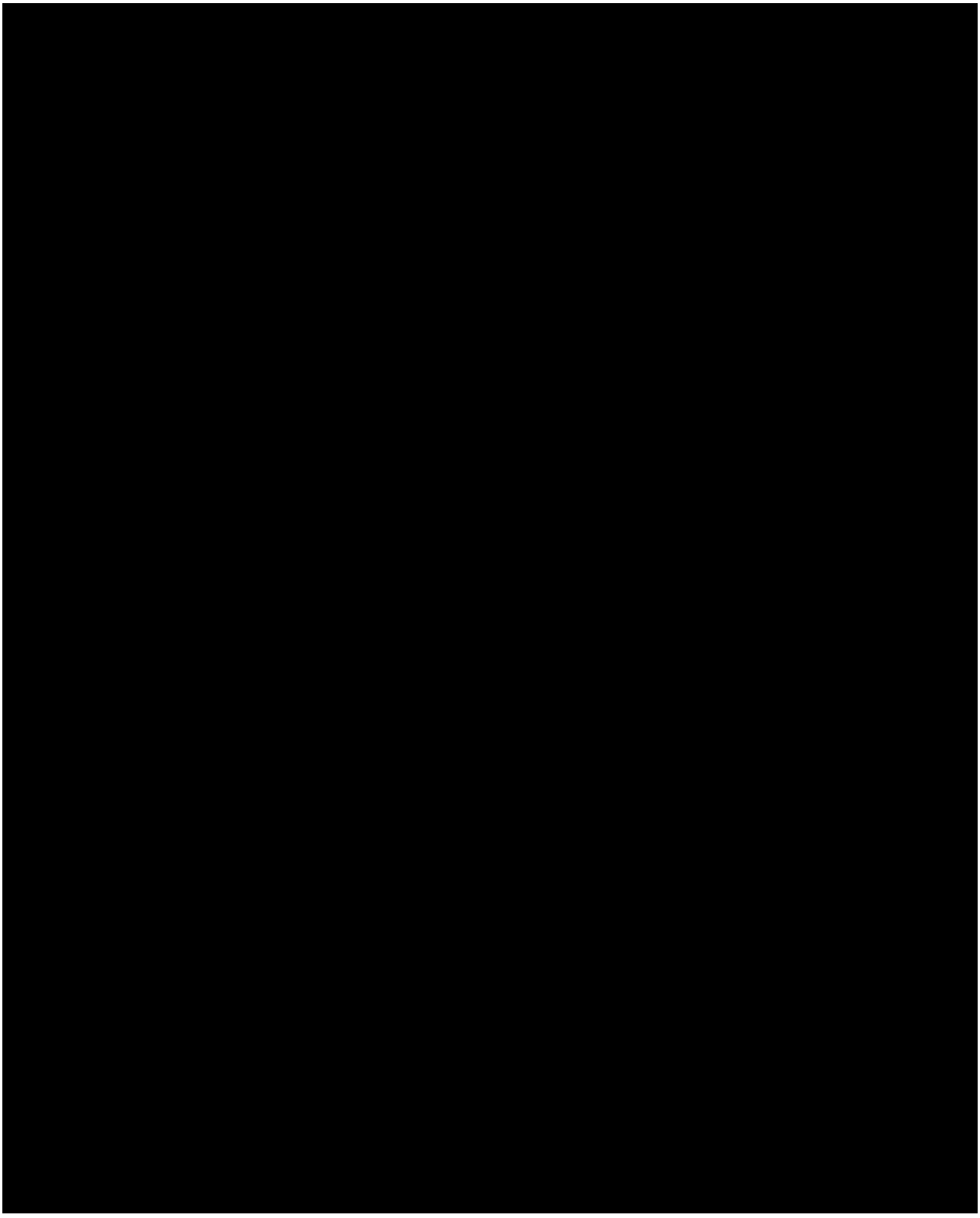
This section is not applicable as no key secondary endpoint has been specified in the protocol.

