TRIAL STATISTICAL ANALYSIS PLAN

Document No.:	**c44120173-01**
BI Trial No.:	**1447-0002**
Title:	Safety, tolerability, pharmacokinetics, and pharmacodynamics of multiple rising oral doses of BI 1569912 (single-blind, partially randomized within dose groups, placebo-controlled, parallel group design) with an optional posology (up-titration) part (single-blind, partially randomized within dose groups, placebo-controlled, parallel group design) in healthy male subjects Revised protocol # 07 [c33746782-07]
Investigational Product(s):	BI 1569912
Responsible trial statistician(s):	[redacted] Phone: [redacted] Fax: [redacted]
Date of statistical analysis plan:	31 JUL 2024
Version:	1.0

1. TABLE OF CONTENTS

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LIST OF TABLES

2. LIST OF ABBREVIATIONS

Term	Definition / description
ADS	Analysis data set
AE	Adverse Event
AESI	Adverse event of special interest
ALQ	Above Limit of Quantification
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC_{0-24}	Area under the plasma concentration-time curve from time zero to 24 h
$AUC_{\tau,ss}$	Area under the concentration-time curve of the analyte in plasma at steady state over a uniform dosing interval τ
$AUC_{0-\infty}$	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity
BI	Boehringer Ingelheim
BLQ	Below Limit of Quantification
CADSS	Clinician Administered Dissociative States Scale
CI	Confidence interval
C_{max}	Maximum measured concentration of the analyte in plasma
$C_{max,ss}$	Maximum measured concentration of the analyte in plasma at steady state over a uniform dosing interval τ
$C_{min,ss}$	Minimum concentration of the analyte in plasma at steady state over a uniform dosing interval τ
CRF	Case Report Form, paper or electronic (sometimes referred to as 'eCRF')
CTP	Clinical trial protocol
CTR	Clinical trial report
C-SSRS	Columbia Suicide Severity Rating Scale
DILI	Drug-induced liver injury
ECG	Electrocardiogram
ECGPCS	ECG pharmacokinetic concentration set
EudraCT	European union drug regulating authorities clinical trials
EEG	Electroencephalogram
ERP	Event-related potential
EudraCT	European Clinical Trials Database

Term	Definition / description
HR	Heart rate
ICH	International Conference On Harmonisation
IPD	Important protocol deviations
LLOQ	Lower limit of quantification
MedDRA	Medical Dictionary For Regulatory Activities
PD	Pharmacodynamic(s)
PKS	Pharmacokinetic parameter analysis set
PK	Pharmacokinetic(s)
PR	Pulse rate
QRS complex	Combination of the Q, R, and S waves
QT interval	Time between start of the Q-wave and the end of the T-wave in an electrocardiogram
QTc	QT interval, heart rate corrected
QTcB	QT interval, heart rate corrected according to Bazett's formula
QTcF	QT interval, heart rate corrected according to Fridericia's formula
$R_{A,AUC}$	Accumulation ratio based on $AUC_{0-\tau}$
$R_{A,Cmax}$	Accumulation ratio based on $C_{max,ss}$
RAGe	Report appendix generator
REP	Residual Effect Period
RR interval	ECG interval from the peak of the R wave to the peak of the subsequent R wave
RPM	Report Planning Meeting
SAE	Serious adverse event
SDL	Subject Data Listing
SMWQ	Study Medication Withdrawal Quesstionnaire
SOC	System Organ Class
TS	Treated set
TSAP	Trial Statistical Analysis Plan
ULN	Upper limit of normal range
ULOQ	Upper Limit of Quantification

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 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 revised 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, randomization.

Study data as collected in the electronic case report form (eCRF) will be stored in a trial database within the RAVE EDC system. All study data also including external data will then be uploaded to the CDR data warehouse.

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).

PK parameters will be calculated using Phoenix WinNonlin™ software (version Phoenix 8.1, [redacted]).

The abbreviation $AUC_{0\text{-}24h}$ of the PK parameter “Area under the plasma concentration-time curve from time zero to 24 h” is not used throughout the TSAP as in the CTP, but in the usual clinical notation $AUC_{0\text{-}24}$, also in the CTP text, which is in italics.

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

All analyses described in this TSAP are in accordance with the statistical methods described in the revised CTP.

5. ENDPOINTS(S)

5.1 PRIMARY ENDPOINT(S)

The primary endpoint for assessment of safety and tolerability of BI 1569912 is the percentage of subjects with treatment-emergent drug-related adverse events, cf. **CTP Section 2.1.2**.

5.2 SECONDARY ENDPOINT(S)

5.2.1 Key secondary endpoint(s)

Not applicable.

5.2.2 Secondary endpoint(s)

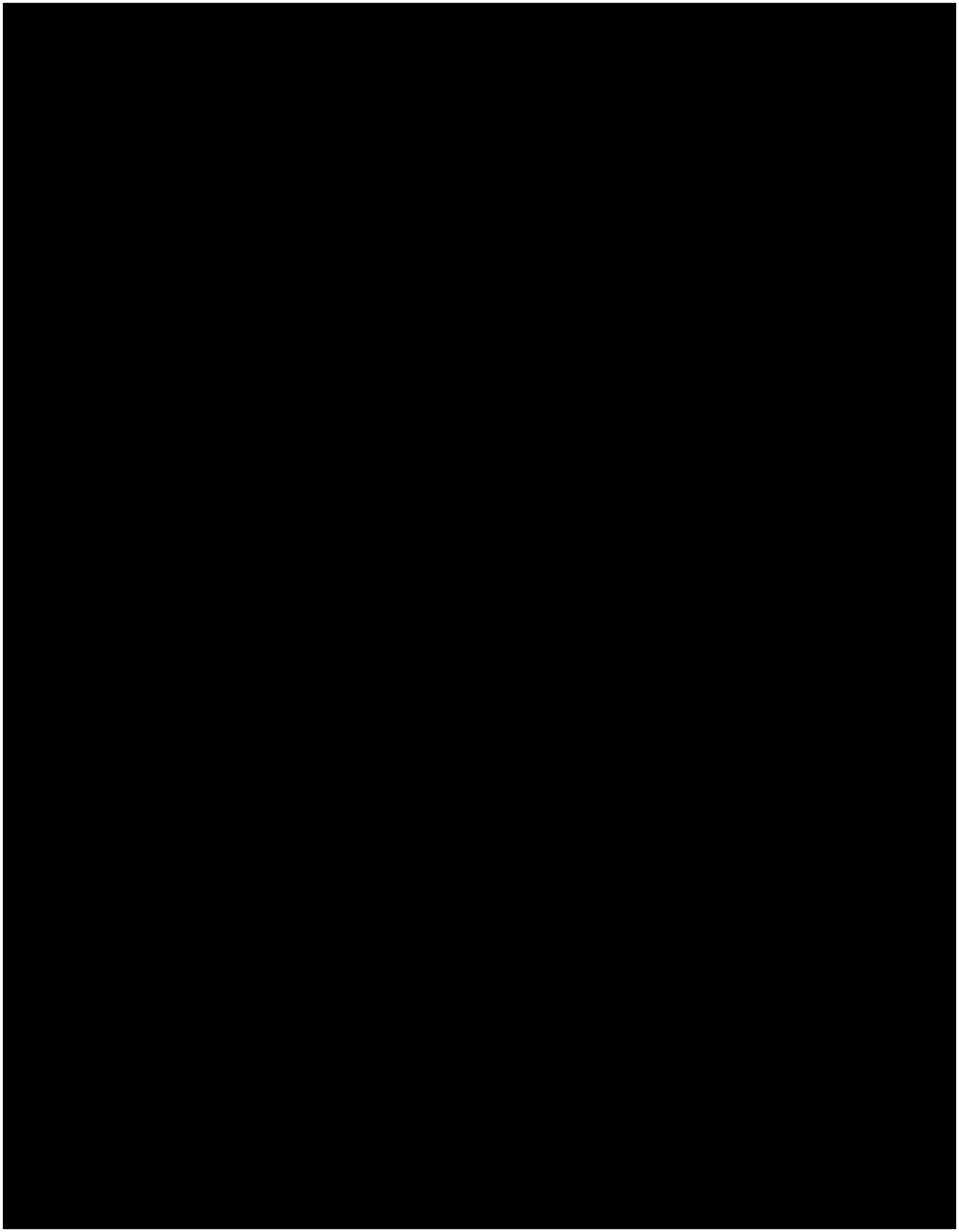
Secondary endpoints are the PK endpoints of BI 1569912, as defined in **Section 2.1.3 of the CTP**.

