TRIAL STATISTICAL ANALYSIS PLAN

c34992306-01

BI Trial No.:	1411-0001
Title:	A randomised, single-blind, placebo-controlled trial to investigate safety, tolerability, and pharmacokinetics of single rising oral doses of BI 474121 administered as oral solution and tablets to healthy male subjects (SRD part), and a randomised, open-label, single-dose, three-way cross-over bioavailability comparison of BI 474121 as tablet versus oral solution and tablet with and without food (BA part). (including Protocol Amendments No.1-5 [c28123079-06]).
Investigational Product:	BI 474121
Responsible trial statistician:	[redacted] Phone: [redacted] Fax:
Date of statistical analysis plan:	26 APR 2021 SIGNED
Version:	1

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LIST OF TABLES

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
AUC_{0-24}	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 to 24 h
BMI	Body mass index
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
Nobs	Number of observations
os	Oral solution
P10	10^{th} percentile
P90	90^{th} percentile
PKS	PK parameter analysis set
PT	Preferred Term

Term	Definition / description
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).

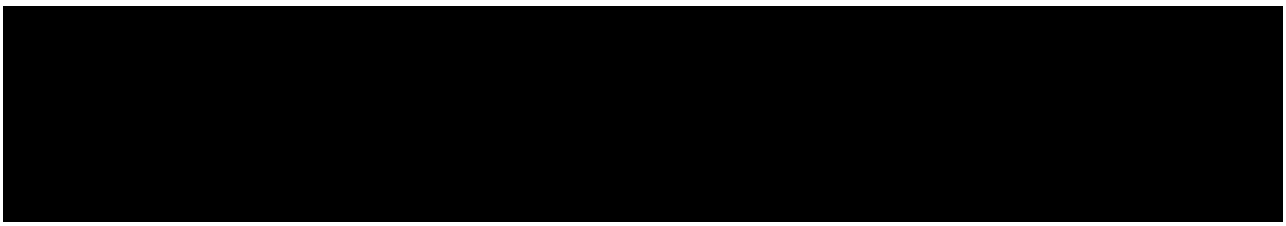
Pharmacokinetic (PK) parameters will be calculated using Phoenix WinNonlin™ software (version 6.3 or higher, [redacted] .

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 change compared to the protocol will be made:

In CTP section 7.3 the following was defined: *Important protocol deviation (iPD) categories will be specified in the Integrated Quality and Risk Management* (IQRM) *Plan, iPDs will be identified no later than in the Report Planning Meeting, and the iPD categories will be updated as needed.* Due to SOP changes, the IPD categories are no longer available in IQRM plan but included in an Excel spreadsheet (3). The IPD categories originally defined in IQRM plan were transferred to the IPD specification file. Minor changes regarding the IPD categories were performed only.



5. ENDPOINTS

5.1 PRIMARY ENDPOINTS

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 (SRD part).

The following pharmacokinetic parameters will be determined if feasible (BA part):

- *$AUC_{0\text{-}tz}$ (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:

