TRIAL STATISTICAL ANALYSIS PLAN

c37170840-01

BI Trial No.:	1411-0012
Title:	Safety, tolerability, and pharmacokinetics of single rising oral doses of BI 474121 in healthy Japanese male subjects (double-blind, randomised, placebo-controlled, parallel group design) (Revised Protocol including Amendment 1 [c33502183-02])
Investigational Product(s):	BI 474121
Responsible trial statistician(s):	[redacted] Phone: +[redacted] Fax: +[redacted]
Date of statistical analysis plan:	16 DEC 2021 SIGNED
Version:	1

1. TABLE OF CONTENTS

[redacted]

[redacted]

LIST OF TABLES

2. LIST OF ABBREVIATIONS

See Medicine Glossary:
http://glossary

Term	Definition / description
ADS plan	Analysis data set plan
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
BMI	Body mass index
CARE	Clinical data Analysis and Reporting Environment
CI	Confidence interval
C_{max}	Maximum measured concentration of the analyte in plasma
CV	Arithmetic coefficient of variation
ECGPCS	ECG Pharmacokinetic Concentration Set
EDMS	Electronic documentation management system
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
P10	10th percentile
P90	90th percentile
PDS	Pharmacodynamic parameter analysis set
PKS	Pharmacokinetic parameter analysis set
PT	Preferred term
Q1	1st quartile
Q3	3rd quartile
RAGe	Report Appendix Generator system
REP	Residual effect period

Term	Definition / description
RPM	Report planning meeting
SD	Standard deviation
SOC	System organ class
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 6.3 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.

5. ENDPOINTS

5.1 PRIMARY ENDPOINT

Section 2.1.2 of the CTP:

The primary endpoint for assessment of safety and tolerability of BI 474121 is the percentage (%) of subjects with drug-related adverse events.

5.2 SECONDARY ENDPOINTS

5.2.1 Key secondary endpoints

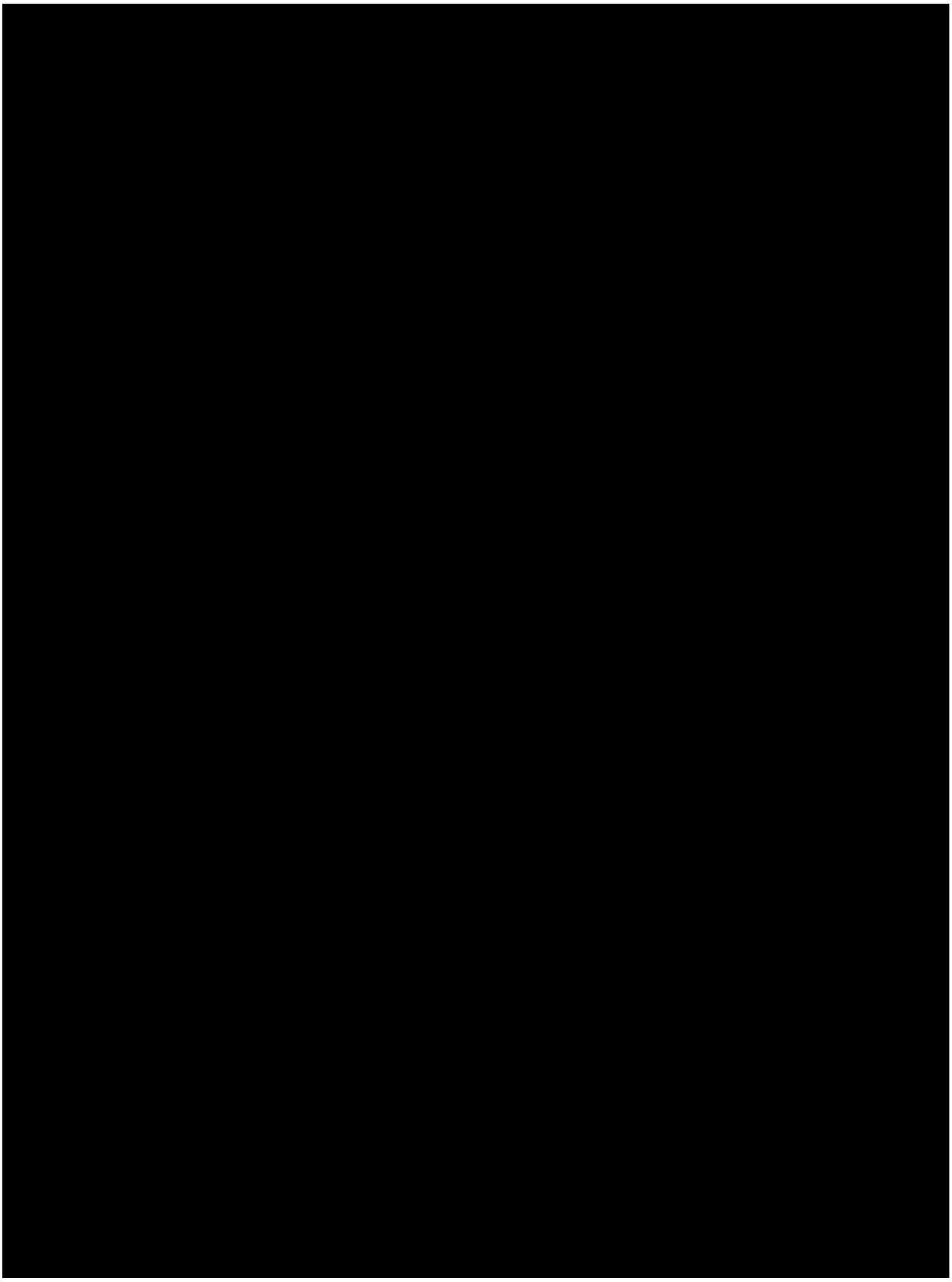
This section is not applicable as no key secondary endpoints have been defined in the CTP.