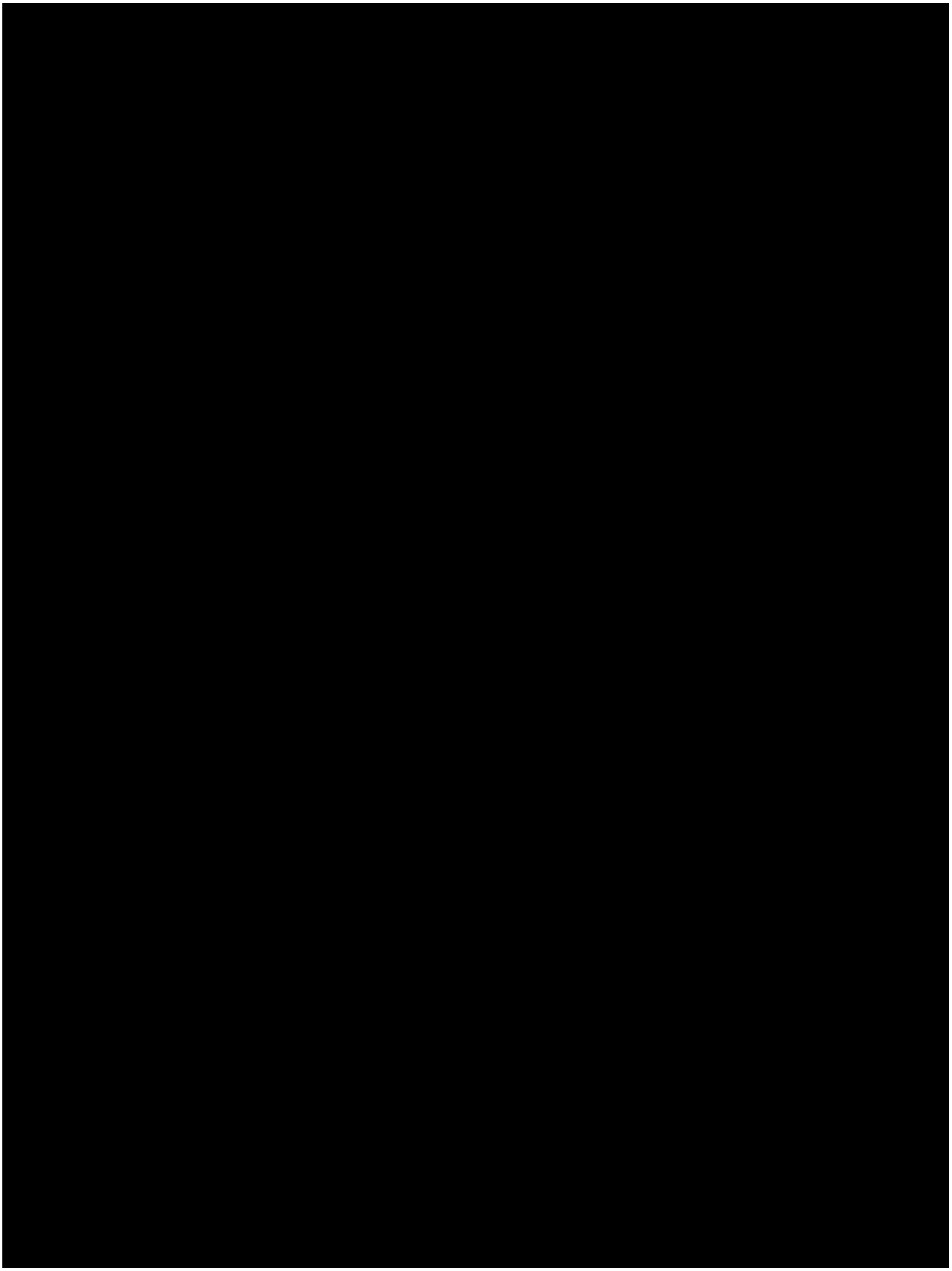
After the first dose:

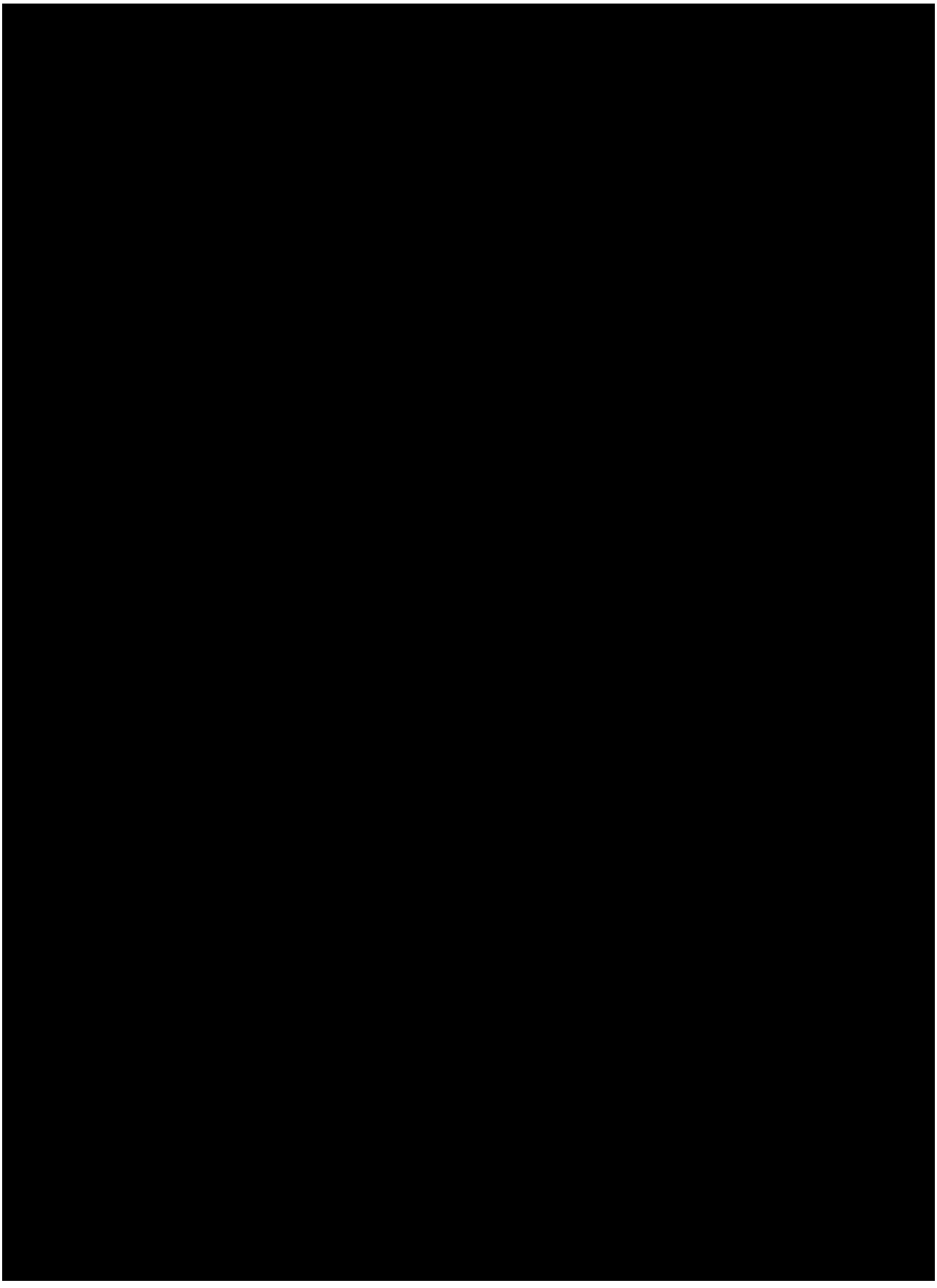
- *AUC_{0-24} (area under the concentration-time curve of the analyte in plasma over a uniform dosing interval of 24 h after administration of the first dose)*
- *C_{max}(maximum measured concentration of the analyte in plasma after the first dose)*

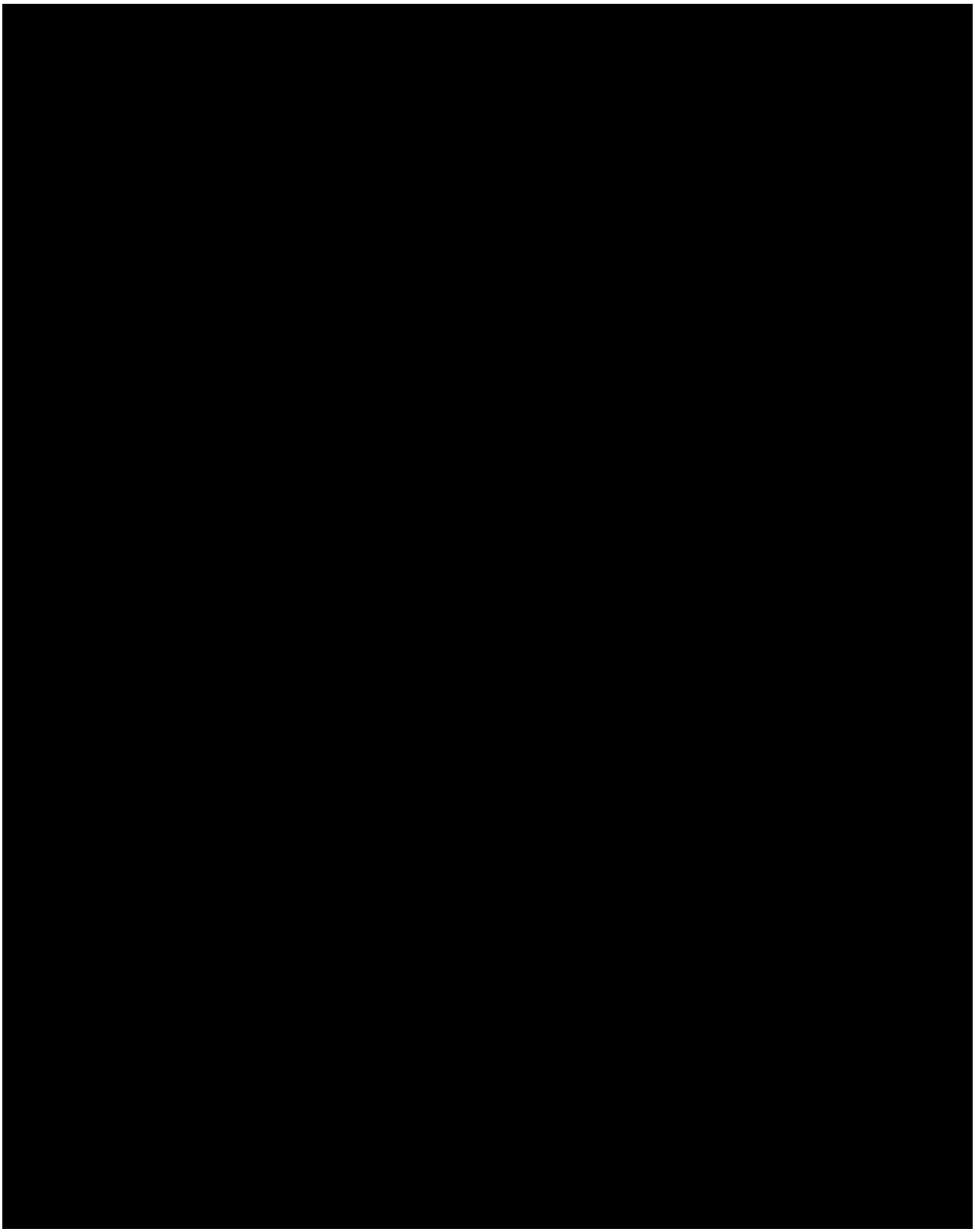
After the last dose:

- *$AUC_{\tau,ss}$ (area under the concentration-time curve of the analyte in plasma at steady state over a uniform dosing interval τ)*
- *$C_{max,ss}$ (maximum measured concentration of the analyte in plasma at steady state over a uniform dosing interval τ)*
- *$C_{min,ss}$ (minimum concentration of the analyte in plasma at steady state over a uniform dosing interval τ)*
- *$R_{A,Cmax}$ (accumulation ratio based on $C_{max,ss}$)*
- *$R_{A,AUC}$ (accumulation ratio based on $AUC_{0-\tau}$)*









6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENT(S)

For basic study information on the treatment to be administered, and selection of dose, **cf. Section 4 of the CTP**.

