TRIAL STATISTICAL ANALYSIS PLAN

c35155956-01

BI Trial No.:	1411-0002
Title:	Safety, tolerability and pharmacokinetics of multiple rising oral doses of BI 474121 in young and elderly healthy male and female subjects (double-blind, randomised, placebo-controlled, parallel group design) and evaluation of midazolam interaction in young healthy male and female subjects (nested, open, fixed-sequence, intra-individual comparison) (including Protocol Amendment No.1-3 [c31468495-04]).
Investigational Product:	BI 474121
Responsible trial statistician:	[redacted] Phone: [redacted] Fax:
Date of statistical analysis plan:	03 NOVEMBER 2021 SIGNED
Version:	1

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2. LIST OF ABBREVIATIONS

See Medicine Glossary:
http://glossary

Term	Definition / description
ALT	Alanine Aminotransferase
ANOVA	Analysis of Variance
AST	Aspartate Aminotransferase
AUC_{0-24}	Area under the concentration-time curve of the analyte in plasma from 0 to 24h
[redacted]	[redacted]
AUC_{0-tz}	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 to the last quantifiable data point
$AUC_{\tau,ss}$	Area under the concentration-time curve of the analyte in plasma at steady state over a uniform dosing interval τ
BMI	Body mass index
CARE	Clinical Analysis and Reporting Environment
CI	Confidence Interval
C_{max}	Maximum measured concentration of the analyte in plasma
$C_{max,ss}$	Maximum measured concentration of the analyte in plasma at steady state over a uniform dosing interval τ
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
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

Term	Definition / description
MedDRA	Medical Dictionary For Regulatory Activities
Min	Minimum
N	Number non-missing observations
P10	10th percentile
P90	90th percentile
PKS	PK parameter analysis set
PO	Per oral
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
[redacted]	[redacted]
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 [redacted] 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 changes 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 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.

[redacted]

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 endpoint

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

5.2.2 Secondary endpoints

Section 2.1.3 of the CTP:

The following pharmacokinetic parameters will be determined if feasible:

BI 474121

After the first dose:

- *AUC_{0-24} (area under the concentration-time curve of the analyte in plasma from 0 to 24h)*
- *C_{max} (maximum measured concentration of the analyte in plasma)*