5.2.2 Secondary endpoints

Section 2.1.3 of the CTP:

The following pharmacokinetic parameters will be determined 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)*



6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENTS

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

It is planned that 32 healthy Japanese male subjects participate in this randomized, double-blind, placebo-controlled study. The subjects will be assigned to one of 4 dose groups consisting of 8 subjects per group, and will be randomized to placebo or active treatment within their dose group. Within each dose group, 6 subjects will receive a single dose of active drug and 2 subjects will receive a single dose of placebo.

Table 6.1: 1 Treatments and labels used in the analysis

Treatment	Label in dataset	Short label
P	Placebo#	Placebo
A	BI 474121, tablet, 2.5 mg, po, qd	BI 2.5mg
B	BI 474121, tablet, 2*2.5 mg, po, qd	BI 5mg
C	BI 474121, tablet, 10 mg, po, qd	BI 10mg
D	BI 474121, tablet, 2*10 mg, po, qd	BI 20mg

#For data analysis purposes, the placebo group will consist of all subjects treated with placebo, regardless of the dose group in which they were treated.

Section 1.2.7 of CTP:

The Residual Effect Period (REP) of BI 474121, when measurable drug levels and/or pharmacodynamic effects are still likely to be present, is not known. Conservatively (...) a REP of 7 days is assumed, i.e. the individual subject's end of trial is on Day 8-15 following dosing with investigational drug.

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

- **Screening** (ranging from 0:00h on day of informed consent until first administration of study medication)
- **On treatment** (ranging from the time of first administration of study medication (BI or Placebo) until 168 hours (7 days) after time of administration)

  ➔ Labelled Placebo, BI 2.5mg, BI 5mg, BI 10mg, BI 20mg
- **Follow-up (F/U)** (ranging from 168 hours (7 days) after administration of BI or Placebo until 0:00 h on the day after trial termination date)

  ➔ Labelled F/U

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

Displays of AEs will be stratified by dose group as specified in Table 6.1: 1. The following AE displays will be provided in the report:

Section 15.3 and Appendix 16.1.13.1.8 (for ClinicalTrials.gov) 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 and follow-up phases will not be included in this analysis. The following totals will be provided in addition (for 15.3 only, except for ECG):

- a total over all BI on treatment phases (**"BI Total"**),
- a total over all on treatment phases included in this analysis (**"Total"**).

In Section 15.4 and Appendix 16.2 (Listings) of the CTR displays, screening and follow-up periods will 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 iPD specification file prior to trial initiation. 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 (i.e. the DV domain specifications) and the decision log. Handling of iPDs in the analysis is included in the DV domain specifications and 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 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 '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.*

- *Pharmacodynamic parameter analysis set (**PDS**): This set includes all placebo subjects and all subjects included in the PKS.*

(…)

Pharmacokinetics
(…)

Plasma and urine 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 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 violations 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.*

All ECG analyses are performed on the TS, except for the exposure-response analyses, which are performed on the ECGPCS defined below.