MRD part:

Subjects in the MRD part will receive once daily for fourteen days 2.5 mg (dose group (DG) 1), 5 mg (DG 2), 10 mg (DG 3), 20 mg (DG 4), 30 mg (DG 5) or 40 mg (DG 6) of BI 1569912 or matching placebo.

POSO part:

The optional POSO part was not performed.

Elderly part:

Subjects in the elderly part will receive from Day 1 to Day 7 once daily 10 mg BI 1569912 and from Day 8 to Day 14 once daily the target dose 20 mg of BI 1569912 or a matching placebo from Day 1 to Day 14.

Placebo subjects within the MRD part will be pooled for the analysis and analysed separately from Placebo subjects from the Elderly part..

In the following the term ‘treatment group’ is used for the placebo groups and the active treatment groups (DG 1-6 and Elderly-part group).

The residual effect period (REP) is estimated up to 36 hours, **cf. Section 1.2.7 of the CTP**.

For statistical analysis of AEs, the following analysis phases will be defined for each subject.

Table 6.1: 1 Analysis phases for statistical analysis of AEs, and actual treatment for analysis of laboratory data and other assessments

Study analysis phase	Actual treatment label	Start (inclusive)	End (exclusive)
Screening[1]	**Screening**	Date of informed consent	Date/time of first administration of study drug
On treatment (MRD and ELDERLY part)	**Placebo MRD** **Placebo Elderly** **DG 1 (2.5 mg BI)** **DG 2 (5 mg BI)** **DG 3 (10 mg BI)** **DG 4 (20 mg BI)** **DG 5 (30 mg BI)** **DG 6 (40 mg BI)** **Elderly (10/20 mg BI)[2]**	Date/time of first administration of study drug	Date/time of last administration of study drug + REP (36 hrs) or 12:00 a.m. on day after subject's trial termination date, whichever occurs earlier
Follow-up	**F/U Placebo MRD** **F/U Placebo Elderly** **F/U DG 1 (2.5 mg BI)** **F/U DG 2 (5 mg BI)** **F/U DG 3 (10 mg BI)** **F/U DG 4 (20 mg BI)** **F/U DG 5 (30 mg BI)** **F/U DG 6 (40 mg BI)** **F/U Elderly (10 mg BI)[3]** **F/U Elderly (20 mg BI)**	Date/time of last administration of study drug + REP (36 hrs)	12:00 a.m. on day after trial termination date

[1] See Section 6.7 for definition of baseline.
[2] In Listings the actual treatment will be displayed as Elderly (10 mg BI) or Elderly (20 mg BI) depending on the actual dose received.
[3] Only applicable if subject prematurely discontinued treatment.

AE displays in CTR Section 9.3, Appendix 10.5.1.8 will present results for the on-treatment phase only (as defined in Table 6.1: 1). Screening and follow-up phase will not be included in this analysis.

All AEs will be listed, based on the "actual treatment" as defined in Table 6.1: 1.

In AE tables in CTR Section 9.3 (but not in displays for ClinicalTrials.gov and EudraCT), the following totals will be provided in addition:

- Total Placebo, defined as the total over all on-treatment phases involving Placebo (with regard to MRD and Elderly part)
- Total BI MRD, defined as the total over all on-treatment phases involving BI 1569912 (with regard to MRD part)
- Total BI, defined as the total over all on-treatment phases involving BI 1569912 (with regard to MRD and Elderly part)
- Total on-trt, defined as the total over all on-treatment phases involving BI 1569912 or Placebo (with regard to MRD and Elderly part)

Laboratory data, other safety assessments (for example vital signs), and biomarker assessments will be analysed based on treatment groups with clear differentiation between baseline (cf. Section 6.7) and post-baseline. Of note, laboratory measurements taken during the follow-up phase will only be listed, but will not be used in descriptive summaries. However, this distinction will not be made in other safety assessments.

More details on the technical implementation of these analyses are provided in the ADS Plan of this TSAP and Analysis Data Reviewers guide.

6.2 IMPORTANT PROTOCOL DEVIATIONS

Consistency check listings (for identification of deviations from time windows) and a list of protocol deviations (e.g., deviations in drug administration, in blood sampling times, etc.) will be provided to be discussed at the Report Planning Meeting (RPM). At this meeting, it will be decided whether a discrepant data value can be used in analyses or whether it must be corrected in the clinical database. Each protocol deviation must be assessed to determine whether it is an important PD (iPD). For definition of iPDs, and for the process of identification of these, refer to the BI reference document "Identify and Manage Important Protocol Deviations (iPD)" (2) and the DV domain template.

If any iPDs are identified, they are to be summarised into categories and will be captured in the decision log. Categories which are considered to be iPDs in this trial are defined in the DV domain specification. If the data show other iPDs, the definition in the DV domain specification will be supplemented accordingly by the time of the RPM.

IPDs will be summarized and listed. The DV domain specification outlines which types of iPDs could potentially lead to exclusion from various analysis sets. The decision on exclusion of participants from analysis sets will be made at the latest at the RPM, after discussion of exceptional cases and implications for analyses.

6.3 INTERCURRENT EVENTS

This Section is not applicable.

6.4 SUBJECT SETS ANALYSED

The treated set (TS) and pharmacokinetic parameter analysis set (PKS) will be used as defined in the **CTP, Section 7.3**.

In addition, the following subject sets will be used:

All ECG analyses will be performed on the TS, except for the exposure-response analyses, which will 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.

The following table provides an overview of the planned analysis and the subject set to be used.

Table 6.4: 1 Subject sets analysed

		Subject set	
Class of analysis	Treated set	PKS	ECGPCS
Disposition	X		
iPDs	X		
Demographic/baseline characteristics, concomitant diseases, concomitant medications and concomitant procedures	X		
Treatment exposure	X		
Primary endpoint	X		
Secondary endpoints		X	
Further pharmacokinetic endpoints (including metabolic biomarker endpoints)		X	
Exploratory biomarker endpoints (including Eye-tracking, EEG, ERP)	X		
Safety parameters (except for exposure-response analyses of ECG data)	X		
Exposure-response analyses of ECG data			X

[redacted]

6.6 HANDLING OF MISSING DATA AND OUTLIERS

CTP Section 3.3.4*: If a subject is removed from or withdraws from the trial prior to the first administration of trial medication, the data of this subject will not be entered in the case report form (CRF) and will not be reported in the clinical trial report (CTR). If a subject is removed from or withdraws from the trial after the first administration of trial medication, this will be documented and the reason for discontinuation must be recorded in the CRF; in addition, the data will be included in the CRF and will be reported in the CTR.*

CTP Section 7.5.1: *It is not planned to impute missing values for safety parameters*.