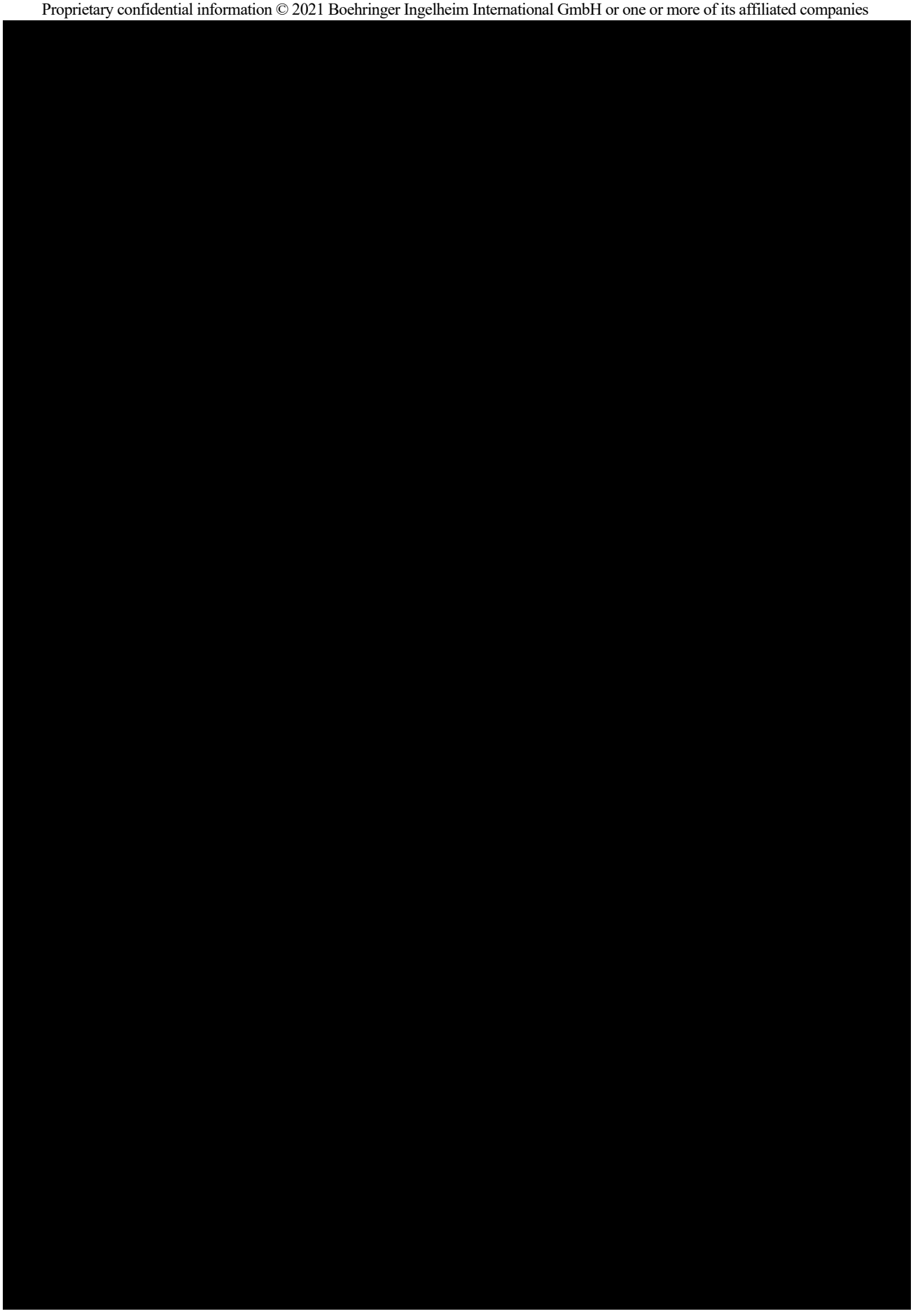
After the last dose:

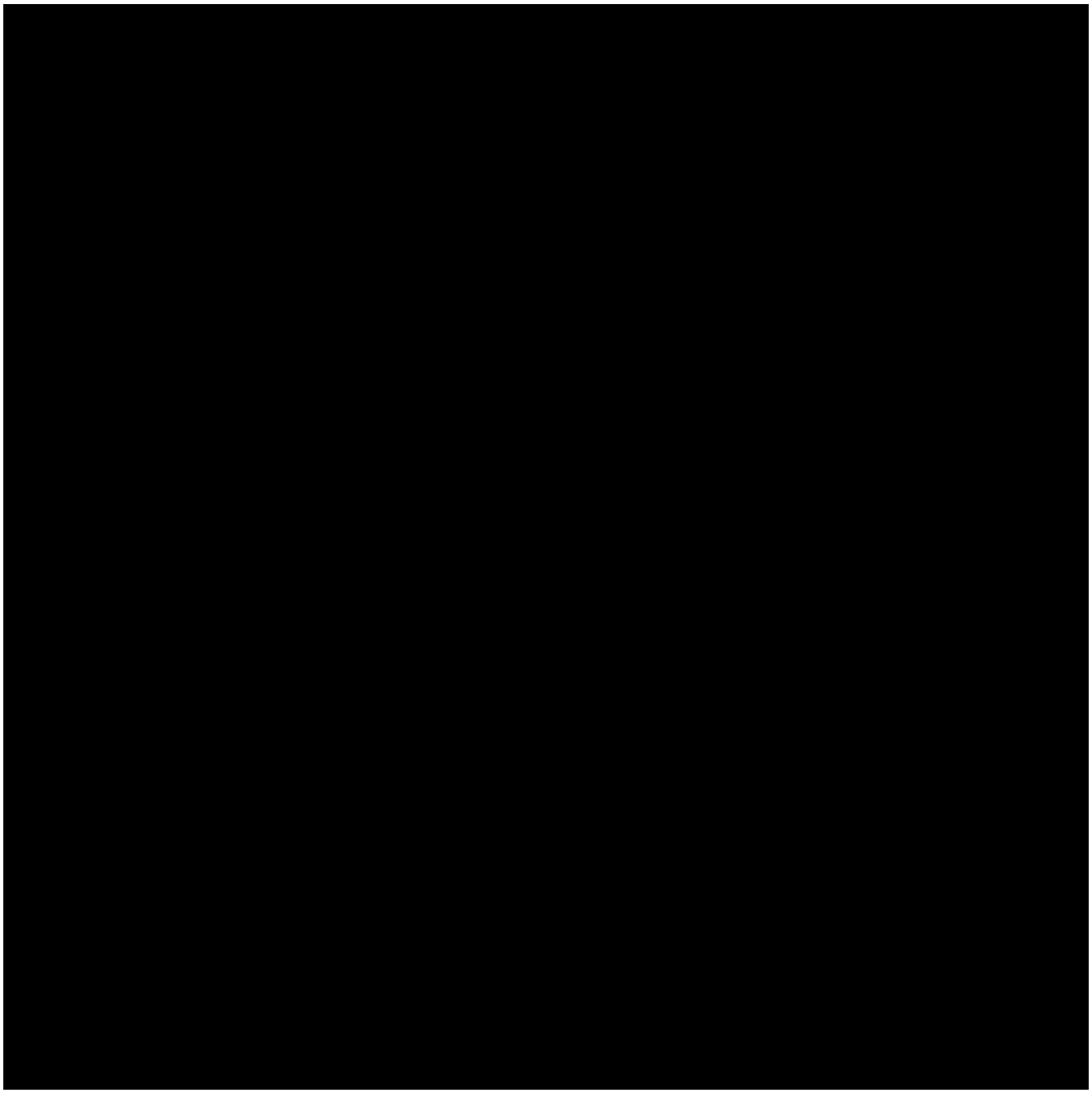
- *$AUC_{\tau,ss}$ (area under the concentration-time curve of the analyte in plasma at steady state over a uniform dosing interval τ)*
- *$C_{max,ss}$ (maximum measured concentration of the analyte in plasma at steady state over a uniform dosing interval τ)*

Midazolam

After each of the three doses:

- *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}*





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 multiple-rising dose (MRD) trial is designed as double-blind, randomised, and placebo-controlled within parallel dose groups.

It is planned to include 50 young healthy male and female subjects (part A) and 20 elderly healthy male and female subjects (part B). The young subjects will be assigned to 5 and the elderly subjects to 2 sequential dose groups consisting of 10 subjects per group (8 subjects will receive BI 474121 and 2 will receive placebo).

For details see Table 6.1:1 below.

Table 6.1: 1 Treatments and labels used in the analysis

Treatment	Label in dataset	Short label
P*/**	Placebo	Placebo - A
		Placebo - B
Q*	Placebo tablet+Midazolam,solution, 75ug,po,qd	Placebo - A
A	BI 474121, tablet, 2.5 mg, po, qd + Midazolam, diluted to 50ug/mL solution, 1.5mL(75ug), po, qd	BI 2.5mg - A
B**	BI 474121, tablet, 2*2.5 mg, po, qd	BI 5mg - A
		BI 5mg - B
C	BI 474121, tablet, 10 mg, po, qd + Midazolam, diluted to 50ug/mL solution, 1.5mL(75ug), po, qd	BI 10mg - A
D	BI 474121, tablet, 2*10 mg, po, qd + Midazolam, diluted to 50ug/mL solution, 1.5mL(75ug), po, qd	BI 20mg - A
I	BI 474121, tablet, 3*10 mg, po, qd + Midazolam, diluted to 50ug/mL solution, 1.5mL(75ug), po, qd	BI 30mg - A
H	BI 474121, tablet, 10 mg, po, qd	BI 10mg - B

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

**: Young and elderly subjects are randomized to this dose group. For analysis the dose group will be separated into a group including young subjects (part A) and a group including elderly subjects (part B)

Section 1.2.1.7 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 for this first human multiple dose 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 subject's end of trial is on Day 21 to Day 23 following dosing with the investigational drug at the earliest.