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

Table 6.3: 1 Subject sets analysed

	Subject analysis set			
Class of endpoint	TS	PKS	PDS	ECGPCS
Primary endpoint and further safety assessments (incl. ECG)	X			
Analyses of PK endpoints		X		
Analyses of PD/biomarker endpoints			X	
ECG exposure response analysis				X
Demographic/baseline parameters	X			
Important protocol deviations	X			
Disposition	X			
Exposure	X			

[redacted]

6.5 POOLING OF CENTRES

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

6.6 HANDLING OF MISSING DATA AND OUTLIERS

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).

[redacted]

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.

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

The baseline value is defined as the last measurement before administration of trial medication (BI 474121 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 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, start of first RR measurement in orthostatic tests, 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 and biomarker sampling as well as for AE questioning of ± 120 min is acceptable.

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

Unscheduled measurements of laboratory data, orthostatic testing 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:

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

Visit	Day	Planned time [hh:mm] (relative to drug administration)	Study phase	Central evaluation
1	-28 to -1		Screening	NA
2	1	-01:00	Baseline	First ECG of each of the 3 triplicate baselines
		-00:45		
		-00:30		
		00:30	On treatment	First single ECG of the triplicate
		01:00		
		01:30		
		02:00		
		03:00		
		04:00		
		06:00		
		08:00		
		12:00		
	2	24:00		
		34:00		
	3	48:00		
	4	72:00		Single ECG
	5	96:00		Single ECG
3	8 to 15		End of trial examination	NA

At Visits 1 and 3 (screening 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 (except for ECGs on day 4 and 5 of Visit 2), 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 plasma concentrations will be built using the same planned time points, e.g., the HR change from baseline and the plasma concentration measured at planned time 0:30 will build one pair. Whether a time deviation between PK blood sampling time and corresponding ECG recording is too big 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.
In line with the tolerated time deviations of previous trials in this project, the acceptable maximum time deviations between ECG recordings and plasma concentration sampling are proposed to be

- 10 minutes for up to 1 hours (including) after dosing,
- 20 minutes for time points from more than 1 hour to 12 hours after dosing, and
- 60 minutes for time points at 12 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.

As the clinical trial protocol permits larger time deviations of ECG measurements from the planned time in the flow chart, and consequently indirectly accepts larger time deviations of ECG and PK sampling, a sensitivity analysis will be done. For the sensitivity analysis, the acceptable maximum time deviation between ECG recording and plasma concentration sampling are proposed to be

- 15 minutes for up to 4 hours (including) after dosing,
- 30 minutes for time points from more than 4h to 24h after dosing,
- 60 minutes for time points at 24h to 48h after dosing,
- 120 minutes for time points at 48 hours or later after dosing.

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 endpoints will 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 endpoints and concentrations will be performed by the [redacted] at [redacted] and will be presented in Section 15.6 of the CTR and in Appendix 16.1.13.5.

Descriptive data analysis of PD/biomarker parameters will be performed by [redacted] and will be presented in Section 15.7 of the CTR and Appendix 16.1.13.6.

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 inferential statistical interim analysis is planned.

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

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

For analyte concentrations, PK and PD 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 and PD 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 and PD parameters

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

Exclusion of PK and PD concentrations

The ADS "ADPC" (PK concentrations per time-point or per time-interval) and "ADYC" (PD concentrations per time-point or per time-interval) contains column variables ACEXC and 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 *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 endpoints

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.*

[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 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 with the most recent version of MedDRA.

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' or 'follow-up' phases as defined in Section 6.1. AEs will be analysed based on actual treatments, as defined in Table 6.1: 1.

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 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). 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.

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, which means transforming to a standard unit and a standard reference range. The original values will be analysed if the transformation into standard unit is not possible for a parameter.

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 and pulse rate). In the listing the change 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), and will be displayed by treatment and in total.

Descriptive statistics over time including change from baseline (by treatment and in total) will also be provided for the orthostatic test results to enable checking of orthostatic hypotension occurrence. Subjects should have spent at least 5 minutes in the supine position before blood pressure and pulse rate will be measured the first time. Further 2 measurements will be performed immediately after standing up and after 3 minutes in a standing position. An orthostatic hypotension is defined as a decline in systolic blood pressure of $\geq$ 20 mmHg or a decline in diastolic blood pressure of $\geq$ 10 mmHg within the first three minutes after standing up. Orthostatic hypotension is assessed for all post dose time points.