One exception where imputation might be necessary for safety evaluation is AE dates. Missing or incomplete AE dates are imputed according to BI standards (3).

CTP Section 7.5.2: *PK parameters that cannot be reasonably calculated based on the available drug concentration-time data will not be imputed.*

Missing data and outliers of PK data are handled according to BI standards (4) and (5).

No imputation will be done for ECG endpoints. If replicate ECG recordings are missing, the arithmetic means per time point will be computed with the reduced (1 or 2) number of recordings. If single cardiac cycles (also denoted as beats or waveforms) are missing, the arithmetic mean for this single ECG will be computed with the reduced (1, 2 or 3) number of cardiac cycles.

For the classification of the on-treatment QTc/QT intervals into 'no new onset' / 'new onset' categories, the handling of missing values is described in Additional Section 10.2.

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

In all analysis (except for analyses of ECG variables), the last non-missing value determined prior to first BI 1569912 or placebo administration will be defined as baseline.

Time windows are defined in Section 6.1 of the CTP. Adherence to time windows will be checked at the RPM.

Centrally evaluated 12-lead ECG time point recording are shown in Table 6.7: 1.

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 will be defined as the mean of the ECG variable values prior to drug administration.

Additional (unscheduled) ECGs may be recorded for safety reasons. Unscheduled ECGs (for safety reasons) will be transferred to the central ECG lab but will not be included into the statistical analysis of interval lengths.

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 outside a maximum acceptable time deviation for a reliable assessment and the pair has to

be excluded from the analysis will be decided no later than at the RPM. When the sampling time of the blood sample or the ECG recording is not available, the pair will also be excluded.

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

Visit 2, Day	**Planned time [hh:mm] - relative to first study drug administration.**	**Study phase**	**Central evaluation**
1	-1:00, -0:45, -0:30	Baseline[1]	first ECG of each of the 3 triplicate baselines
	00:15, 00:30, 00:45, 01:00, 01:15, 01:30, 02:00, 02:30, 03:00, 04:00, 06:00, 08:00, 10:00, 12:00	on-treatment	first single ECG of the triplicate
2	23:00		
14	311:00, 312:15, 312:30, 312:45, 313:00, 313:30, 314:00, 314:30, 315:00, 316:00, 318:00, 320:00, 322:00, 324:00		
15	335:00		
16	359:00	Follow-up	NA
17	383:00		

[1] see Section 10.1 for derivation of analysis values in case of triplicate ECGs at a time point.

For Screening ECG, no central evaluation is performed. At baseline, i.e., Day 1, planned time -1:00h (prior to drug administration) 3 triplicate ECGs are recorded within approximately 1h, which are captured at times -1:00h, -0:45h and -0:30h. Planned times 359:00h and 383:00h are considered as follow-up due to the estimated REP of up to 36 h of BI 1569912.

7. PLANNED ANALYSIS

The format of the listings and tables will follow the BI guideline "Reporting of clinical trials and project summaries" (6).

The individual values of all subjects will be listed. Listings will be sorted by treatment, subject number and visit (if visit is applicable in the respective listing). AE listings will be sorted by assigned treatment (see Section 7.8.1 below for details). The listings will be contained in Appendix 16.2 (SDL) of the CTR.

The following standard descriptive statistical parameters will be displayed in summary tables of continuous variables:

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

For plasma concentrations and for metabolic biomarkers as well as for all PK parameters the following descriptive statistics will additionally be calculated:

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

For plasma concentrations, metabolic biomarker, and PK parameters the following descriptive statistics will additionally be calculated

P10	10th percentile
Q1	1st quartile
Q3	3rd quartile
P90	90th percentile

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

Tabulations of frequencies for categorical data will include all possible categories and will display the number of observations in a category as well as the percentage (%) relative to the respective treatment group. Percentages will be rounded to integer numbers. The category missing will be displayed, if and only if there actually are missing values. Percentages will be based on all subjects in the respective subject set whether they have non-missing values or not.

No formal interim analysis is planned.

Exclusion of subject's data:

Certain PK endpoints of a participant may be missing or excluded for the following reasons:

Exclusion of PK parameters

The ADS ADPP contains column variables APEX and APEXCO indicating inclusion/exclusion (APEX) of a PK parameter and an analysis flag comment (APEXCO). All analyses based on the PKS are based on PK parameter values which are not flagged for exclusion, i.e. with APEX equal to "Included".

CTP Section 7.3*: Plasma/ urine concentration data and parameters of a subject which are flagged for exclusion will be reported with its individual values but will not be included in the statistical analyses.*

Exclusion of PK concentrations

The ADS ADPC (PK concentrations per time-point or per time-interval) contains column variables ACEX or ACEXCO indicating inclusion/exclusion (ACEX) 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 only; the value is included for all other analyses. Excluded concentration itself will be listed in the CTR associated with an appropriate flag.

Further details are given in "Noncompartmental Pharmacokinetic / Pharmacodynamic Analyses of Clinical Studies"(4) and "Description of Analytical Transfer Files and PK/PD Data Files" (5)

Biomarker data:

CTP Section 7.3: *Biomarker data and parameters of a subject will be included in the statistical biomarker analyses, if they are not flagged for exclusion due to a protocol deviation relevant to the evaluation of biomarkers (to be decided no later than in the Report Planning Meeting) or due to non-evaluability (as revealed during data analysis).*

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Only descriptive statistics are planned for this section of the report.

7.2 CONCOMITANT DISEASES AND MEDICATION

Concomitant diseases and non-drug therapies will be coded according to the most recent version of MedDRA. Concomitant medication will be coded according to the most recent version of the World Health Organisation - Drug Dictionary.

Only descriptive statistics are planned for this section of the CTR. These will be based on the TS.

CTP Section 7.3.4: *Previous and concomitant therapies will be presented per treatment group without consideration of time intervals and treatment periods.*

A medication will be considered concomitant to a treatment group, if it

- is ongoing at the time of study drug administration, or
- starts within the analysis phase of the respective treatment (see Section 6.1 for a definition of treatments and analysis phases).

The relevance of the concomitant therapies to the evaluation of PK will be decided no later than at the RPM.

7.3 TREATMENT COMPLIANCE

Treatment compliance will not be analysed as a specific endpoint (cf. Section 5.4.2). Any deviations from complete intake will be addressed in the Report Planning Meeting (cf. Section 6.2) and described in the CTR.

7.4 PRIMARY OBJECTIVE ANALYSIS

Independent of the main objectives stated in the CTP, this section describes further details of the primary endpoint analyses outlined in the CTP.

7.4.1 Main analysis

Refer to Section 7.8.1 for a description of the analysis of AEs, and in particular the analysis of the percentage of subjects with treatment-emergent drug related AEs, which is the primary endpoint of this trial.

CTP Section 7.3.4: *Safety will be assessed as defined by the endpoints listed in* CTP *Section 2.1.2 and 2.2.2 based on the treated set (TS). Safety analyses will be descriptive in nature and will be based on BI standards.*

[redacted]

7.4.4 Supplementary analysis

Not applicable.

