TRIAL STATISTICAL ANALYSIS PLAN

c30150578-01

BI Trial No.:	1425-0001
Title:	Safety, tolerability, and pharmacokinetics of single rising oral doses of BI 706321 in healthy male subjects (single-blind, randomised, placebo-controlled, parallel group design) Including Protocol Amendments 1 - 6 [c26547838-07]
Investigational Product:	BI 706321
Responsible trial statistician:	[redacted] Phone: [redacted] Fax:
Date of statistical analysis plan:	14 JAN 2021 SIGNED
Version:	1

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2. LIST OF ABBREVIATIONS

See Medicine Glossary:
website: glossary

Term	Definition / description
ALT	Alanine Aminotransferase
ANCOVA	Analysis of Covariance
AST	Aspartate Aminotransferase
$AUC_{0-\infty}$	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity
AUC_{0-tz}	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 to the last quantifiable data point
BMI	Body mass index
cap	Capsule
CARE	Clinical Analysis and Reporting Environment
CI	Confidence Interval
C_{max}	Maximum measured concentration of the analyte in plasma
CV	Arithmetic Coefficient of Variation
DBLM	Database Lock Meeting
DILI	Drug induced liver injury
ECGPCS	ECG Pharmacokinetic Concentration Set
gCV	Geometric Coefficient of Variation
gMean	Geometric Mean
LLT	Lower Level Term
Max	Maximum
MedDRA	Medical Dictionary For Regulatory Activities
Min	Minimum
N	Number non-missing observations
NE	Neutrophil elastase
os	Oral solution
P10	10^{th} percentile
P90	90^{th} percentile
PDS	Pharmacodynamic parameter analysis set

Term	Definition / description
PKS	PK parameter analysis set
PT	Preferred Term
Q1	1st quartile
Q3	3rd quartile
QD	Quaque die, once daily
R	Reference
RAGe	Report Appendix Generator system
REP	Residual Effect Period
SD	Standard Deviation
SOC	System Organ Class
t_{max}	Time from dosing to maximum measured concentration of the analyte in plasma
T	Test
TS	Treated Set
TSAP	Trial Statistical Analysis Plan
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 6.3 or higher, Certara USA Inc., Princeton, NJ, USA).

The statistical analyses will be performed within the validated working environment CARE, including SAS® (current Version 9.4, by SAS Institute Inc., Cary, NC, USA), and a number of SAS™-based tools (e.g., macros for the analyses of AE data or laboratory data; Report Appendix Generator system (RAGe) for compilation/formatting of the CTR appendices).

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

All analyses as planned in the CTP will be performed and are described in more detail in this TSAP.

5. ENDPOINTS

5.1 PRIMARY ENDPOINTS

Section 2.1.2 of the CTP:

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

Part II: The following pharmacokinetic parameters will be determined for BI 706321:

- *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)*
- *C_{max} (maximum measured concentration of the analyte in plasma)*