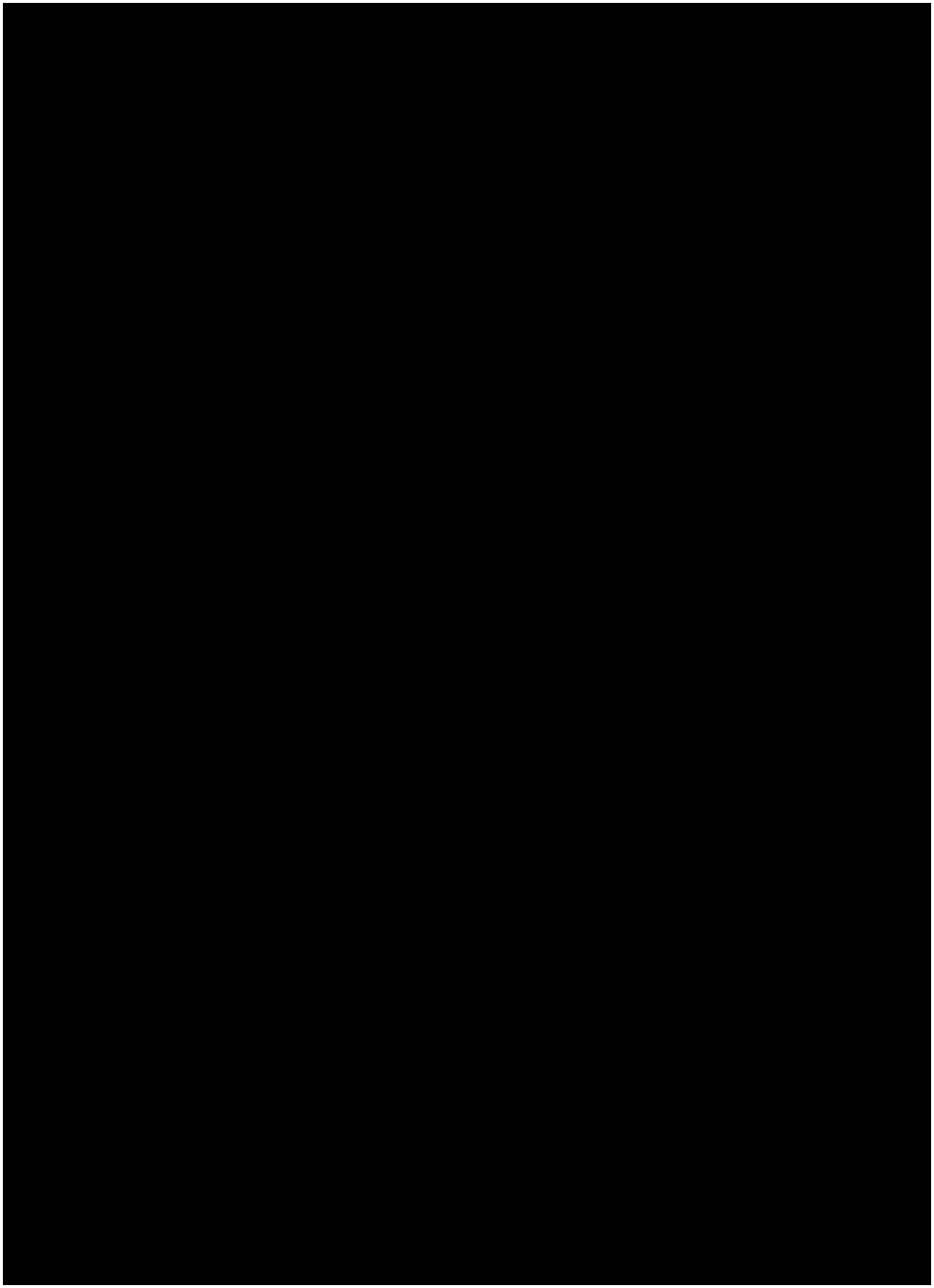
The following pharmacokinetic parameters will be determined if feasible:

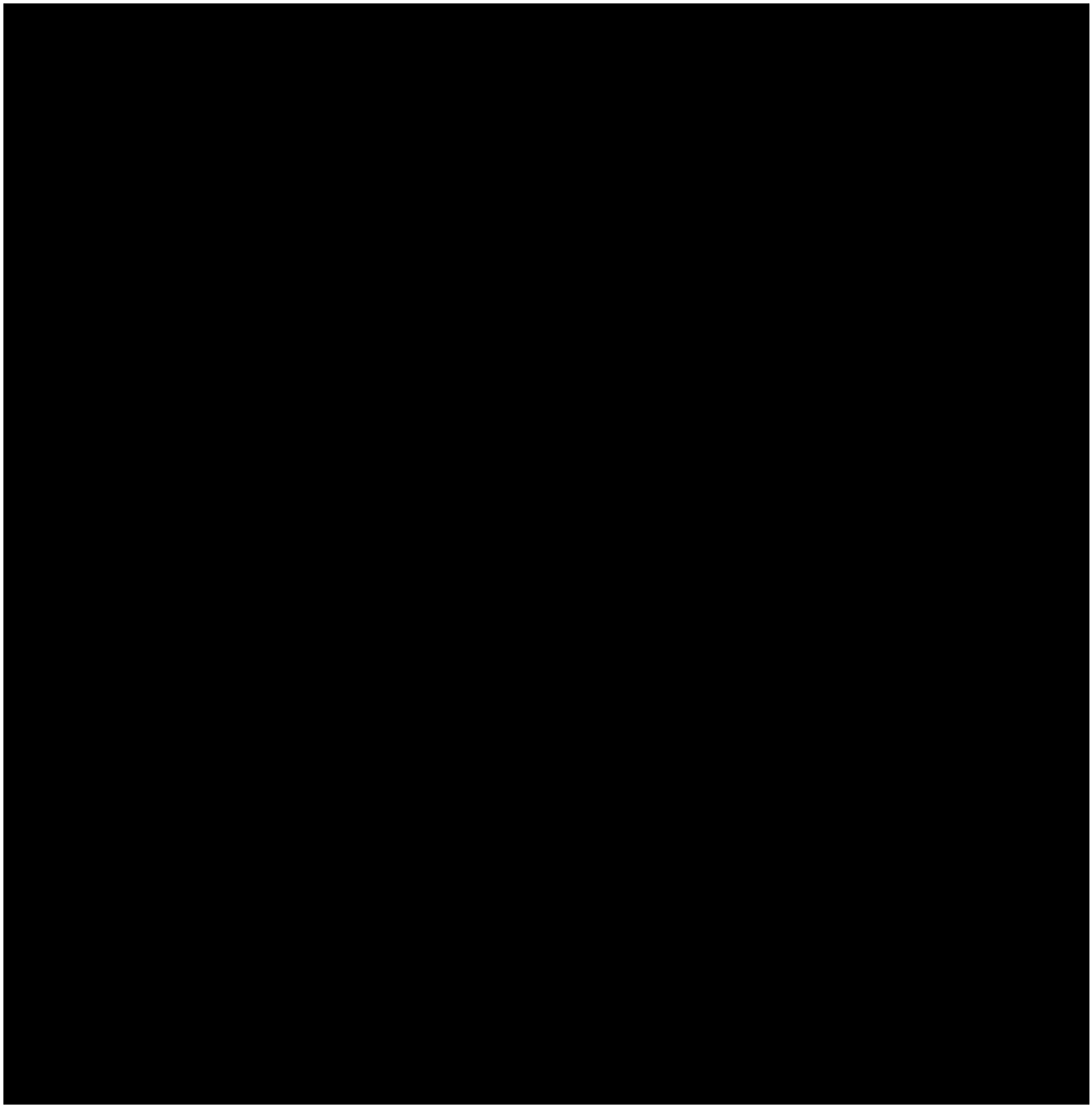
SRD part:

- *$AUC_{0\text{-}tz}$ (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)*

BA part:

- *$AUC_{0\text{-}\infty}$ (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

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

The SRD part is designed as single-blind within dose groups, randomised, and placebo-controlled within parallel dose groups. It is planned to include 56 healthy male subjects in this part of the trial. The subjects will be assigned to 7 groups consisting of 8 subjects per group (6 subjects will receive BI 474121 and 2 will receive placebo).

The BA part will be performed as randomised, open-label, three-way, six-sequence, crossover trial in healthy male subjects. It is planned to include 12 healthy male subjects. The subjects will be randomly allocated to the 6 treatment sequences. There will be a wash out period of at least 7 days between the treatments.

For details see Table 6.1:1 and Table 6.1:2 below.

Table 6.1: 1 Treatments and labels used in the analysis – SRD part

Treatment	Label in dataset	Short label
P*	Placebo, solution, po, qd	Plc os
Q*	Placebo, tablet, qd	Plc tab
A	BI 474121, 0.5 mg/mL solution, 0.25 mg, po, qd	BI 0.25mg os
B	BI 474121, 0.5 mg/mL solution, 1.0 mg, po, qd	BI 1mg os
C	BI 474121, tablet, 2.5 mg, po, qd	BI 2.5mg tab
D	BI 474121, tablet, 2*2.5 mg, po, qd	BI 5mg tab
E	BI 474121, tablet, 10 mg, po, qd	BI 10mg tab
F	BI 474121, tablet, 2*10 mg, po, qd	BI 20mg tab
G	BI 474121, tablet, 4*10 mg, po, qd	BI 40mg tab

*: Each placebo group in the safety evaluation will consist of all placebo treated patients in SRD part, regardless of the dose group in which they were treated.