The following study phases will be defined for the analysis of adverse events (AEs):

- **Screening** (ranging from 0:00 h on day of informed consent until first administration of study medication (BI/Placebo/Midazolam))

- **Mida** (Treatments Q, A, C, D, I only (Part A): Midazolam treatment ranging from the first time of administration of midazolam until the time of first administration of BI/Placebo treatment)

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

- **Follow-up (F/U)** (ranging from 168 hours (7 days) after last administration of BI or Placebo 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 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 of the CTR displays:

In these displays, the on treatment phase (and Midazolam phase, if applicable) 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 BI treated on treatment phases (**"BI Total"**)
- 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 the on treatment phase (and Midazolam phase, if applicable) 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 part A (**"Placebo – A"**)
- a total over all BI treated on treatment phases in part A (**"BI Total – A"**)
- a total over all on treatment phases in part A included in this analysis (**"Total – A"**)
- a total over all Placebo treated on treatment phases in part B (**"Placebo – B"**)
- a total over all BI treated on treatment phases in part B (**"BI Total – B"**)
- a total over all on treatment phases in part B included in this analysis (**"Total – B"**)
- a total over all Placebo treated on treatment phases (**"Placebo Total"**)
- 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:

- *Treated set (TS): The treated set includes all subjects who were randomized and treated with at least one dose of study drug* (BI 474121, Placebo, Midazolam)*. The treatment assignment will be determined based on the first treatment the subjects received. The treated set will be used for safety analyses*, [redacted]
- *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 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.*

All ECG analyses are performed on the TS, [redacted]

Plasma and urine concentration data and parameters of a subject will be included in the statistical pharmacokinetic (PK) analyses if they are not flagged for exclusion due to a protocol 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 deviations may be

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

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

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

Plasma/urine concentration data and parameters of a subject which is flagged for exclusion will be reported with its individual values but will not be included in the statistical analyses.

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

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	
[redacted]	[redacted]		
[redacted]			[redacted]
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.

[redacted]

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.

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

The baseline value is defined as the last measurement before first administration of BI 474121 or Placebo, which is planned as visit 2, day 1, ptm -1:00h or day -1, ptm -25:30h for the analysis of orthostatic testing.

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 below:

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	-21 to -3		Screening	NA
2	-1	-25:30		NA (part A only)
	1	-1:00	Baseline	first ECG of each of the 3 triplicates at baseline
		-0:45		
		-0:30		
	2	23:45	On-treatment	first single ECG of the triplicate
	5	95:45		
	8	167:45		
	11	239:45		

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

Visit	Day	Planned time [hh:mm] (relative to drug administration)	Study phase	Central evaluation
2	13	287:45	On-treatment	first single ECG of the triplicate
	14	311:45		
		313:00		
		314:00		
		316:00		
		320:00		
		324:00		
	15	336:00		
	16	360:00		
3	21 to 23		End-of-trial examination	NA

At Screening and End-of-trial 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 all transferred ECG variable values prior to drug administration.

[redacted]

[redacted]

7. PLANNED ANALYSIS

Results are shown separately for part A and part B (except some outputs in Appendix 16.1.13.1).

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.

[redacted]

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, 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 [redacted] parameters is:

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

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

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

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

Tabulations of frequencies for categorical data will include all possible categories available in 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 [redacted] parameters

The ADS "ADPP" (PK parameters) [redacted] contains column variables APEXC and APEXCO indicating inclusion/exclusion (APEXC) of a PK [redacted] 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 [redacted] concentrations

The ADS "ADPC" (PK concentrations per time-point or per time-interval) [redacted] 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 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 usually be coded using the latest version of the coding system of the Medical Dictionary for Drug Regulatory Activities (MedDRA). Medications will usually be coded using the latest version of the World Health Organization Drug Dictionary (WHO-DD). The coding version number will be specified during RPM. 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 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 ENDPOINT