5.2 SECONDARY ENDPOINTS

5.2.1 Key secondary endpoints

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

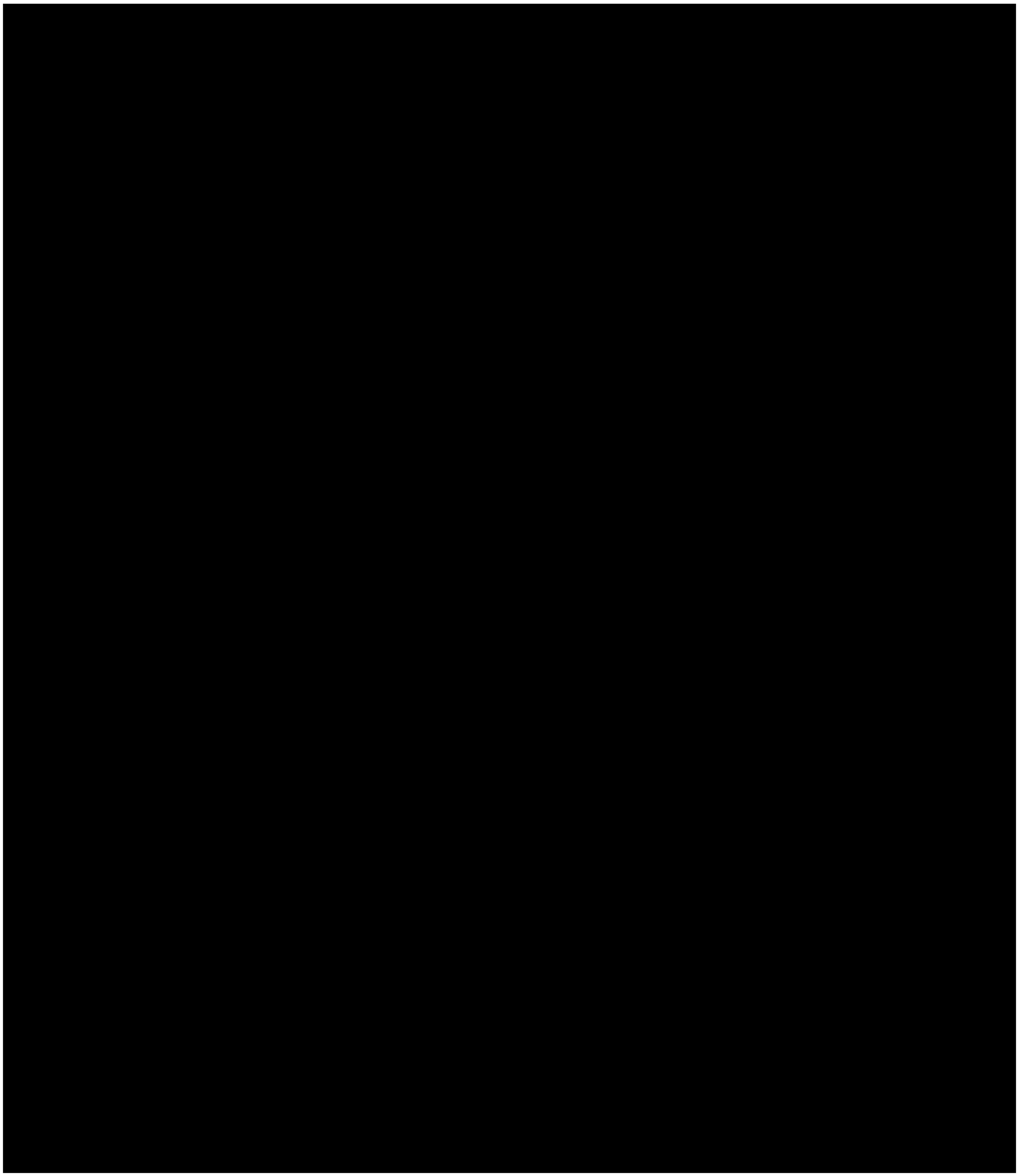
5.2.2 Secondary endpoints

Section 2.1.3 of the CTP:
Part I: The following pharmacokinetic parameters will be determined for BI 706321 if feasible:

- *$AUC_{0-\infty}$ (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 the maximum measured concentration of the analyte in plasma)*

Part II: The following pharmacokinetic parameter will be determined for BI 706321:

- *$AUC_{0-\infty}$ (area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity)*



6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENTS

It is planned that in total up to 80 healthy male subjects participate in this study.

In Part I 64 subjects are planned to be included, according to 8 sequential groups comprising 8 subjects per group. Within each dose group, 6 subjects will receive the active drug and 2 will receive placebo.
Two additional higher dose groups with BI 706321 40mg and 60mg (capsule) are considered and will only be dosed after approval of a substantial amendment.
In Part II 12 subjects are to be randomly allocated to one of 3 treatment sequences R-T1-T2, T1-T2-R or T2-R-T1. In addition, up to 4 replacement subjects may be included. There will be a washout period of at least 12 days between the treatments.

For details of dosage and formulation see Table 6.1:1 and Table 6.1:2 below.

Table 6.1: 1 Labels for treatments for use in the CTR – Part I

Dose group	Sort order	Treatment		Short label
1, 2, 9	1	P*	Placebo, oral solution, po, qd	Placebo os
3-8, 11	2	R*	Placebo, capsule, qd	Placebo cap
1	3	A	BI 706321, oral solution, 0.3 mg, qd	BI 0.3mg os
9	4	I	BI 706321, oral solution, 0.6 mg, qd	BI 0.6mg os
2	5	B	BI 706321, oral solution, 1.2 mg, qd	BI 1.2mg os
11	6	K	BI 706321, capsule, 2*1 mg, qd	BI 2mg cap
3	7	C	BI 706321, capsule, 4*1 mg, qd	BI 4mg cap
4	8	D	BI 706321, capsule, 8*1 mg, qd	BI 8mg cap
5	9	E	BI 706321, capsule, 3*5 mg, qd	BI 15mg cap
6	10	F	BI 706321, capsule, 5*5 mg, qd	BI 25mg cap
*7***	*11*	*G*	*BI 706321, capsule, 2*20 mg, qd*	*BI 40mg cap*
*8***	*12*	*H*	*BI 706321, capsule, 3*20 mg, qd*	*BI 60mg cap*

*: The placebo group in the safety evaluation will consist of all placebo treated subjects, regardless of the dose group in which they were treated, but separated by pharmaceutical formulation (capsule and oral solution).
**: Dose groups 40 mg and 60 mg will only be dosed after approval of a substantial amendment.

Table 6.1: 2 Labels for treatments for use in the CTR – Part II

Treatment		Short label	Test/Reference
X	BI 706321, tablet, 2*2mg, qd, fasted	BI tab fasted	T1
Y	BI 706321, tablet, 2*2mg, qd, fed	BI tab fed	T2
Z	BI 706321, capsule, 4*1mg, qd, fasted	BI cap fasted	R

The following separate study phases will be defined for the analyses of AEs:

Part I:

- **Screening** (ranging from 0:00h (midnight) on day of informed consent until first administration time of study drug (BI 706321 or Placebo))
- **On treatment**
  - **BI/Placebo treatment** (separately for each treatment, ranging from the time of administration of BI 706321/Placebo until 0.00 h (midnight) on the day after trial completion date (planned 15-22 days after administration of BI 706321/Placebo)

Part II:

- **Screening** (ranging from 0:00h (midnight) on day of informed consent until first administration time of study drug in first study period (BI 706321))
- **On treatment**
  - **BI treatment** (labelled 'BI tab fasted', 'BI tab fed', 'BI cap fasted') (separately for each treatment, ranging from the time of first administration of BI 706321 in each period until next administration or 0.00 h (midnight) on the day after trial completion date, whatever occurs first)

Please note that all AEs reported between start of trial drug administration until end of individual's trial or until starting next treatment period will be considered on-treatment. Hence, on-treatment is defined until at least 15 days (Part I) and at least 8 days (Part II) after first treatment administration.