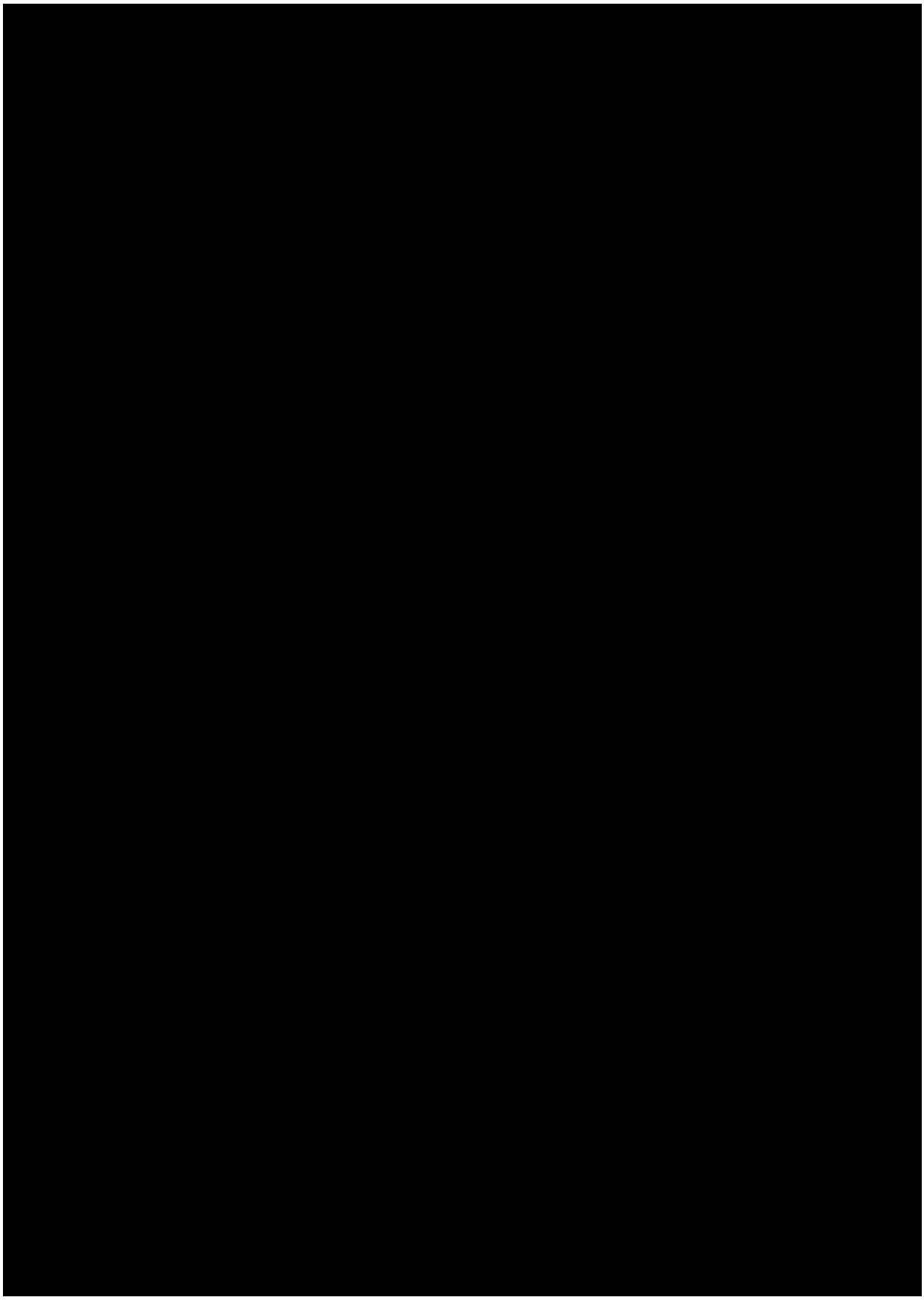
7.5.2 (Other) Secondary endpoints

Section 7.3.2 of the CTP:

Primary analyses

The secondary endpoints (refer to Section 5.2.2) will be analysed descriptively. Analyses will be performed for BI 706321.





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 except for the exposure-response analyses, which are based on the ECGPCS.

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', 'on treatment' and 'follow-up' 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 5.2.5.1.4 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 total bilirubin ≥2-fold ULN measured in the same blood sample, 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).
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.

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).