Body temperature will be listed only.

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 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 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.

For QTcF and HR changes from baseline, the relationship to the corresponding plasma concentrations will be evaluated using a random coefficient model. For subjects in the ECGPCS, all time points with available ECG endpoints and valid time-matched drug plasma concentrations will be included. For the handling of missing values, see Section 6.6.
The response variable will be the change from baseline in QTcF (ΔQTcF). The placebo subjects will be included in the analysis, setting their plasma concentrations to zero.

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

The relationship between BI 474121 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 474121 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 474121 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.

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.

7.8.5 Others

Physical examination

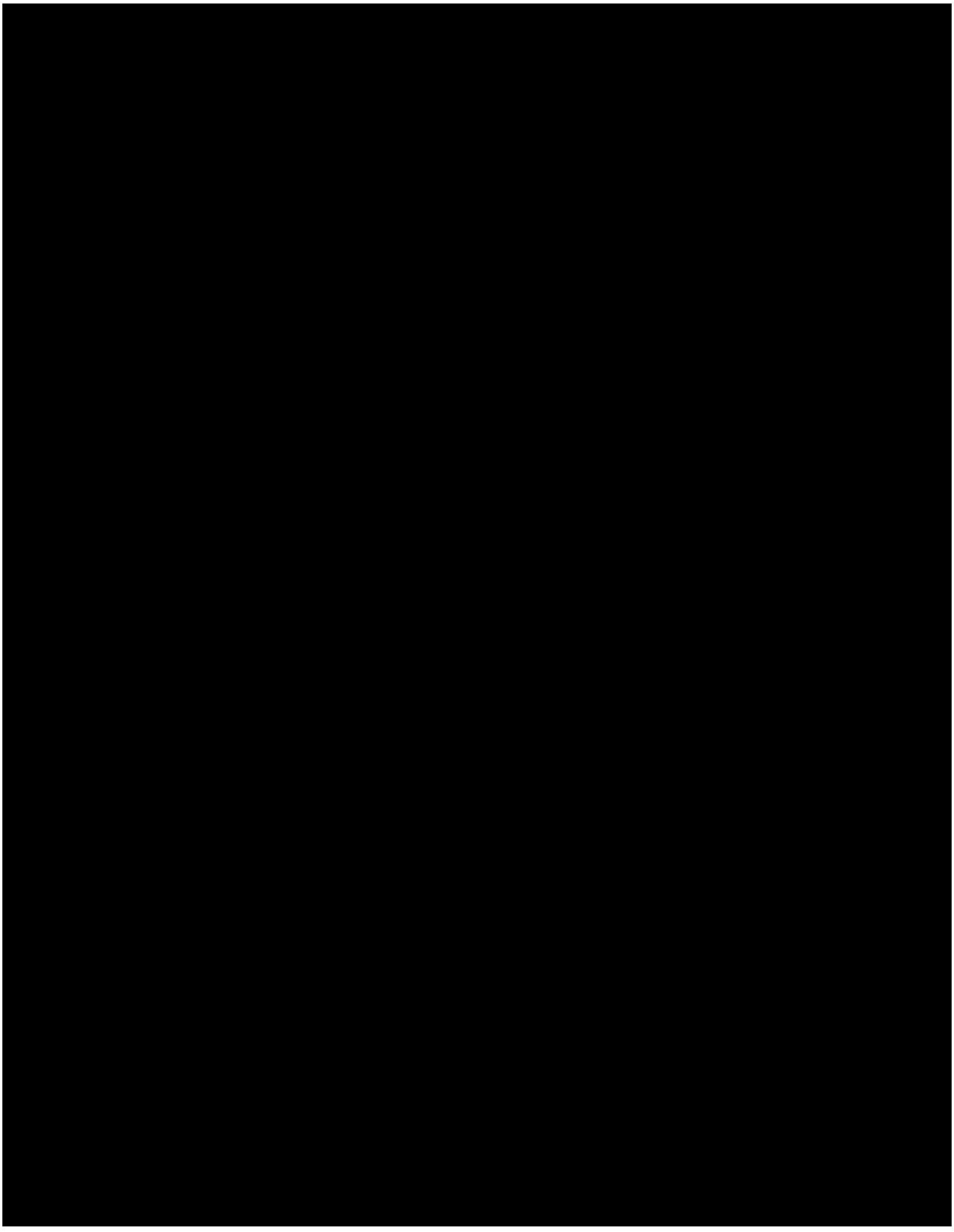
Physical examination findings will be reported as relevant medical history/baseline condition (i.e., a condition already existent before intake of study drug) or as AE and will be summarised as such.
No separate listing or analysis of physical examination findings will be prepared.