The following AE displays will be provided in the report:

Section 15.3 and Appendix 16.1.13.1.8 (for ClinicalTrials.gov and EudraCT) of the CTR displays:

In these displays, the on treatment phase will be analysed (labelled with the name of the study treatment (short label)). Screening will not be included in this analysis.

In section 15.3, the following totals will be provided in addition:

- a total over all BI treated phases ("**BI Total**") – Part I only
- a total over all placebo treated phases ("**Plc Total**") – Part I only
- a total over all on treatment phases included in this analysis ("**Total**")

In outputs for ClinicalTrials.gov and EudraCT both study parts will be combined in one table and the following totals will be provided:

- a total over all BI treated phases of Part I ("**BI Total Part I**")
- a total over all placebo treated phases ("**Plc Total**")
- a total over all on treatment phases of Part I ("**Total Part I**")
- a total over all BI treated phases of Part II ("**BI Total Part II**")
- a total over all on treatment phases included in this analysis ("**Total**")

In Section 15.4 and Appendix 16.2.7 (Listings) of the CTR displays screening will be included and no totals will be provided.

Tables of vital signs, ECG and laboratory values will present results by the above mentioned on treatment phase.

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.

Section 7.3 of the CTP: *Important protocol* deviation (IPD) *categories will be specified in the TSAP,* IPDs *will be identified no later than in the Report Planning Meeting, and the* IPD *categories will be updated as needed.*

Consistency check listings (for identification of deviations from time windows) and a list of protocol deviations (e.g. deviations in drug administration, in blood sampling times, etc.) will be provided to be discussed at the combined report planning and database lock meeting (RPM/DBLM). At this meeting, all manual deviations identified at the sites by the Clinical Research Associate (CRAs) and deviations too complex to program will be reviewed by the trial team to decide which are considered important. For definition of iPDs, and for the process of identification of these, refer to the Boehringer Ingelheim (BI) Standard Operating Procedure (SOP) "Identify and Manage Important Protocol Deviations (iPD)" (2).

If any iPDs are identified, they are to be summarised into categories and will be captured in the RPM minutes (decision log) via an accompanying Excel spreadsheet (3).

The iPDs will be summarised and listed.

Table 6.2: 1 below specifies which kind of iPDs could potentially lead to exclusion from which analysis set. The decision on exclusion of patients from analysis sets will be made at the latest at the Report Planning Meeting, after discussion of exceptional cases and implications for analyses.

Table 6.2: 1 Handling of iPDs

iPD code	iPD Category & Brief Description	Excluded from which analysis set
iPD A1	Inclusion Criteria Not Met	PKS, PDS, ECGPCS
iPD A2	Exclusion Criteria Met	PKS, PDS, ECGPCS
iPD B1	Informed consent not available/not done	All
iPD B2	Informed consent too late	None
iPD B3	Wrong informed consent form signed	All
iPD C1	Randomisation not followed	PKS, PDS, ECGPCS
iPD C2	Non-compliance	PKS, PDS, ECGPCS
iPD C3	Incorrect preparation (e.g. incorrect reconstitution of oral solution), administration or intake of trial medication	PKS, PDS, ECGPCS
iPD C4	Improper washout between treatments (Part II)	PKS, PDS, ECGPCS
iPD D1	Prohibited medication use	PKS, PDS, ECGPCS
iPD D2	Improper washout of prohibited concomitant medication	PKS, PDS, ECGPCS
iPD E1	Certain deviations from procedures used to measure primary or secondary data	PKS, PDS, ECGPCS
iPD F1	Certain deviations of time schedule used to measure primary or secondary data	PKS, PDS, ECGPCS
iPD G1	PDs affecting efficacy, safety and rights of subjects	PKS, PDS, ECGPCS
iPD Q1	Missed examination	PKS, PDS, ECGPCS
iPD Q2	Missed visit	PKS, PDS, ECGPCS
iPD Q3	Drug shipment	PKS, PDS, ECGPCS

6.3 SUBJECT SETS ANALYSED

Section 7.3 of the CTP: *For both trial parts, statistical analyses will be based on the following analysis sets:*

- *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* […] *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.*

[redacted]

[…]

Pharmacokinetics

[…]

Plasma and urine (in part I of the trial) 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 (in part I) 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.*

In addition, plasma concentrations and/or parameters of a subject will be considered as nonevaluable in the BA part of the trial, if for example

- *The subject experiences emesis at any time during the labelled dosing interval.*
- *A predose concentration is >5% C_{max} value of that subject*

[…]

All ECG analyses in Part I are performed on the TS, except for the exposure-response analyses, which are performed on the ECGPCS defined below. The exposure-response analysis will only be performed if relevant findings for ECG parameters are found (the decision will be made during RPM).

- ECG Pharmacokinetic Concentration Set (ECGPCS):
  This subject set includes all subjects of part I from the TS who provide at least one pair of a valid drug plasma concentration of BI 706321 and a corresponding (i.e. time-matched) ECG endpoint to be used in the exposure-response analyses. For placebo subjects, the plasma concentration is set to zero and hence always considered as valid. The decision whether a time deviation between PK blood sampling and ECG recording is acceptable (and thus whether the pair of values will be used) is to be made no later than at the RPM before data base lock.