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

For vital signs (blood pressure, pulse rate and body temperature), descriptive statistics including change from baseline will be calculated by treatment group and by planned time point based on the value of the subject that was originally assigned to the respective planned time point (unscheduled measurements will not be considered). Additionally, individual time profiles of body temperature will be provided, including unscheduled measurements using the actual time of measurement. In the listings the difference from baseline will also be displayed.

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.

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.

Exposure-response assessment

For QTcF and HR changes from baseline, the relationship to the corresponding plasma concentrations (if applicable both for BI 706321 and BI 706062) will be analysed. For Part I, the relationship will be evaluated using figures and 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 a list of time points with scheduled ECG assessments and time-matched plasma concentrations as well as for definition of "time-matched", refer to Section 6.7. 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 for Part I, 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 treatment group (presented in the End-of-Text part of the CTR).

For Part I, analysis will proceed like follows:

The relationship between BI 706321 plasma 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 706321 and placebo of QTcF change from baseline and its 90% confidence interval at the geometric mean of C_{max} after single dose and of $C_{max,ss}$ for each 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, 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 10.1.4.

For visualization, a scatterplot of the BI 706321 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 and the geometric mean of C_{max} and $C_{max,ss}$ 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, and if applicable for metabolite BI 706062 (both QTcF and HR) instead of the parent drug BI 706321.

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.

7.8.5 Others

Physical examination

Physical examination findings will be reported as relevant medical history/baseline condition (i.e., a condition already existent before intake of study drug) or as AE and will be summarised as such.

No separate listing or analysis of physical examination findings will be prepared.

8. TIMEPOINT OF RELEASE OF TREATMENT INFORMATION

This trial is double-blind, but will be handled open label regarding trial functions of the sponsor (including clinical trial leader, data manager, statistician, bioanalyst, pharmacokineticist, pharmacometrician, drug metabolism scientist as well as dedicated contract research organization (CRO) personnel).

The treatment information will be loaded into the trial database once all subjects in a dose group are randomized.

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-HTG-0025*: "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).

10. ADDITIONAL SECTIONS

10.1 DETAILS FOR ANALYSES OF CENTRALIZED ECG

10.1.1 Detailed descriptions of ECG endpoints

QT, PR, QRS and RR baseline and on-treatment measurements (see Table 6.7: 1) are included in the centralised ECG evaluation.

For each single ECG, measurements of QT, PR, QRS and preceding RR interval of four cardiac cycles will be determined and stored in the database as raw data. Their mean values will be used as the QT, PR, QRS and RR interval values, respectively, for this ECG.

QTcF, HR and QTcB will be calculated based on the derivation rules as follows:

From the four cardiac cycles of a single ECG, the HR (measured in beats per minute, beats/min) will be calculated as

$$\text{HR [beats/min]} = \frac{60\,000}{\overline{\text{RR}}}$$

where $\overline{RR}$ is the mean of the four RR intervals (measured in msec).

Similarly, the QT interval corrected for HR according to Fridericia's formula (QTcF) for a single ECG will be derived as

$$\overline{\text{QTcF}}\ [\text{msec}] = \left(\frac{1000}{\overline{\text{RR}}}\right)^{1/3} * \overline{\text{QT}}[\text{msec}],$$

where $\overline{\text{QT}}$ is the mean of the four QT intervals and $\overline{\text{RR}}$ is the mean of the corresponding preceding RR intervals of the four cardiac cycles for this ECG.

Likewise, the HR-corrected QT interval according to Bazett's formula (QTcB) for a single ECG is given by

$$\overline{\text{QTcB}}\ [\text{msec}] = \left(\frac{1000}{\overline{\text{RR}}}\right)^{1/2} * \overline{\text{QT}}[\text{msec}].$$

In case of triplicate ECGs at a time point, the respective ECG variable will be averaged over the triplicate ECG measurements at this time point (arithmetic mean). Note that in case of missing values the averaging is simply done for the available values.