Table 6.1: 2 Treatments and labels used in the analysis – BA part

Treatment sequence	Short label in dataset	Short label
UVW	BI 474121 10 mg solution / tablet fasted / tablet fed	R/T2/T1
UWV	BI 474121 10 mg solution / tablet fed / tablet fasted	R/T1/T2
VUW	BI 474121 10 mg tablet fasted / solution / tablet fed	T2/R/T1
VWU	BI 474121 10 mg tablet fasted / tablet fed / solution	T2/T1/R
WUV	BI 474121 10 mg tablet fed / solution / tablet fasted	T1/R/T2
WVU	BI 474121 10 mg tablet fed / tablet fasted / solution	T1/T2/R

U=R (Reference treatment)
V=T2 (Test treatment 2)
W=T1 (Test treatment 1)
The short label will be used whenever tables/listings are displayed by treatment sequence. If actual treatment is shown the following labels will be used: BI 10mg tab fed, BI 10mg tab fasted, BI 10mg solution (e.g. AE tables).

Section 1.2.6 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 for this first-in-human trial. Conservatively, a minimum observation period of at least 5-fold estimated $t_{1/2}$ has been selected, and thus a REP of 7 days is assumed, i.e. the individual subjects end of trial is on Day 8-15 following dosing with investigational drug at the earliest.

SRD part:
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)

- **On treatment** (BI/Placebo treatment ranging from the first time of administration of study medication until 168 hours (7 days) after the last time of administration of study medication)

- **Follow-up (F/U)** (ranging from 168 hours (7 days) after last administration of study medication until 0:00 h on day after trial termination date)

BA part:
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)

- **On treatment (BI 10mg tab fed / BI 10mg tab fasted / BI 10mg solution)** (ranging from the first time of administration of study medication until 168 hours (7 days) after

the last time of administration of study medication or until time of next drug administration (whatever occurs first))

- **Follow-up (F/U BI 10mg tab fed / F/U BI 10mg tab fasted / F/U BI 10mg solution)** (ranging from 168 hours (7 days) after last administration of study medication until 0:00 h on day after trial termination date)

Section 7.3.4 of the CTP: *Note that AEs occurring after the last per protocol contact but entered before 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 and table 6.1:2.
The following AE displays will be provided in the report:

Section 15.3 of the CTR displays:

In these displays, the on-treatment phase will be analysed (labelled with the name of the study treatment (short label in SRD part)). Screening and Follow up phases will not be included in this analysis.
The following totals will be provided in addition:

- a total over all Placebo treated on-treatment phases (**"Plc Total"**) – *SRD part only*
- a total over all BI treated on-treatment phases (**"BI Total - tab"**) – *SRD part only*
- a total over all BI treated on-treatment phases (**"BI Total - os"**) – *SRD part only*
- a total over all BI treated on-treatment phases (**"BI Total"**) – *SRD part only*
- a total over all on treatment phases included in this analysis (**"Total"**)

In Appendix 16.1.13.1.8 (for ClinicalTrials.gov and EudraCT only) of the CTR, SRD part and BA part will be combined:

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:

- a total over all Placebo treated on treatment phases in SRD part (**"Plc Total – SRD part"**)
- a total over all BI treated on treatment phases in SRD part (**"BI Total – SRD part"**)
- a total over all on treatment phases in SRD part included in this analysis (**"Total – SRD part"**)
- a total over all on treatment phases in BA part included in this analysis (**"Total – BA part"**)
- a total over all BI treated 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).

Categories which are considered to be iPDs in this trial were defined in the integrated quality and risk management plan (IQRMP) prior to trial initiation. The iPD list was transferred into the iPD specification file (due to changes in the SOP) (3). Within this transfer some minor adaptations were done to comply with new naming conventions and categorisations. IPDs will be identified no later than in the Report Planning Meeting and the iPD categories in the iPD specification file will be updated as needed. If any iPDs are identified, they are to be summarised into categories and will be captured in the RPM/DBLM minutes (the decision log) and in the iPD specification file. The decision on exclusion of subjects from analysis sets will be made after discussion of exceptional cases and implications for analyses.