7.5 SECONDARY OBJECTIVE ANALYSIS

Independent of the main objectives stated in the CTP, this section describes further details of the secondary endpoint analyses.

7.5.1 Key secondary objective analysis

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

7.5.2 Secondary objective analysis

The analysis of secondary endpoints will be based on the PKS.

7.5.2.1 Secondary endpoint analysis

CTP Section 7.3.2: *The secondary endpoints (refer to* CTP *Section 2.1.3) will be analysed descriptively.*

The analysis of standard PK parameters is performed according to BI standards (4).

7.5.2.2 Further exploratory analyses of secondary endpoints

Dose proportionality will be evaluated as defined in the **CTP Section 7.3.2** by use of the power model for pharmacokinetic endpoints $AUC_{\tau,ss}$ and $C_{max,ss}$ at steady state, and also at Day 1 with $AUC_{0\text{-}24}$ and C_{max}.

Data of the Elderly part will not be included in the analysis as the population characteristics are different and treatment regimens (duration) are different.

CTP Section 7.3.2:

The power model describes the functional relationship between the dose level and PK endpoint on the log scale via

$$y_{km} = log\,(x_{km}) = \mu + \beta \cdot log\,(D_k) + e_{km},$$

where

y_{km} *logarithm of response (PK parameter) measured on subject m receiving dose k,*
μ *the overall mean,*
β *slope parameter of linear regression line,*
D_k *level of dose k, k=1,…,I,*
e_{km} *the random error associated with the* m^{th} *subject who was administered dose k* ($e_{km} \sim N(0, \sigma^2)$ *iid).*

The slope parameter β together with its two-sided 90% confidence interval will be estimated. Additionally, the r-fold change $r^{\beta-1}$ *together with its 90% CI will be derived.*

The r-fold change will be derived for the following values of r:

- 2
- ratio of highest dose to lowest dose (for respective dose range; either entire dose range or subrange, cf. following paragraph)

CTP Section 7.3.2*: As some small doses at the beginning and/ or some doses at the upper end might not contribute to the linear relationship between dose and PK, dose proportionality over the entire dose range investigated might not be shown. In that case, an attempt will be made to identify a subrange of at least 3 consecutive doses where dose proportionality can be concluded.*

Exclusion of PK parameters and exclusion of plasma concentrations are handled as described in Section 7.

7.6 FURTHER OBJECTIVE ANALYSIS

7.6.1 Safety parameters

Safety endpoints and tolerability of BI 1569912 will be analysed as described in Section 7.8 of this TSAP.

7.6.2 Further pharmacokinetic parameters

Exclusion of PK parameters, exclusion of plasma concentrations as well as exclusion of metabolic biomarker values are handled as described in Section 7.

Analyses of PK parameters will be based on the PKS.

7.6.2.1 Further pharmacokinetic endpoints

Further pharmacokinetic endpoints related to BI 1569912, as defined in **CTP Section 2.2.2.2,** will be analysed descriptively.

In addition, following pharmacokinetic parameters will be calculated.

- $t_{max,ss}$ (time from dosing last dosing to maximum measured concentration of the analyte in plasma at steady state)
- $t_{min,ss}$ (time from (last) dosing to the minimum concentration of the analyte in plasma over the dosing interval τ at steady state)
- $RC_{max,T/R}$ (Ratio of C_{max} in fed to C_{max} in fasted at steady state)
- $RAUC_{0\_24,T/R}$ (Ratio of $AUC_{\tau,ss}$ in fed to $AUC_{\tau,ss}$ in fasted at steady state)

7.6.2.2 Linearity index

CTP Section 7.3.3.1*: Linearity with respect to multiple administration will be explored using the linearity index (LI) that will be computed as follows:*

$$LI = \frac{AUC_{\tau,ss}}{AUC_{0-\infty}}$$

In order to construct a confidence interval for LI a linear model on the logarithmic scale including effects for 'subject' and 'AUC type' can be applied, where 'subject' is a random and 'AUC type' a fixed effect.

$$log(AUC_{ij}) = Y_{ij} = \mu + \tau_i + e_{ij}$$

where

Y_{ij} *logarithm of the response (AUC after first dose, AUC after last dose) for subject j and AUC type i; where i = 1 (after first dose), 2 (after last dose) and j=1, 2,…, n*

μ *the overall mean*

τ_i *the AUC type i*

e_{ij} *random error associated with subject j at AUC type i*

The errors e_{ij} are assumed to be independent of one another and are assumed to be normally distributed with mean zero and covariance matrix Ψ. The covariance matrix is chosen to be an unstructured matrix to allow for different variances for the two AUC types. A pairwise comparison of both areas via the log transformed difference

$$log(\frac{AUC_{\tau,ss}}{AUC_{0-\infty}}) = log(AUC_{\tau,ss}) - log(AUC_{0-\infty})$$

will then be performed including calculation of a two-sided 90% CI. The back-transformed point estimate then provides the estimate of the LI. Perfect linearity with respect to multiple administrations holds true if this index equals unity.

Generally, this model will be applied to each dose level separately. If there is evidence that the areas are comparable for different dose levels, they can be analysed simultaneously. The corresponding model will then include the log-transformed dose as an (additional) covariate.

Administered dose on Day 1 and Day 14 is different in Elderly part, resulting that $AUC_{0-\infty}$ with 10 mg and $AUC_{\tau,ss}$ with 20 mg. Therefore, LI will not be assessed in Elderly part.

7.6.2.3 Attainment of steady state

CTP Section 7.3.3.1: *Attainment of steady state in the MRD-part will be explored by using the trough concentrations of BI 1569912 between Days 1 and 9 for each dose level.*

The trough concentrations of BI 1569912 at the time points 23:00, 47:00, 71:00, 95:00, 119:00, 143:00, 167:00, and 191:00 will be used.

Attainment of steady state will be explored via graphical investigations (e.g., individual time-courses of trough plasma concentrations and the geometric mean plotted by dose level) and if applicable via a repeated measures linear model on the log scale. The statistical model is described by

$$Y_{ijk}=\mu + \tau_i + \zeta_k + (\tau\zeta)_{ik} + e_{ij} ,$$

where

Y_{ijk}	*logarithm of the concentrations for subject j at time i receiving dose k, i = 1, 2, … I and j=1, 2,…, n*
μ	*the overall mean,*
τ_i	*the effect associated with time point i (repeated effect),*
ζ_k	*the effect associated with dose group k,*
$(\tau\zeta)_{ik}$	*the interaction effect of time i and dose group k,*
e_{ij}	*random error associated with subject j at time i (assumed to be independent and identically normally distributed between subjects). Within subjects the following multivariate normal-distribution is assumed* $(e_{1j}, \dots, e_{Ij}) \sim N_I\ (0, \Psi).$

Depending on the relevance of the interaction effect, it will be removed or kept. As default, the unstructured (UN or UNR) type of the covariance matrix will be used for Ψ.