10.1.2 Appropriateness of heart rate correction methods of QT interval

For the appropriateness check of the HR correction the following SAS code is used:

```
PROC MIXED DATA=xxxx CL METHOD=REML;
CLASS subject;
MODEL QTcF = RR / DDFM= KENWARDROGER ALPHA=0.05 CL;
RANDOM INT RR / TYPE=UN SUBJECT=subject;
ESTIMATE 'Population slope' RR 1 / ALPHA=0.05 CL;
/* individual slope estimates:*/
ESTIMATE 'Slope f. subj.1' RR 1 | RR 1 /SUBJECT 1   ALPHA=0.05 CL;
ESTIMATE 'Slope f. subj.2' RR 1 | RR 1 /SUBJECT 0 1 ALPHA=0.05 CL;
/* etc. */
BY active;
RUN;
```

Note: active is a dummy 0/1 variable indicating the active treatment (1=active, 0=placebo + predose values).
In case of convergence problems see Section 10.1.5.

10.1.3 Details for the derivation of categorical ECG endpoints

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

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

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

[1]: E.g., in case of three triplicate baseline recordings, the baseline consists of three time points.

10.1.4 SAS code for ECG exposure-response analyses

```
PROC MIXED DATA=myDATA METHOD=REML;
      CLASS subject active(ref='0') [time day];
      MODEL ECGep = base conc active [time day] / NOINT CL ALPHA=0.1
      DDFM=KR; */ time is only included in case no baseline day is
      available/*
      RANDOM INT conc / TYPE=UN SUBJECT=subject;
      ESTIMATE 'Pred. value at conc. xx.xx' conc xx.xx active 1 -1 / CL
            ALPHA=0.1;
      ESTIMATE 'Intercept' conc 0 active 1 -1/CL ALPHA=0.1;
      ESTIMATE 'Slope estimate' conc 1 / CL ALPHA=0.1;
RUN;
```

Here `ECGep` is the QTcF change from baseline, `base` is the centered baseline value of `ECGep` (i.e. the baseline value minus the mean of the baseline values from all subjects), `active` is a dummy 0/1 variable indicating the active treatment (1=active, 0=placebo), `time` is a categorical variable indicating the time point, `day` is a categorical variable indicating the day, `conc` is the corresponding plasma concentration value of the drug, and `xx.xx` is the given concentration value (usually the value of the geometric mean C_{max} of a given treatment group). Note that the fixed effect `time` should be coded as the (planned) time of the day, i.e. as 24 hour clock time within the interval [0:00, 24:00) and not as the nominal time after first dose. That is, the time variable value for e.g. 08:00 on Day 1 should have the same value as for 08:00 on Day 2. The `TYPE=UN` option causes the two specified random coefficients to have a bivariate normal distribution. In case of convergence problems see Section 10.1.5.

10.1.5 Convergence problems and numerical issues in the ECG analyses

In the exposure response analyses estimation problems may occur because of numerical issues resulting from the concentration values given in a specific unit (results may all be very small or very large numbers); to avoid such problems it will be checked whether a transformation (e.g. by a factor of 1000) would be appropriate for the analysis.

In case of convergence problems in general, the following steps will be applied:

- Set MAXITER=100 and/or MAXFUNC=200
- Set SINGULAR=1E-10 as option (in the model statement)
- Use option SCORING=4 in the final run to request a Fisher scoring algorithm to be used for the first 4 iterations
- Perform an initial run including the statement
  ODS OUTPUT COVPARMS=covstart;
  followed by a final run using
  PARMS / PARMSDATA=covstart;
  In the special case with the note “Convergence criteria met but final hessian is not positive definite” try instead/in addition
  PARMS / OLS;
  to request ordinary least squares starting values.
- One may also use estimates from a simpler model (e.g. using AR(1)) as starting values for the run with TYPE=UN or UNR

In case an unstructured covariance matrix (i.e. TYPE=UN or UNR) does not work, also in conjunction with all steps mentioned above, TYPE=FA0(2) will be used, which requests a G matrix estimate that is constrained to be nonnegative definite)

If the note “estimated G matrix is not positive definite” occurs in the SAS log file, the random slope (conc or rr) will be removed from the RANDOM statement. (If random slope rr is to be removed in model to check on appropriateness of the HR correction, no individual slopes can be calculated.)

11. HISTORY TABLE

Table 11: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
1	**28-SEP-22**	[redacted]	None	This is the final TSAP
2	**19-AUG-24**		Title page Sections 4.0, 5.2, 6.1, 6.7, and 7.8.4	Update the name for responsible trial statistician (TSTAT) Descriptions regarding the analyses for Part II (which was not initiated anymore) have been removed from this TSAP.