Table 6.3: 1 Analysis sets for endpoints/data description

Endpoint/data description	TS	PKS	[redacted]	ECGPCS
Primary and further safety endpoints (incl. ECG)	X			
[redacted]			[redacted]	
ECG endpoints and plasma concentrations used in exposure-response analysis (Part I only) – if needed				X
Primary/Secondary/[redacted] endpoints		X		
Demographic/baseline data	X			
Important protocol deviations	X			
Disposition	X			

[redacted]

6.5 POOLING OF CENTRES

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

6.6 HANDLING OF MISSING DATA AND OUTLIERS

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

The only exceptions where imputation might be necessary for safety evaluation are AE dates. Missing or incomplete AE dates are imputed according to BI standards (see 001-MCG-156_RD-01 (4)).

Missing data and outliers of PK/[redacted] are handled according to BI standards (see 001-MCS-30-476) (5).

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 Appendix Section 9.1.3.

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

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

The baseline value is defined as the last measurement before first administration of BI 706321 or Placebo in each treatment period.
The baseline for analysis of laboratory data is the last measurement before first administration of study drug (e.g. ptm -1:30 (part I), screening (part II)).

Section 6.1 of the CTP: *Exact times of measurements outside the permitted time windows will be documented. The acceptable time windows for screening and the end of trial examination are provided in the* CTP *Flow Chart.*

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 and biomarkers).

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, and ± 120 min from 48 h post administration onwards.

[…] Starting from 48 h post administration a deviation from the scheduled time for PK [redacted] sampling of ± 120 min is acceptable.

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

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

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

Visit	Day	Planned time [hh:mm] (relative to drug administration)	Study phase	Central evaluation
1	-21 to -1		Screening	NA
2	1	-02:00	Baseline	All 3 single ECGs
		-01:45		
		-01:30		
		00:30	On treatment	Single ECG
		01:00		Single ECG
		01:30		Single ECG
		02:00		Single ECG
		02:30		Single ECG
		03:00		Single ECG
		04:00		Single ECG
		08:00		Single ECG
		12:00		Single ECG
	2	24:00		Single ECG
		34:00		NA (dose groups 1, 2, 9, 11) Single ECG (dose groups 3-8)
	3	48:00		NA (dose groups 1, 2, 9, 11) Single ECG (dose groups 3-8)
3	15 to 22		End of trial examination	NA

At Visits 1 and the End of trial examination single ECGs will be recorded, as well as at visit 2. At visit 2 ECGs will be centrally evaluated.
All single ECGs will be transferred to the database. The baseline value of an ECG variable is defined as the mean of the transferred baseline ECG measurements prior to drug administration.

Section 5.2.4.1 of the CTP: *Central ECG lab evaluation will be performed post-study per time point indicated in the* CTP *Flow Chart. For baseline, all 3 ECGs will be evaluated.*

This will include the determination of cardiac QRS-axis as assessed by the ECG machine's algorithm as well as the intervals RR, PR, QRS and QT measured semi-automatically. […].

For the exposure response analyses, pairs of ECG variables and corresponding plasma concentrations will be built using the same planned time points, e.g. 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.

7. PLANNED ANALYSIS

The placebo group in the safety evaluation will consist of all placebo treated subjects, regardless of the dose group in which they were treated but separated by pharmaceutical formulation (capsule and oral solution).

Trial Parts will be reported separately if not otherwise stated.

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.

Inferential statistical analyses of PK endpoints (refer to Section 7.5.2) will also be performed by [redacted] and will be presented in Section 15.5 of the CTR and in Appendix 16.1.13.3.

Descriptive data analysis of PK [redacted] parameters and concentrations will be performed by the department [redacted] at [redacted] and will be presented in Sections 15.6 and 15.7 of the CTR and in Appendices 16.1.13.5 and 16.1.13.6.

The format of the listings and tables will follow the standards defined in the BI corporate guideline "Reporting of Clinical Trials and Project Summaries" [001-MCG-159] (6) with the exception of those generated for PK-calculations.

The individual values of all subjects will be listed, sorted by treatment group (Part I) / treatment sequence (Part II), subject number, and visit and actual treatment (Part II). The listings will be included in Appendix 16.2 of the CTR.

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, the following descriptive statistics will additionally be calculated:

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

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

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 with the data format of the respective concentrations. The descriptive statistics of PK parameters will be calculated using the individual values with the number of decimal places as provided by the evaluation program. Then the individual values as well as the descriptive statistics will be reported with three significant digits in the CTR.

Tabulations of frequencies for categorical data will include all possible categories and will display the number of observations in a category, as well as the percentage (%) for each treatment group. 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 square brackets (e.g. [mg]).

Exclusion of PK parameters

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

Exclusion of PK concentrations

The ADS ADPC (PK concentrations per time-point or per time-interval) contains column variables ACEXC or ACEXCO indicating inclusion/exclusion (ACEXC) of a concentration and an analysis flag comment (ACEXCO). Exclusion of a concentration depends on the analysis flag comment ACEXCO. For example, if ACEXCO is set to ‘ALL CALC’, the value will be excluded for all types of analyses based on concentrations. If ACEXCO is set to ‘DESC STATS’, the value will be excluded from descriptive evaluations per planned time point/time interval. If ACEXCO contains the addition ‘TIME VIOLATION’ or ‘TIME DEVIATION’, the value can be used for further analyses based on actual times. If ACEXCO is set to ‘HALF LIFE’, the value will be excluded from half-life calculation (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 001-MCS-30-476 “TMCP Data Analysis” (5).