7.4.1 Primary analysis of the primary endpoint

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

7.5 SECONDARY ENDPOINTS

7.5.1 Key secondary endpoint

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

7.5.2 Secondary endpoints

Section 7.3.2 of the CTP: *The secondary endpoints (refer to* Section 5.2.2*) will be analysed descriptively. Analyses will be performed for the parent drug and will be based on the PKS.*

[redacted]

Midazolam:

Relative bioavailability will be estimated for dose groups A, C, D and I *of young only for* $AUC_{0\text{-}tz}$ *and* C_{max} *of midazolam. These endpoints will be compared separately between the last dose of midazolam and the first dose of midazolam and between the second dose of midazolam and the first dose of midazolam (test/reference). The statistical analysis will be performed separately for each dose group and separately for the group of subjects receiving placebo. Analyses will be conducted for the placebo group to better account for variability in plasma concentrations seen between midazolam treatment periods. The statistical model used*

for the analysis of the secondary endpoints will be an ANOVA model on the logarithmic scale. This model will include effects accounting for the following sources of variation: 'subjects', and 'time point'. The effect 'subjects' will be considered as random, whereas the other effects will be considered as fixed. The model is described by the following equation:

$Y_{ij} = \mu + \tau_i + s_j + e_{ij}$ *, where*

Y_{ij} *logarithm of the endpoint for subject j (j=1, 2,..., 8) at time point i: Day -1 (first dose of midazolam, i=1), Day 1 (second dose of midazolam) or at Day 14 (last dose of midazolam, i=2) respectively,*
μ *the overall mean,*
τ_i *the effect associated with time point i (Day -1 i=1 , Day 1 or Day 14, i=2),*
s_j *(random) effect of subject j, j=1, 2, ..., 8, and*
e_{ij} *random error associated with subject j at time i (assumed to be independent and identically normally distributed).*

The effect of BI 474121 on midazolam will be estimated by the difference in the expected means log(test)-log(reference) (with the second and the last doses of midazolam respectively as the test and the first dose of midazolam as the reference) estimated by the difference in the corresponding adjusted means (Least Squares Means) for C_{max} and $AUC_{0\text{-}tz}$. Additionally, their two-sided 90% confidence intervals (CIs) will be calculated based on the residual error from ANOVA. These quantities will then be back transformed to the original scale to provide the point estimate and 90% CIs for each secondary endpoint. This method corresponds to the two one-sided t-tests procedure, each at the 5% significance level. Since the main focus is on estimation and not testing, an acceptance range is not specified.

The implementation for this analysis will be accomplished by using the CSD macros based on PKS. The following SAS code can be used:

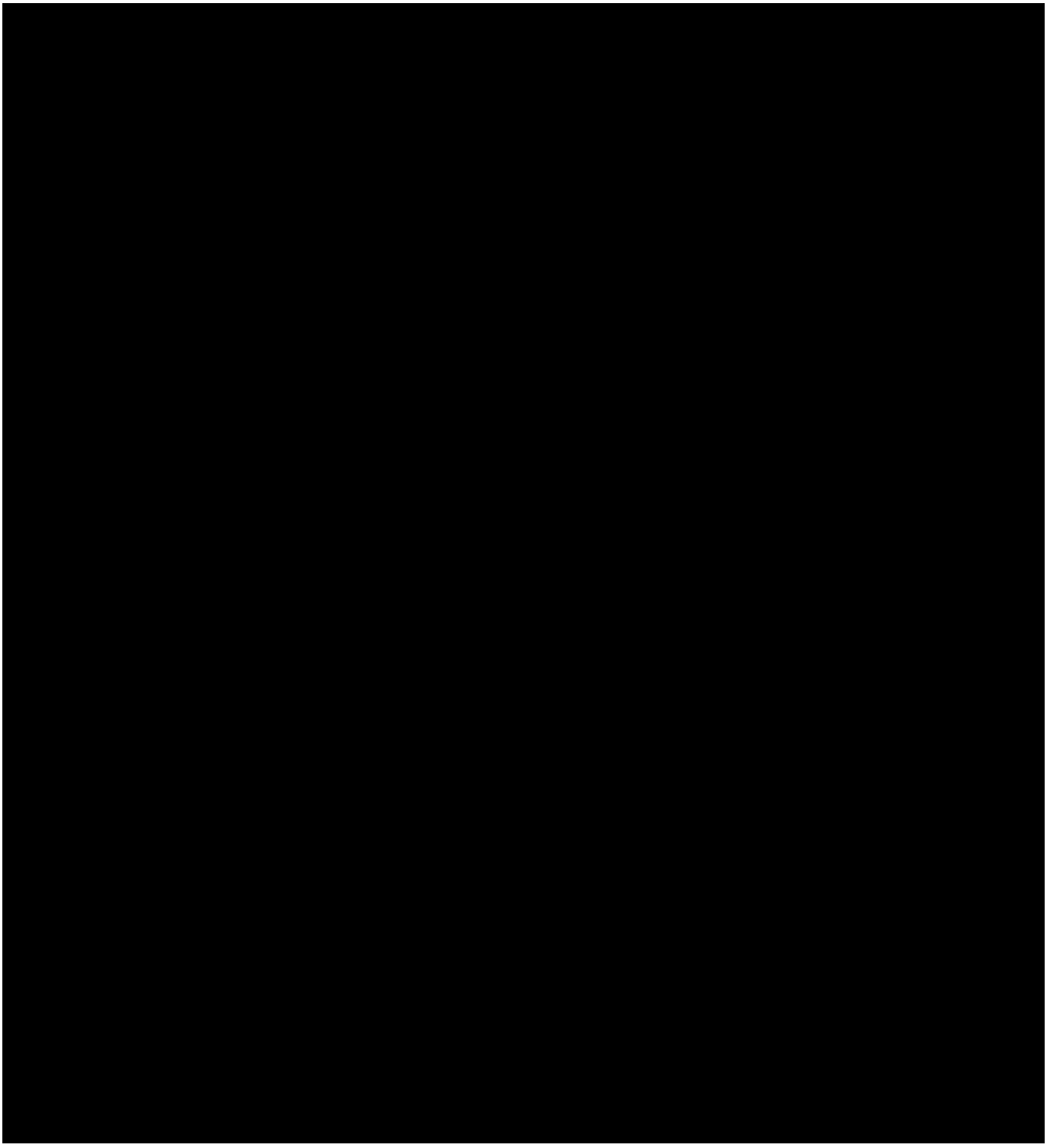
```
PROC MIXED DATA=indata;
        CLASS subject timepoint;
        MODEL logpk = timepoint / DDFM=KR;
        RANDOM subject;
        LSMEANS timepoint / PDIFF CL ALPHA=0.1;
        ESTIMATE 'T-R' timepoint-1 1;
RUN;
```

(to be analysed separately with T=endpoint after second dose of Midazolam and T=endpoint after last dose of Midazolam, R is the endpoint after first dose of Midazolam in both analyses)

[redacted]

[redacted]

[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 each drug administration will be listed for each subject.

7.8 SAFETY ANALYSIS

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

If not stated otherwise, the safety results will be sorted by treatment group.

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 usually be coded with the most recent version of MedDRA. The version to be used will be specified in RPM.

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 will be assigned to 'screening', 'Mida' (part A only), 'on-treatment' or 'follow-up' phases as defined in 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 5.2.8.1.4 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 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 ≥ 20 mmHg or a decline in diastolic blood pressure of ≥ 10 mmHg within the first three minutes after standing up.

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

Body temperature will be listed only.

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, [redacted]

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.

[redacted]

[redacted]

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 (separately for part A and part B).
In addition, the model will be applied to the pairs of log-transformed uncorrected QT and log-transformed RR, in order to obtain the population slope.

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.

Suicidality assessment - Columbia Suicidal Severity Rating scale (C-SSRS)

The C-SSRS will be done at screening, visit 2 ptm -25:30 (day -1) (part A only) and visit 2 ptm 360:00 (day 16). The results will be listed only.