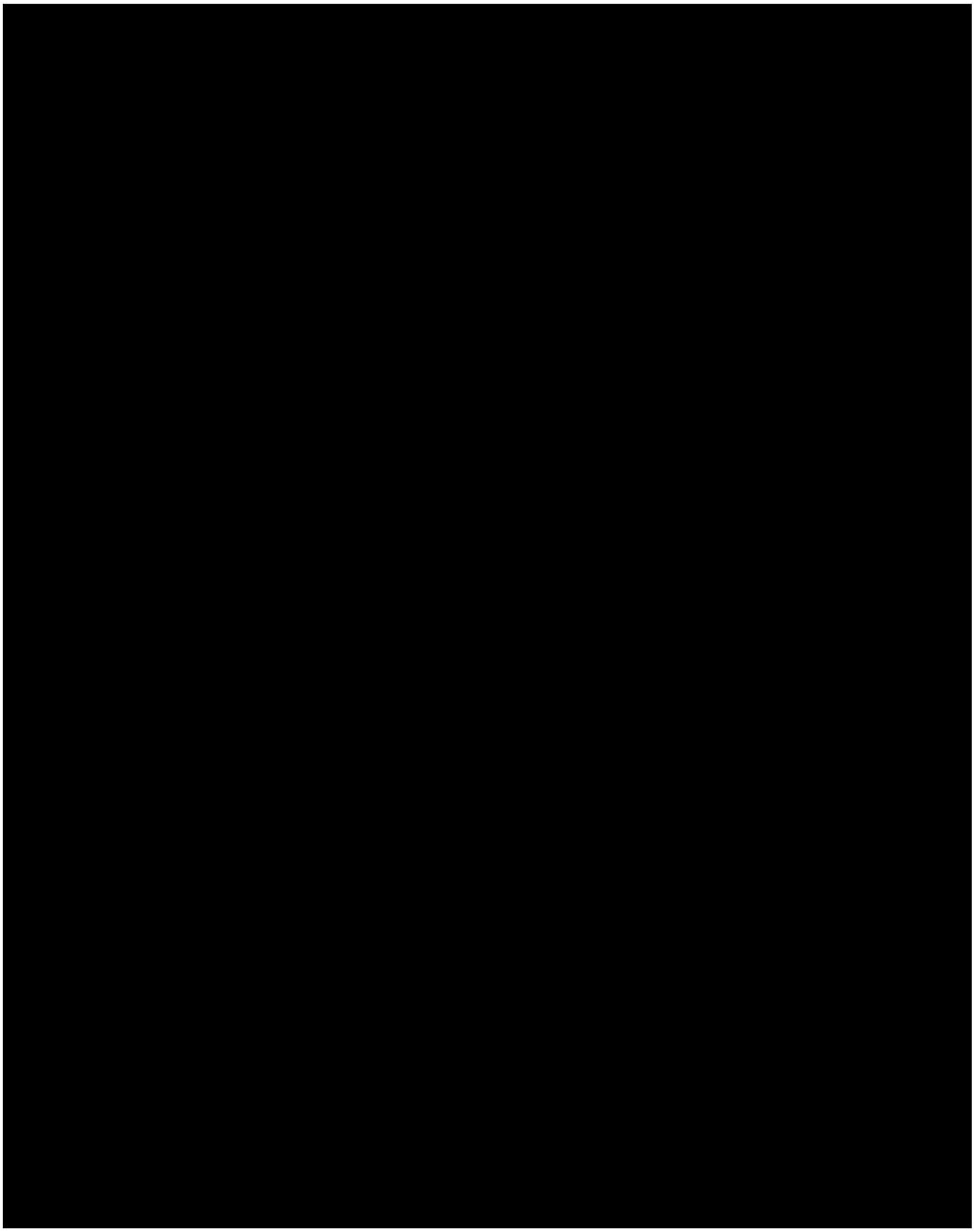
8. TIMEPOINT OF RELEASE OF TREATMENT INFORMATION