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Only descriptive statistics are planned for this section of the report, based on the TS.

For trial part I, the data will be summarised by treatment group and in total.
For trial part II, the data will be summarised by treatment sequence 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 latest version of the coding system of the Medical Dictionary for Drug Regulatory Activities (MedDRA). Medications will be coded using the latest version of 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 should 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/DBLM.

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 the 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/DBLM (cf. TSAP Section 6.2) and described in the CTR.

7.4 PRIMARY ENDPOINTS

Part I:
Refer to TSAP Section 7.8 for a description of the analysis of safety and tolerability of BI 706321 (primary endpoint of Part I).

Part II:
Section 7.2 of the CTP: *The relative bioavailability of BI 706321 tablets compared with BI 706321 capsules*, as well as the food effect comparison on tablets, *will be estimated by the ratios of the geometric means (Test 1/Reference; Test 2/Test 1), and their corresponding 2-sided 90% confidence intervals (CIs) will be provided.*

Section 7.3.1 of the CTP: *The primary endpoints (refer to Section 5.1) will be calculated according to the BI Standard Operating Procedure (SOP) 'Standards and processes for analyses performed within Clinical Pharmacokinetics/ Pharmacodynamics' (001-MCS-30-476)* (5).

The statistical model used for the analysis of the primary endpoints will be an analysis of variance (ANOVA) model on the logarithmic scale. That is, the PK endpoints will be log-transformed (natural logarithm) prior to fitting the ANOVA model. This model will include effects accounting for the following sources of variation: sequence, subjects within sequences, period and treatment. The effect 'subject within sequences' will be considered as random, whereas the other effects will be considered as fixed. The model is described by the following equation:

$y_{ijkm} = \mu + \zeta_i + s_{im} + \pi_j + \tau_k + e_{ijkm}$, *where*

y_{ijkm} = *logarithm of response measured on subject m in sequence i receiving treatment k in period j,*

μ = *the overall mean,*

ζ_i = *the* i^{th} *sequence effect,* $i = 1, 2$

s_{im} = *the effect associated with the* m^{th} *subject in the* i^{th} *sequence,* $m = 1, 2, ..., n_i$

π_j = *the* j^{th} *period effect,* $j = 1, 2$

τ_k = *the* k^{th} *treatment effect,* $k = 1, 2,$

e_{ijkm} = *the random error associated with the* m^{th} *subject in sequence i who received treatment k in period j.*

where $s_{im} \sim N(0, \sigma_B^2)$ *i. i. d. ,* $e_{ijkm} \sim N(0, \sigma_W^2)$ *i.i.d. and* s_{im}, e_{ijkm} *are independent random variables.*

Point estimates for the ratios of the geometric means (test/reference) for the primary endpoints and their two-sided 90% confidence intervals (CIs) will be provided.

For each endpoint, the difference between the expected means for log(T)-log(R) will be estimated by the difference in the corresponding adjusted means (Least Squares Means). Additionally their two-sided 90% confidence intervals will be calculated based on the residual error from the ANOVA and quantiles from the t-distribution. These quantities will then be back-transformed to the original scale to provide the point estimate and 90% CIs for each endpoint.

[redacted]

In addition to the model-based approach all parameters will be calculated and analysed descriptively.

7.5 SECONDARY ENDPOINTS

7.5.1 Key secondary endpoints

This section is not applicable as no key secondary endpoints have been specified in the protocol.

7.5.2 Secondary endpoints

Section 7.3.2 of the CTP:

Primary analyses

Part I:
The secondary endpoints (refer to Section 5.2.2) will be analysed descriptively. Analyses will be performed for the parent drug.

Part II:
The PK endpoint $AUC_{0-\infty}$ will be assessed statistically using the same methods as described for the primary endpoint in part II.

[redacted]

[redacted]

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.

If not stated otherwise, the safety results will be sorted by treatment group (Part I) / treatment sequence (Part II).

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 with the most recent version of MedDRA.

The analyses of AEs will be descriptive in nature and will be based on BI standards as presented in the corporate guideline: “Analysis and Presentation of Adverse Event Data from Clinical Trials” [BI-KMED-BDS-HTG-0041] (7).

The standard AE analyses will be based on the number of subjects with AEs (and not on the number of AEs).

No collapsing and condensing of adverse event episodes is planned.

For further details on summarization of AE data, please refer to [001-MCG-156] (7).

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 aminotransferase) and/or ALT (alanine aminotransferase) ≥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*

  These lab findings constitute a hepatic injury alert, and the subjects showing these lab abnormalities need to be followed up according to the 'DILI checklist' provided in the ISF. In case of clinical symptoms of hepatic injury (icterus, unexplained encephalopathy, unexplained coagulopathy, right upper quadrant abdominal pain, etc.) without lab results (ALT, AST, total bilirubin) available, the Investigator should make sure that these parameters are analysed, if necessary in an unscheduled blood test. Should the results meet the criteria of hepatic injury alert, the procedures described in the DILI checklist should be followed.