The iPD specification file (e.g. the DV domain specifications) will be stored within the TMF in EDMS.

The iPDs will be summarised and listed.

6.3 SUBJECT SETS ANALYSED

Section 7.3 of the CTP:

For both parts, statistical analyses will be based on the following analysis sets:

- *Treated set (TS): The treated set includes all subjects who were randomised 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 primary or secondary 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.*

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 of the SRD part 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.

Pharmacokinetics

The pharmacokinetic parameters for drug BI 474121 listed in TSAP Section 5 *will be calculated according to* BI standard (see BI-KMED-TMCP-MAN-0014 (6)).
Plasma and urine (in the SRD part 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 the SRD part of the trial) 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 non-evaluable 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*

Plasma and urine (in the SRD part of the trial) 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. Descriptive and inferential statistics of PK parameters will be based on the PKS.

Table 6.3: 1 Subject sets analysed

		Subject set	
Class of endpoint	Treated set	PKS	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		

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 BI-KMED-BDS-HTG-0035) (4).

Missing data and outliers of PK data are handled according to BI standards (see BI-KMED-TMCP-MAN-0012 (5) and BI-KMED-TMCP-MAN-0014 (6)).

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 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.
For PK analysis, missing data and outliers of PK data are handled according to BI standards (6) and (9)."

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

SRD part: The baseline value is defined as the last measurement before first administration of trial medication (BI 474121 or Placebo).

BA part: The baseline value is defined as the last measurement before administration of trial medication in each treatment period (e.g. ptm -2:00).
For laboratory analysis, the last value on treatment will be defined as the last value during corresponding treatment period (usually 96:00h in first and second treatment period).

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

Unscheduled measurements of laboratory data 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 of the SRD part at the time points and for the ECG recordings specified in Table 6.7: 1 below:

Table 6.7: 1 Time schedule of 12-lead ECG recordings (SRD part)

Visit	Day	Planned time [hh:mm] (relative to drug administration)	Study phase	Central evaluation
1	-21 - -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
5	8-15		End-of-study examination	NA

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

For the exposure-response analyses, acceptable maximum time deviations between ECG recordings and plasma concentration sampling are necessary (see the definition of the ECGPCS in Section 6.3). These are defined as 10 min until 1 hour after dosing, 20 min from including 1.5 hours up to 12 hours after dosing and as 1 h for time points including 12 hours after dosing and later. 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.

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.

Tables and listings will be provided separately for the SRD part and BA part.

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 (7)) with the exception of those generated for PK-calculations following BI standards for PK/PD analysis (8).

The individual values of all subjects will be listed, sorted by dose group/placebo (SRD part) or treatment sequence (BA part), subject number and visit.
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 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 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 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 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.

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 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” (6) and *BI-KMED-TMCP-MAN-0010*: “Description of Analytical Transfer Files and PK/PD Data Files” (9).

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 / 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. Patients 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 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

7.4.1 Primary analysis of the primary endpoints

SRD part: Please refer to Section 7.8.1 for the description of the analysis of the primary endpoint.

BA part:
Section 7.3.1 of the CTP:
Primary analysis:
The primary *endpoints* (refer to Section 5.1) *will be calculated according to the BI Standard (see* BI-KMED-TMCP-MAN-0014 (6)*).*

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 'subjects 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, … , 6*
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, 3*
τ_k = *the* k^{th} *treatment effect, k = 1, 2, 3*
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 (T1/T2 and T2/R) for the primary endpoints (see TSAP Section 5.1*) 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) (e.g. log(T1)-log(T2) or log(T2)-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.*

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 Other Secondary endpoints

Section 7.3.2 of the CTP:
SRD part:
The secondary endpoints (refer to Section 5.2.2*) will be analysed descriptively.* […]

BA part:
The secondary endpoints (refer to Section 5.2.2*) will be calculated according to the BI Standard (see* BI-KMED-TMCP-MAN-0014 (6)*) and will be assessed statistically using the same methods as described for the primary endpoints.*

7.7 EXTENT OF EXPOSURE

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

7.8 SAFETY ANALYSIS

All safety analyses will be performed on the TS, separately for SRD and BA part.