Mini-Mental State Examination (MMSE) – part B only

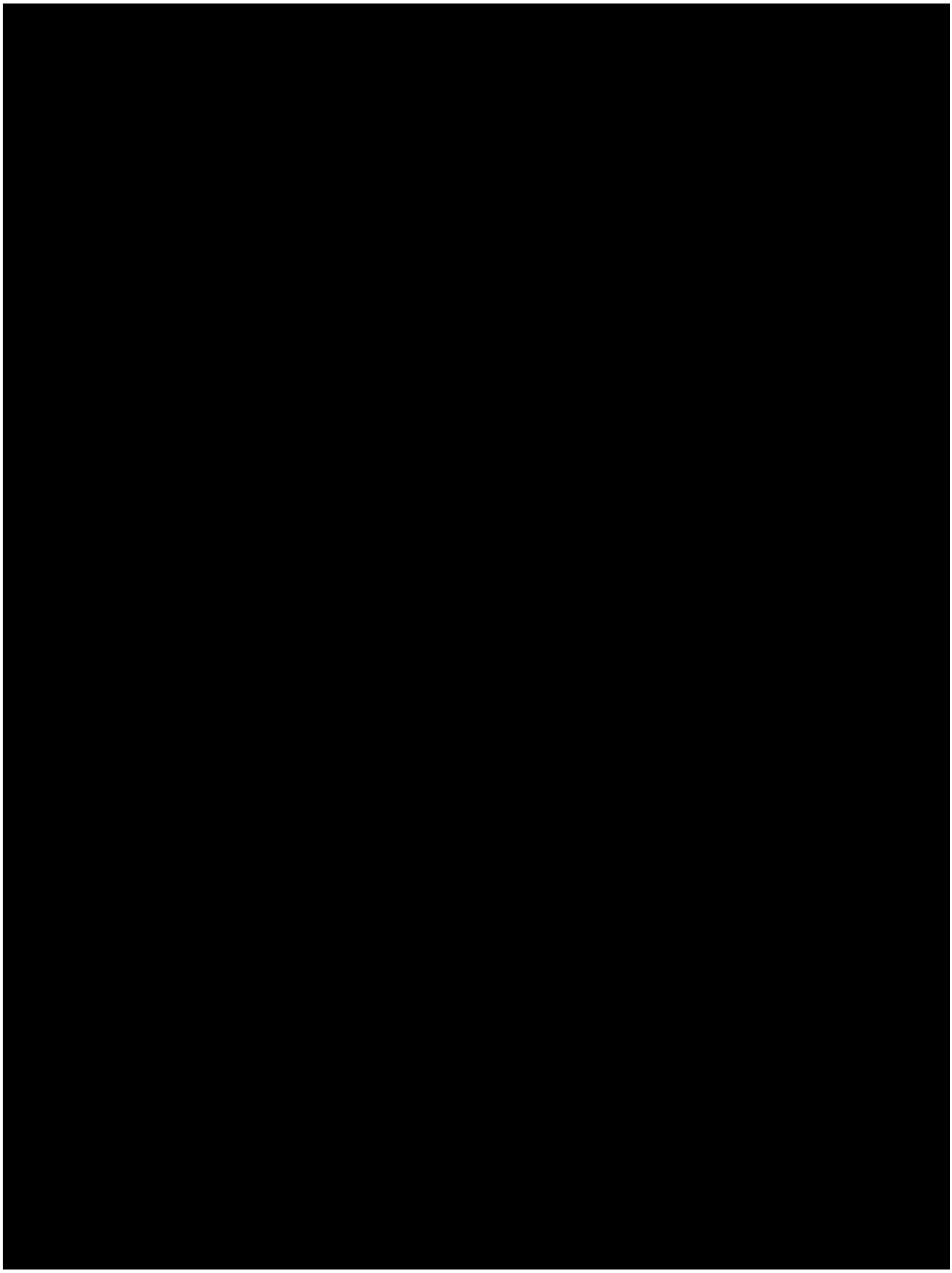
The MMSE will be done at screening and end of trial examination in elderly subjects. The data is not transferred into the database, so no separate listing will be prepared.