The analysis of adverse events will be based on the concept of treatment emergent adverse events. That means that all AEs will be assigned to screening or on-treatment phases as defined in Section 6.1. AEs will be analysed based on actual treatments, as defined in Table 6.1: 1 and Table 6.1: 2.

Section 1.2.2 of the CTP: *The Residual Effect Period (REP) is the period after the last dose with measurable drug levels and/or pharmacodynamic effects still likely to be present. For BI 706321, a residual effect period has been determined at 8 days based on Part I. In Part 1, the conservatively, a minimum observation period of 2 weeks has been selected, i.e. the individual subject's end of trial is on day 15 following dosing at the earliest (see* CTP *Flow Chart). In Part II it is at 8 days.*

Nevertheless, all *AEs reported between administration of BI 706321 and the individual subject's end of trial will be counted as on-treatment AEs.*

According to ICH E3 (8), in addition to Deaths and Serious Adverse Events, 'other significant' AEs need to be listed in the clinical trial report. These will be any non-serious adverse event that led to an action taken with study drug (e.g. discontinuation or dose reduced or interrupted).

An overall summary of adverse events will be presented.

The frequency of subjects with AEs will be summarised by treatment, primary system organ class and PT. Separate tables will be provided for subjects with SAEs, for subjects with drug-related AEs, for subjects with drug-related serious AEs, for subjects with AESIs and for

subjects with AEs leading to treatment discontinuation. 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 by frequency, 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 [001-MCG-157] (9).

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 possible clinically significant will be flagged in the data listings.

It is the investigator's responsibility to decide whether a lab value is clinically significant abnormal or not (at the RPM/DBLM at the latest).

7.8.3 Vital signs

Descriptive statistics over time including change from baseline will be performed for vital signs (blood pressure, pulse rate; and oral body temperature (part I)).

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 – part I only

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 set.

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 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.

For QTcF and HR changes from baseline, the relationship to the corresponding plasma concentrations will be evaluated using a random coefficient model. For subjects in the ECGPCS, all time points with available ECG endpoints and valid time-matched drug plasma concentrations will be included. For the handling of missing values, see Section 6.6.

The response variable will be the change from baseline in QTcF (ΔQTcF). The placebo subjects will be included in the analysis ('Plc Total'), setting their plasma concentrations to zero.

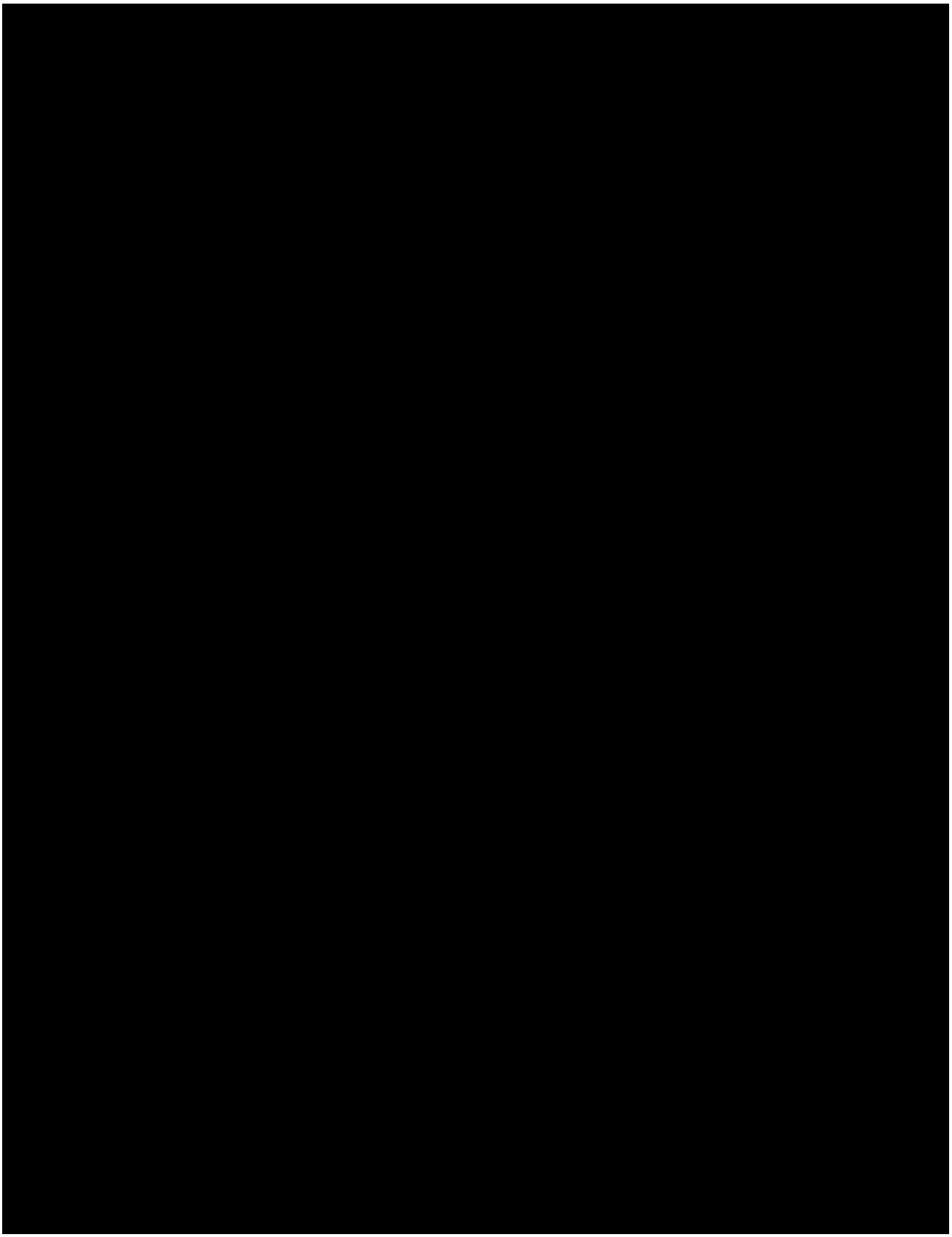
As a first step, it is investigated if there is a potential delayed or accelerated (e.g. due to metabolites) effect of the drug on QTcF. A general visual impression is provided by overlaying time profiles of plasma concentrations and QTcF changes from baseline (ΔQTcF). These figures will be generated for each subject (presented in Statistical Appendix of the CTR), as well as for means per treatment group (presented in the End-of-Text part of the CTR).