Attainment of steady state of BI 1569912 will be explored by use of a repeated measures linear model on the logarithmic scale as described above; time point and dose group will be included as fixed effects and the interaction term time by dose will also be included.

It will be checked if the interaction between 'time' and 'dose' is present, i.e. whether the attainment of steady-state depends on the dose. To this end the model as described above (i.e. including, 'time' as a discrete repeated effect (using the blocking factor ‘subject’), 'dose' as a fixed effect and a variable for the interaction between 'time' and 'dose') can be used. Using this statistical model allows simultaneous analysis for all dose levels, while still allowing for between-dose differences with regards to timing of steady state attainment. The check whether the attainment of steady-state depends on dose will be done by investigating whether the p-value for the interaction is < 0.1. This will be accompanied by visual inspection of the data. Performing these checks there is the possibility to identify a (sub-) range of doses for which the interaction can be considered not relevant.

If the interaction is relevant, then there will be no further step and the relevant comparisons will be retrieved based on the model described above. If the interaction is not relevant (at least for a range of dose groups), the model without the interaction term will be used as the final repeated-measures model for the investigation of steady-state (11).

The model will be estimated using an unstructured covariance matrix. In case convergence criteria are not met when using this covariance structure, the following covariance structures will be chosen, in the pre-defined order: Toeplitz or AR1. A compound symmetry structure of

the covariance matrix will not be considered, as this structure already postulates a steady state. The SAS code is presented in Additional Section 10.6.

CTP Section 7.3.3.1: *The model will be used to explore the time to steady state by making pairwise comparisons of concentrations from different time points, usually each time point vs. the last time point: log-transformed differences between time points will be back-transformed by exponentiation to give the corresponding (adjusted) gMean ratio and 90% two-sided confidence interval.*

Graphical displays will include (but is not limited to) individual time-courses of trough plasma concentrations and the (geometric) mean plasma concentration time profiles.

Attainment of steady state in the ELDERLY-part will only be explored via graphical investigations at the time points 23:00, 47:00, 71:00, 95:00, 119:00, 143:00 and 167:00 because the increase to the target dose is planned on Day 8. The individual time-courses of pre-dose plasma concentrations and the descriptive geometric mean plasma concentration time profile of the starting dose 10 mg will be plotted.

7.6.2.4 Food effect on Day 9 compared to Day 14

CTP Section 7.3.3.1: *The food effect in the MRD part will be assessed descriptively.*

The PK parameter $AUC_{\tau,ss}$ and $C_{max,ss}$ after administration of BI 1566912 on Day 9 and Day 14 respectively will be used to investigate the food effect. The geometric mean ratios of the PK parameters of Day 9/Day14 will be calculated.

7.6.2.5 Metabolic biomarkers

Further pharmacokinetic endpoints related to the biomarkers 4-beta hydroxycholesterol (plasma) and 6-beta hydroxyl cortisol (urine) and cortisol (urine), as defined in **CTP Section 2.2.2.2,** will be analysed descriptively based on the PKS for the MRD-part only (**cf. CTP Section 5.3.2.4 and 5.3.2.5**).

7.6.3 Exploratory biomarkers

[redacted]

7.6.3.1 Eye-tracking (MRD part only)

Eye-tracking endpoints listed in Section 5.3.3.1 will be descriptively summarized by time point and treatment group as continuous variable. Descriptive statistics will be provided for absolute values, the change from baseline as well as the percent change from baseline (see Section 6.7 for baseline definition).

For the active drug groups, also placebo corrected mean change from baseline values will be presented (calculated as (mean change from baseline for the respective active drug group at

the respective individual time point) – (mean change from baseline for placebo at the respective individual time point)).

7.6.3.2 qEEG, including baseline EEG

qEEG endpoints listed in Section 5.3.3.2 will be descriptively summarized by time point and treatment group as continuous variable. Descriptive statistics will be provided for absolute values, the change from baseline as well as the percent change from baseline (see Section 6.7 for baseline definition).

In addition, for the active drug groups, also placebo-corrected values will be summarised.

Calculation will be as described in Section 7.6.3.1. Placebo-corrected values will be calculated based on Placebo subjects in the respective part.

The CTR analyses will focus on the FZ electrode location only.

7.6.3.3 ERP

ERP endpoints listed in Section 5.3.3.3 will be descriptively summarized by time point and treatment group as continuous variable. Descriptive statistics will be provided for absolute values, the change from baseline as well as the percent change from baseline (see Section 6.7 for baseline definition).

In addition, for the active drug groups, also placebo corrected mean change from baseline values will be presented. Calculation will be as described for Section 7.6.3.1. Placebo-corrected values will be calculated based on Placebo subjects in the respective part.

The CTR analyses will focus on the FZ electrode location only.

7.7 EXTENT OF EXPOSURE

Descriptive statistics based on the TS are planned for this section of the report.

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.

7.8.1 Adverse Events

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.

For further details on summarization of AE data, please refer to "Analysis and Presentation of Adverse Event Data from Clinical Trials" (7) and "Handling of missing and incomplete AE dates" (3).

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 phase as defined in Section 6.1. AEs will be analysed based on actual treatments, as defined in Table 6.1: 1.

An overall summary of AEs will be presented. This overall summary will comprise summary statistics for the class of AESIs.

CTP Section 5.2.6.1.4*: 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*

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

No other AESIs have been defined for this trial.

The investigator had to classify on the eCRF whether an observed AE was an AESI or not.

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

The frequency of subjects with AEs will be summarised by treatment, primary SOC and preferred term. Separate tables will be provided for subjects with

- AEs which were considered by the investigator to be drug related
- AEs summarized by worst intensity
- SAEs
- AESIs
- AEs leading to treatment discontinuation

The SOCs and preferred terms within SOCs will be sorted by descending frequency over all treatment groups.

For disclosure of AE data on ClinicalTrials.gov, the frequency of subjects with non-serious AEs occurring with an incidence of greater than 5% (in preferred terms) will be summarised

by treatment, primary SOC and preferred term. The frequency of subjects with SAEs will also be summarised.

For disclosure of AE data in the EudraCT register, the frequency of AEs, the frequency of non-serious AEs with an incidence of greater than 5% (in preferred terms) and the frequency of SAEs will be summarized.

For support of lay summaries, the frequency of subjects with drug-related SAEs will be summarized by treatment, primary SOC and preferred term.

Clinically relevant findings in laboratory data, vital signs or abnormal findings in ECG (irrespective of whether they originate from central or local evaluation) will be reported as AEs (after first administration of study treatment) or as baseline conditions (prior to first administration of study treatment) if judged clinically relevant by the investigator, and will be analysed as such.

7.8.2 Laboratory data

The analyses of laboratory data will be descriptive in nature and will be based on BI standards "Handling, Display and Analysis of Laboratory Data" (9).

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.