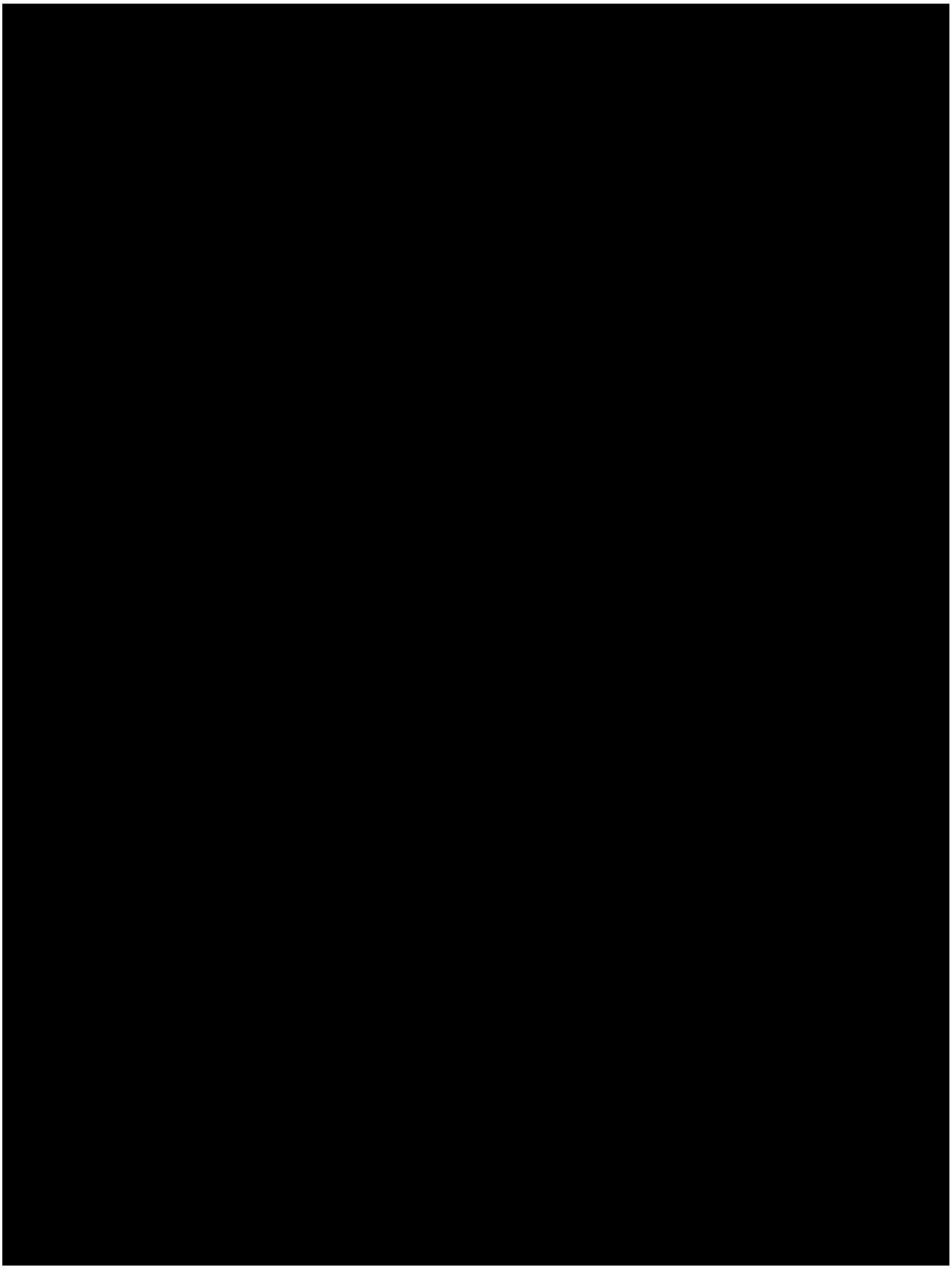
This trial was double-blind, but was handled open label regarding trial functions of the sponsor (including clinical trial leader, data manager, statistician, bioanalyst, pharmacokineticist, pharmacometrician, drug metabolism scientist as well as dedicated contract research organization (CRO) personnel).
The treatment information was loaded into the trial database once all subjects in a dose group were 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-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	**16-DEC-21**	[redacted]	None	This is the final TSAP.