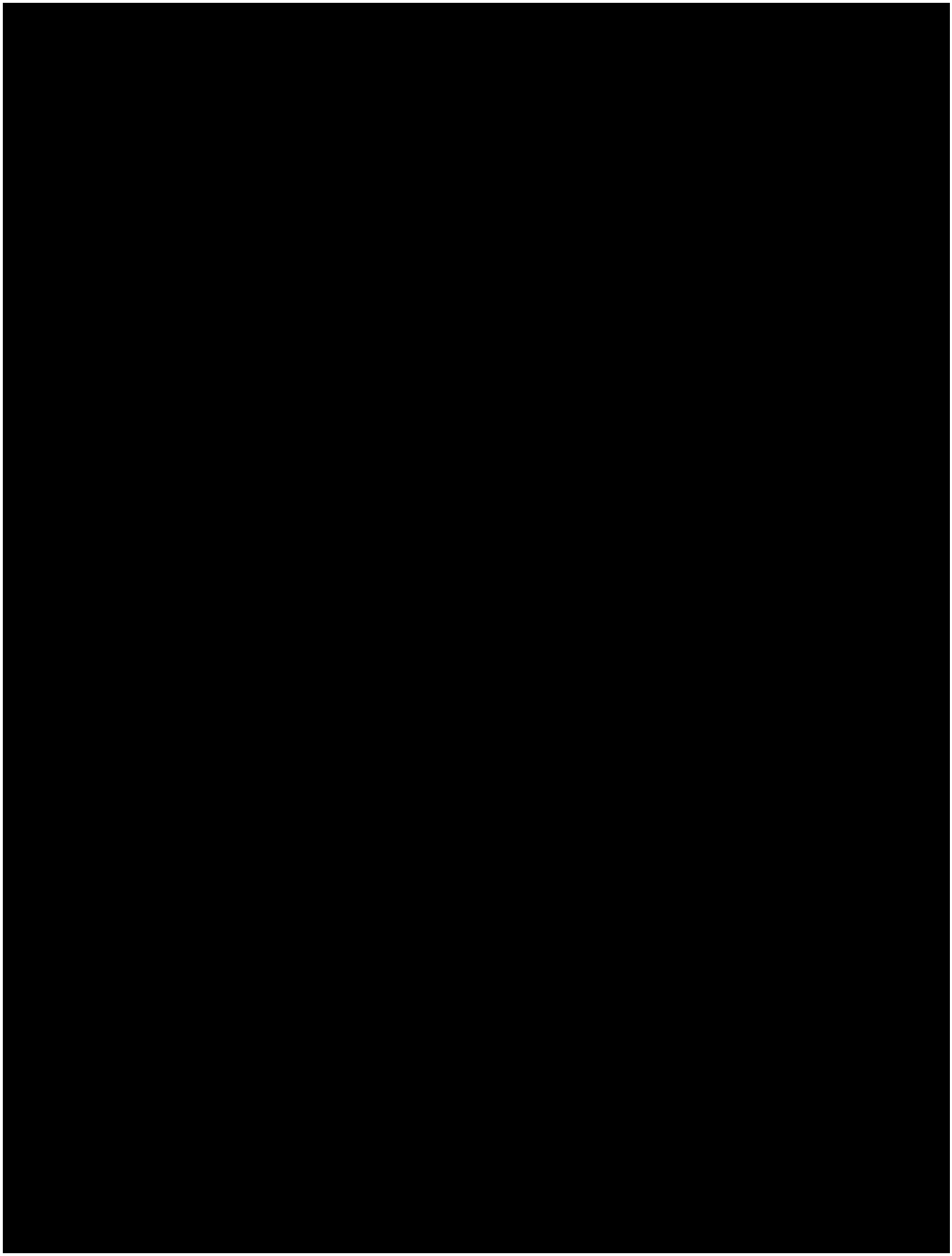
Appropriateness of heart rate correction methods of QT interval