If not stated otherwise, the safety results will be sorted by treatment group (SRD part) or by actual treatment (BA part).

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

The analyses of AEs will be descriptive in nature and will be based on BI standards as presented in "Analysis and Presentation of Adverse Event Data from Clinical Trials – Display Template" [BI-KMED-BDS-HTG-0041] (10) and [BI-KMED-BDS-HTG-0066] (11). All analyses of AEs will be based on the number of subjects with AEs and NOT on the number of AEs.

The analysis of AEs will be based on the concept of treatment emergent AEs. That means that all AEs occurring between first drug intake till 7 days after last drug intake will be assigned to

the randomised treatment. All AEs occurring before first drug intake will be assigned to 'screening' and all AEs occurring after last drug intake + 7 days will be assigned to 'follow-up' (for listings only). For details on the treatment definition, see Section 6.1.

According to ICH E3 (12), 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 (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 SOCs and PTs will be sorted by frequency (within SOC). The MedDRA version number (most recent version) will be displayed as a footnote in the respective output.

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*

In addition, frequencies of subjects with non-serious AEs that had an incidence of > 5% for at least one treatment will be summarised by treatment, primary SOC and PT.

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

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

7.8.2 Laboratory data

The analyses of laboratory data will be descriptive in nature and will be based on BI standards [BI-KMED-BDS-HTG-0042] (13).

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 and pulse rate), descriptive statistics including change from baseline will be calculated by dose group and by planned time point based on the last value of the subject at that planned time point (or assigned to that planned time point). In the listing the difference from baseline will also be displayed.

Descriptive statistics over time will also be provided for the orthostatic test results (SRD part only) to enable checking of orthostatic hypotension occurrence. Subjects should have spent at least 5 min 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 min 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.

Clinically relevant findings in vital signs will be reported as AEs.

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 (SRD part only) 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.

Categorical endpoints will also include morphological findings that might be attributable to treatment. In particular, new onsets of findings not present at baseline will be explored. A morphological finding observed on treatment that was not reported at baseline will be categorized as a ‘new onset’ of this finding.

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, HR, QT, PR and QRS. The time profiles of mean and SD for the changes from baseline on treatment will be displayed graphically by treatment.

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} 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. (14) 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 means of C_{max} for each dose will additionally be displayed in the plot.

The goodness of fit of the above model will be checked. The visual checks will include the inspection of concentration-QTcF quantile plots (14) 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, including visual inspection of the skin of palms and soles and oral cavity 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.