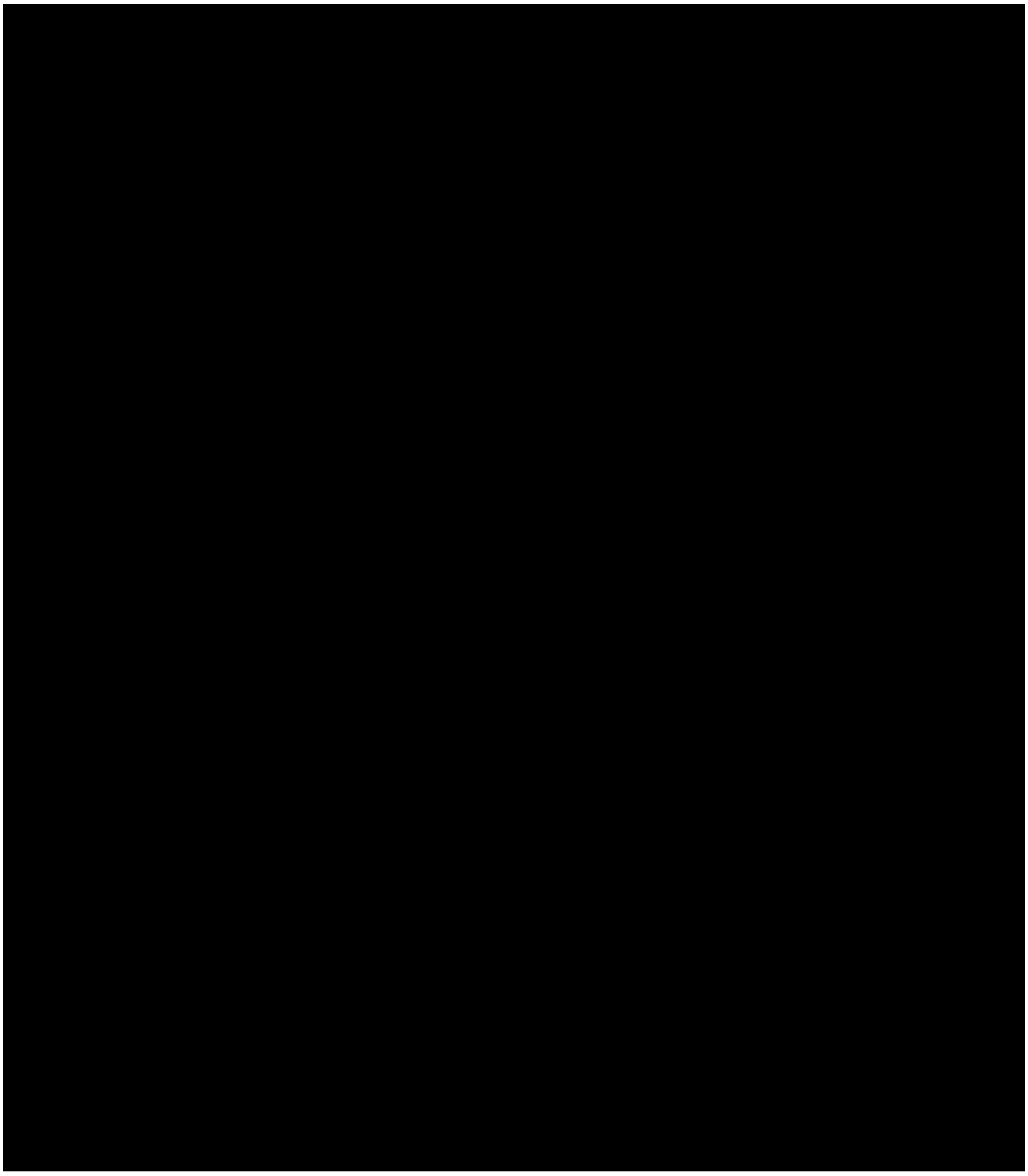
8. TIMEPOINT OF RELEASE OF TREATMENT INFORMATION

The treatment information was released to unblind the trial database per dose group after the last patient has completed their End-of-Study/Follow-up visit and the randomization was complete for the respective dose group as defined in the "Data Ready to be Unblinded and/or Final Trial Closure Notification" (RUN) form.

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	**03-NOV-21**	[redacted]	None	This is the final TSAP