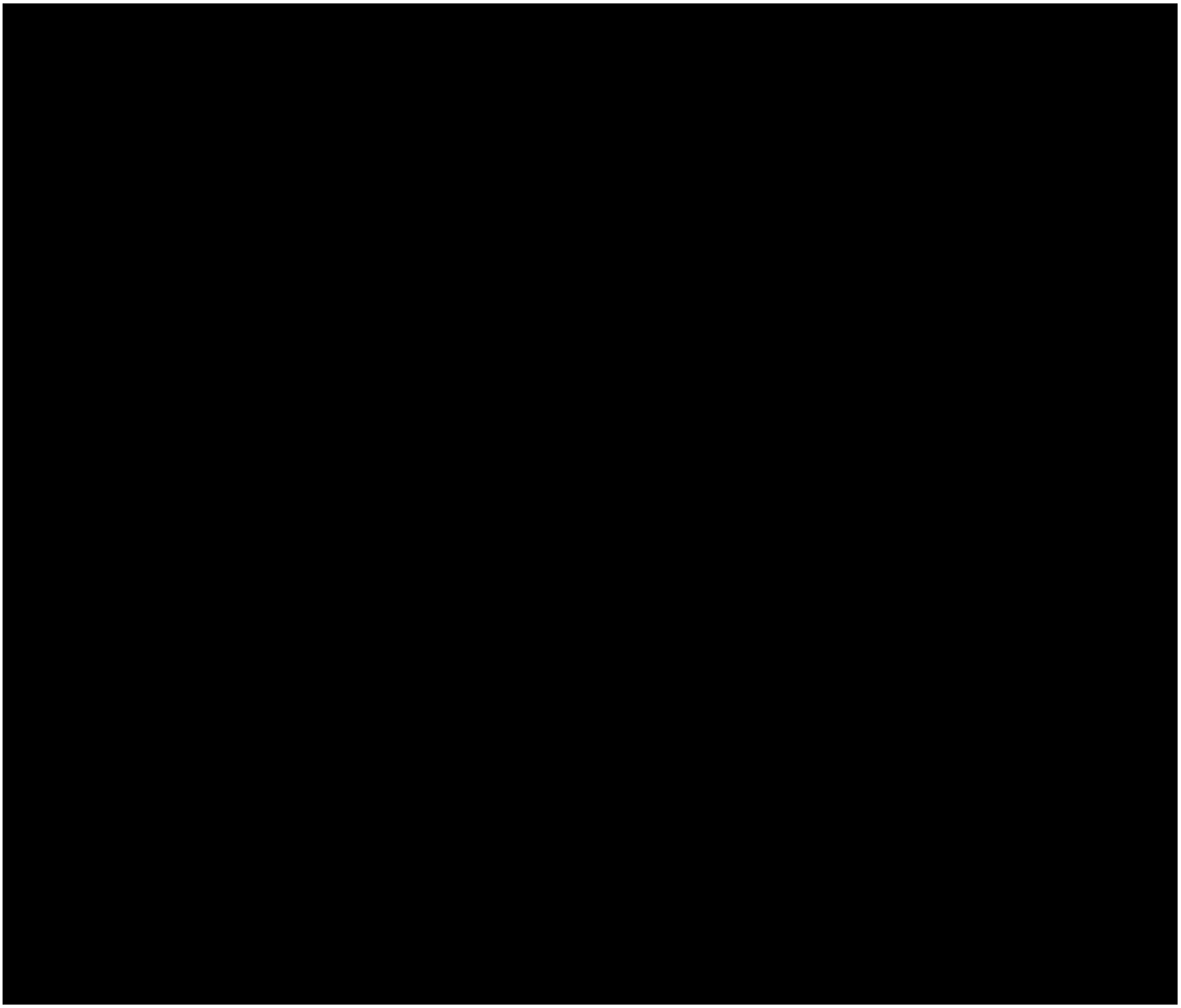
To evaluate the appropriateness of the heart rate correction methods, the slope of the relationship of QTcF interval versus RR interval will be estimated separately for off-drug values and active treatment by applying the random coefficient model described in Section 9.1.2 using the QTcF and RR variable values per time point. A scatterplot of QTcF vs RR including the overall regression line will be included in the Statistical Appendix of the CTR.

8. 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, BIRDS
3.	*BI-KMED-BDS-TMP-0059:* "iPD specification document (sdtm-dv-domain-specification)", version 1.6; KMED
4.	*001-MCG-156_RD-01:* "Handling of Missing and Incomplete AE Dates", current version; IDEA for CON.
5.	*001-MCS-30-476*: "TMCP Data Analysis", current version; IDEA for CON.
6.	*001-MCG-159*: "Reporting of Clinical Trials and Project Summaries", current version; IDEA for CON.
7.	*001-MCG-156*: "Analysis and Presentation of Adverse Event Data from Clinical Trials", current version; IDEA for CON.
8.	*CPMP/ICH/137/95*: "Structure and Content of Clinical Study Reports", ICH Guideline Topic E3; Note For Guidance on Structure and Content of Clinical Study Reports, current version
9.	*001-MCG-157*: "Handling, Display and Analysis of Laboratory Data", current version; IDEA for CON.
10.	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 [R18-0143]
11.	BI Statistical Position Paper - Statistical Methods for PK - Reference Document 3: Regulatory recommendations for BA/BE trials and implementation instructions in clinical trial documents, version 1.0 (2017).
12.	Ring A. Statistical models for heart rate correction of the QT interval. Stat Med 2010 [R10-2920]







10. HISTORY TABLE

Table 10: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
1	14-JAN-21	[redacted]	None	This is the final TSAP without any modification