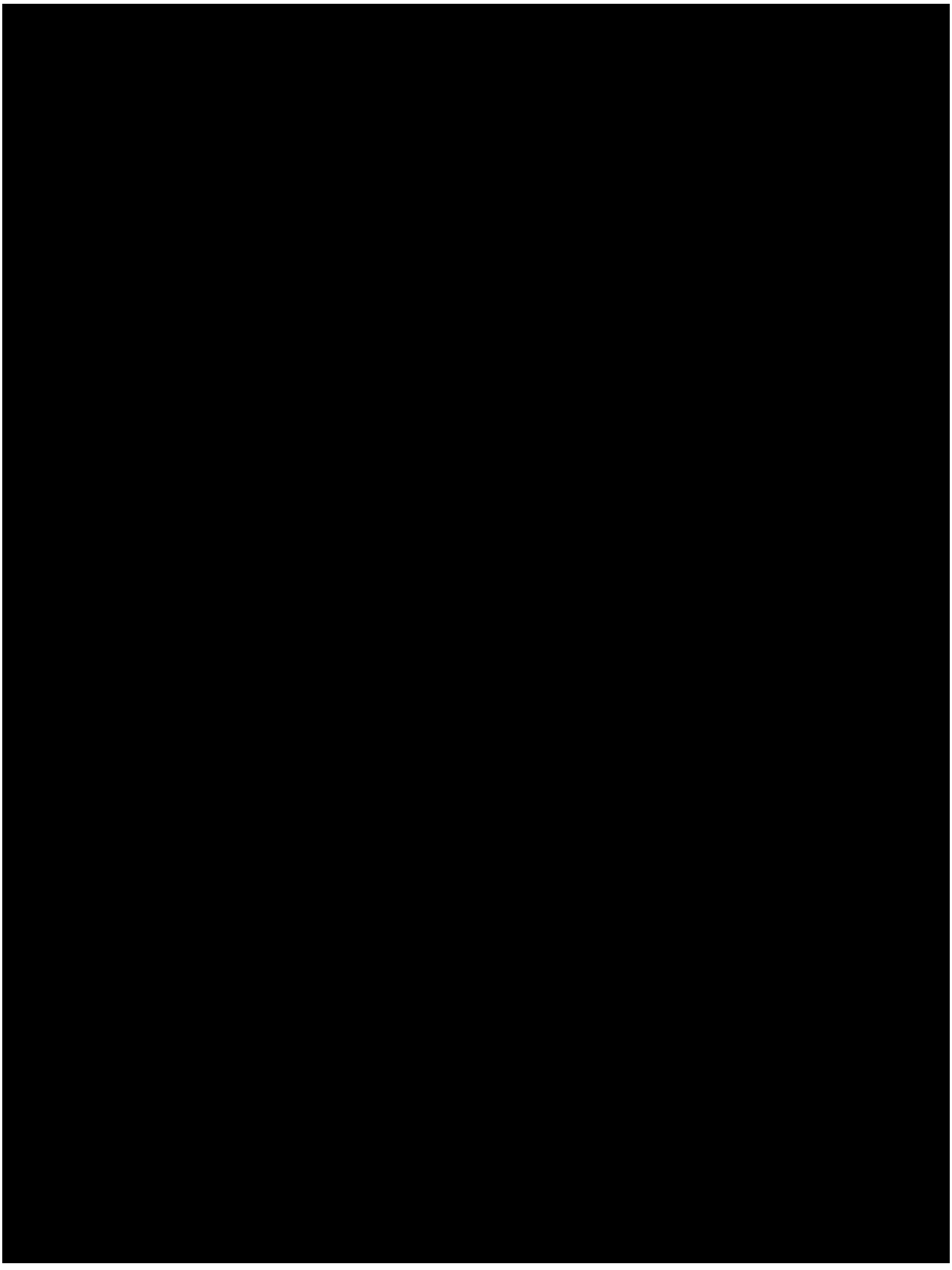
8. TIMEPOINT OF RELEASE OF TREATMENT INFORMATION

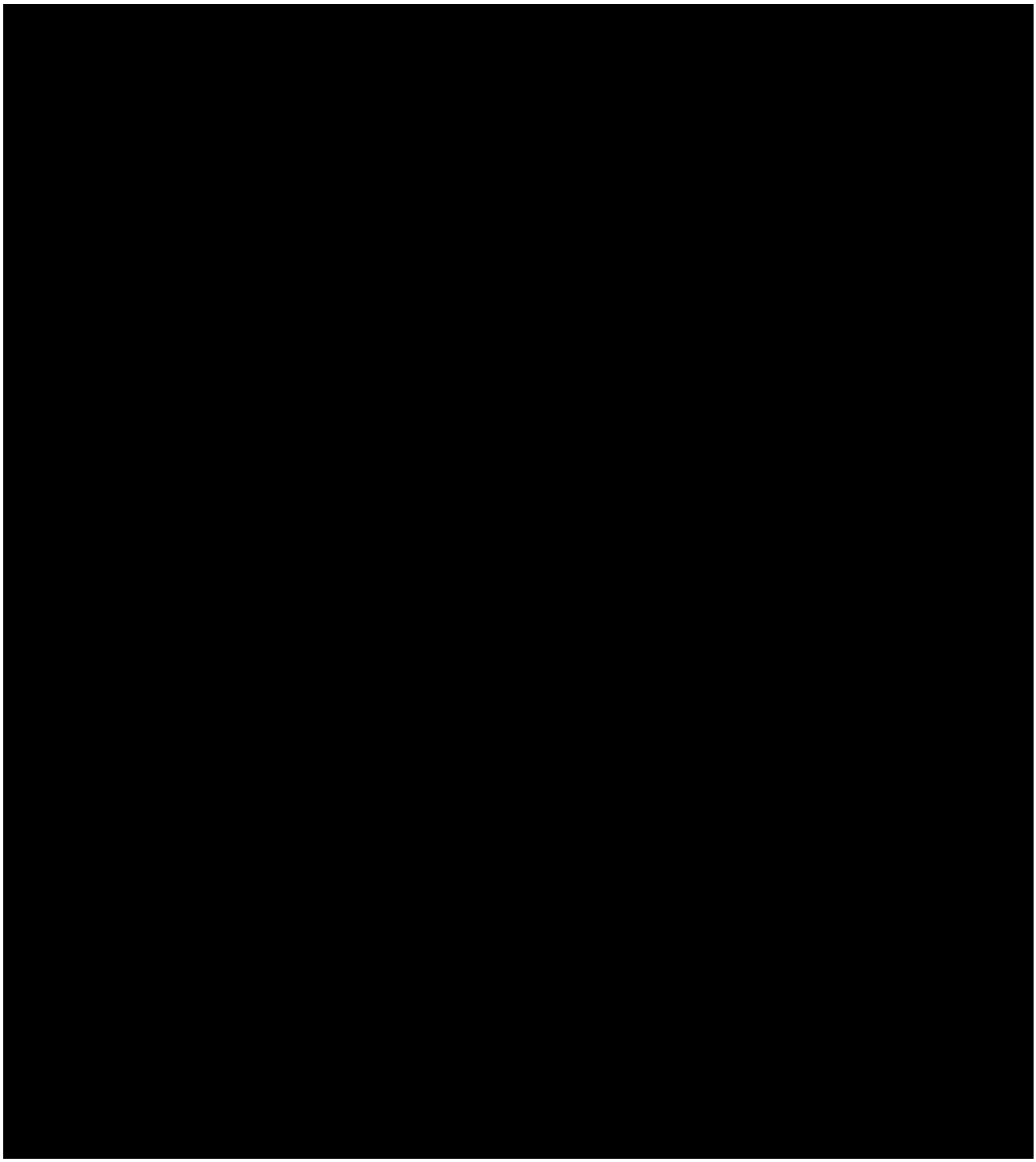
The treatment information of the SRD part (single-blind) was released for both interim analysis according to the details specified in the logistics plan after completion of the respective dose groups.

The treatment information of the BA part (open-label) was loaded into the trial database after completion of enrolment, i.e. the randomization has been completed.

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-TMP-0059:* "iPD specification document (sdtm-dv-domain-specification)", template, current version, KMED.
4.	*BI-KMED-BDS-HTG-0035:* "Handling of Missing and Incomplete AE Dates", current version; KMED.
5.	*BI-KMED-TMCP-MAN-0012:* "Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics", current version; KMED.
6.	*BI-KMED-TMCP-MAN-0014:* "Noncompartmental Pharmacokinetic / Pharmacodynamic Analyses of Clinical Studies", current version; KMED.
7.	*BI-KMED-BDS-HTG-0045:* "Standards for Reporting of Clinical Trials and Project Summaries", current version; KMED.
8.	*BI-KMED-TMCP-OTH-0003:* "Graphs and Tables for Clinical Pharmacokinetics and Pharmacodynamic Noncompartmental Analyses", current version, KMED.
9.	*BI-KMED-TMCP-MAN-0010*: "Description of Analytical Transfer Files and PK/PD Data Files", current version; KMED.
10.	*BI-KMED-BDS-HTG-0041:* "Analysis and Presentation of Adverse Event Data from Clinical Trials – Display Template", current version; KMED.
11.	*BI-KMED-BDS-HTG-0066:* "Analysis and Presentation of AE data from clinical trials", current version, KMED.
12.	*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.
13.	*BI-KMED-BDS-HTG-0042:* "Handling, Display and Analysis of Laboratory Data", current version; KMED.
14.	R18-0143: 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	**26-APR-21**	[redacted]	None	This is the final TSAP