Descriptive statistics of laboratory values over time and for the difference from baseline (see Section 6.7) will be provided. Frequency tables of changes between baseline and last value on treatment with respect to the reference range will be presented.

Unscheduled measurements of laboratory 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. Descriptive statistics will be calculated by planned time point based on the worst value of the participant at that planned time point (or assigned to that planned time point).

Laboratory data will be compared to their reference ranges. Values outside the reference range as well as possibly clinically significant values (according to standard BI criteria defining possibly clinically significant abnormalities) will be highlighted in the listings. Possibly clinically significant laboratory values will be listed in Section 15.4.1.

7.8.3 Vital signs

The analyses of vital signs (blood pressure, pulse rate and body temperature) will be descriptive in nature. Descriptive statistics of vital signs over time and for the difference from baseline (see Section 6.7) will be provided.
Unscheduled measurements of vital signs will be assigned to planned time points in the same way as described above for laboratory data. However, for vital signs, descriptive statistics will

be calculated by planned post-baseline time point based on the first value of the participant at that planned time point (or assigned to that planned time point). If the time of measurement is missing for a scheduled post-baseline measurement the scheduled measurement will be used in calculation of descriptive statistics (as time difference between scheduled and unscheduled cannot be assessed).

7.8.4 ECG

No separate listing or analysis of local continuous ECG monitoring or Holter ECG recording will be prepared.

CTP Section 5.2.4.1: *Abnormal findings, irrespective of whether they originate from central or local evaluation, will be reported as AEs (during the trial) or baseline conditions (at screening), if judged clinically relevant by the investigator.*

Central 12-lead ECG

Descriptive analysis of ECG endpoints will be based on the TS.

The evaluation of the relationship between plasma concentration and ECG endpoints (exposure-response analysis) will be based on the ECGPCS.

ECG measurements will not be included in the statistical analysis if one of the following applies:

- No date or time available for ECG measurement
- Pre-dose measurement done after first drug administration
- On-treatment measurement done before first drug administration
- Measurement is a repeated measurement
- More than 3 single ECGs (i.e., measurements from 4th single ECG onwards will not be included)
- Unscheduled measurements

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.

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 presented in figures.

For more details to categorical endpoint definition refer to Additional Section 10.2.

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.

Exposure-response analysis

Data collected during the on-treatment and follow-up phase (see Table 6.7: 1) from all MRD treatment groups will be used for the ECG exposure-response analysis.

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 1569912 plasma concentrations and QTcF changes from baseline will be investigated in an exploratory manner using a random coefficient model to estimate the difference in mean QTcF change from baseline between BI 1569912 and placebo and its 90% confidence interval at the geometric mean of C_{max} (after single dose) and of $C_{max,ss}$ (in steady state) for each treatment group. 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. [R18-0143] (10) with ΔQTcF as response variable, centered baseline QTcF and plasma concentration as continuous covariates, treatment, time and day as fixed categorical effects, and a random intercept and slope for each subject.

Restricted maximum likelihood estimation will be performed, and the Kenward-Roger method will be applied to adjust standard errors and estimate denominator degrees of freedom. For more details refer to Additional Section 10.3.

For visualization, a scatterplot of the BI 1569912 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 the geometric mean 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 (see [R18-0143] (10)) and residual plots.

To check model assumptions, the conditional residuals will be plotted and presented in the Statistical Appendix of the CTR. 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 (e.g. effect compartment models, non-linear models, etc.).

All of the above described graphical and statistical analyses for the exposure-response analysis will be also performed for HR in place of QTcF.

Elderly-part:

For the active treatment group in the Elderly part a possible effect of age on PK concentration cannot be ruled out. A separate analysis will be carried but the number of pairs of ECG variables and corresponding plasma concentrations is insufficient to fit a random coefficient model. Furthermore, the planned number of placebo subjects in this part (n=3) is low and only one active treatment group will be investigated in this part. 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). These figures will also be presented for HR.

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 Additional Section 10.5 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. The resulting (fixed effect) slope together with two-sided 95% confidence intervals will be included in the footnote for this plot.

7.8.5 Other

7.8.5.1 Physical findings

Physical findings will be reported as relevant medical history/baseline condition (if a condition already exists before first administration of study treatment) or as AE (if condition emerges after first administration of study treatment) and will be summarized as such. No separate listing or analysis of physical examination findings will be prepared.

7.8.5.2 Assessment of suicidal ideation and behavior (SIB) based on C-SSRS

Suicidality monitoring will be performed as described in Section 5.2.5.2 of the CTP. Results will be listed. Findings will also be reported as AEs as described in the CTP Section 5.2.5.2.

7.8.5.3 Standardized mental and neurological assessment

CTP Section 5.2.5.1: *Clinically relevant findings of the mental and neurological examination will be reported as adverse events (during the trial) or as baseline conditions (at screening).*

No further outputs of standardized mental and neurological are provided in the CTR.

7.8.5.4 Assessment of dissociative symptoms (CADSS)

CADSS single items and total score will be listed only.

A table presenting frequency of subjects categorized by CADSS total score '0' or '>=1' by treatment group and planned time point might be considered if some subjects with a total score '>=1' are observed.

7.8.5.5 Safety EEG

CTP Section 5.2.5.5: *While an 'abnormal/ epileptiform' finding will lead to exclusion of the subject at screening (refer also to Section* CTP *3.3.3 an 'abnormal/ non-epileptiform' finding at screening will be reported as baseline condition. 'Abnormal/ epileptiform' or 'abnormal/ non-epileptiform' findings during the trial will be reported as AEs, if judged clinically relevant by the investigator.*

Frequency of subjects categorized by EEG abnormalities (normal, abnormal/epileptiform, abnormal/ non-epileptiform) will be presented by treatment group and time point.

7.8.5.6 BAC

The three total scores listed in Section 5.3.1.3 will be descriptively summarized by time point and treatment group as continuous variable. Descriptive statistics will be provided for absolute values and the change from baseline (see Section 6.7 for baseline definition). Furthermore, individual time-courses of the three total scores and the mean will plotted.

7.8.5.7 SMWQ

The total score (absolute value) will be summarized descriptively by time point and treatment group.

7.8.5.8 Body weight

As body weight is only collected at screening and Visit 3 (End of trial examination), it will be listed. However, body weight at screening is part of the summary of the baseline characteristic (see Section 5.4.1).

7.9 OTHER ANALYSIS

7.9.1 Biomarker analyses

Analysis of EEG endpoints is described in Section 7.6.3.

7.9.2 PK / PD analyses

CTP Section 5.3.4: *The relationship between plasma concentrations and ECG endpoints will be investigated in an exploratory manner.*

The exposure-response analysis is described in Section 7.8.4.

CTP Section 5.3.4: *If data allows, an exploratory and descriptive PK/ PD analysis of plasma concentrations/ PK parameters of BI 1569912 will be plotted against pharmacodynamics readouts, e.g., qEEG parameters. […]Other correlations will be explored, if applicable.*

No correlation analysis is planned.

7.9.3 Pharmacogenomic analyses

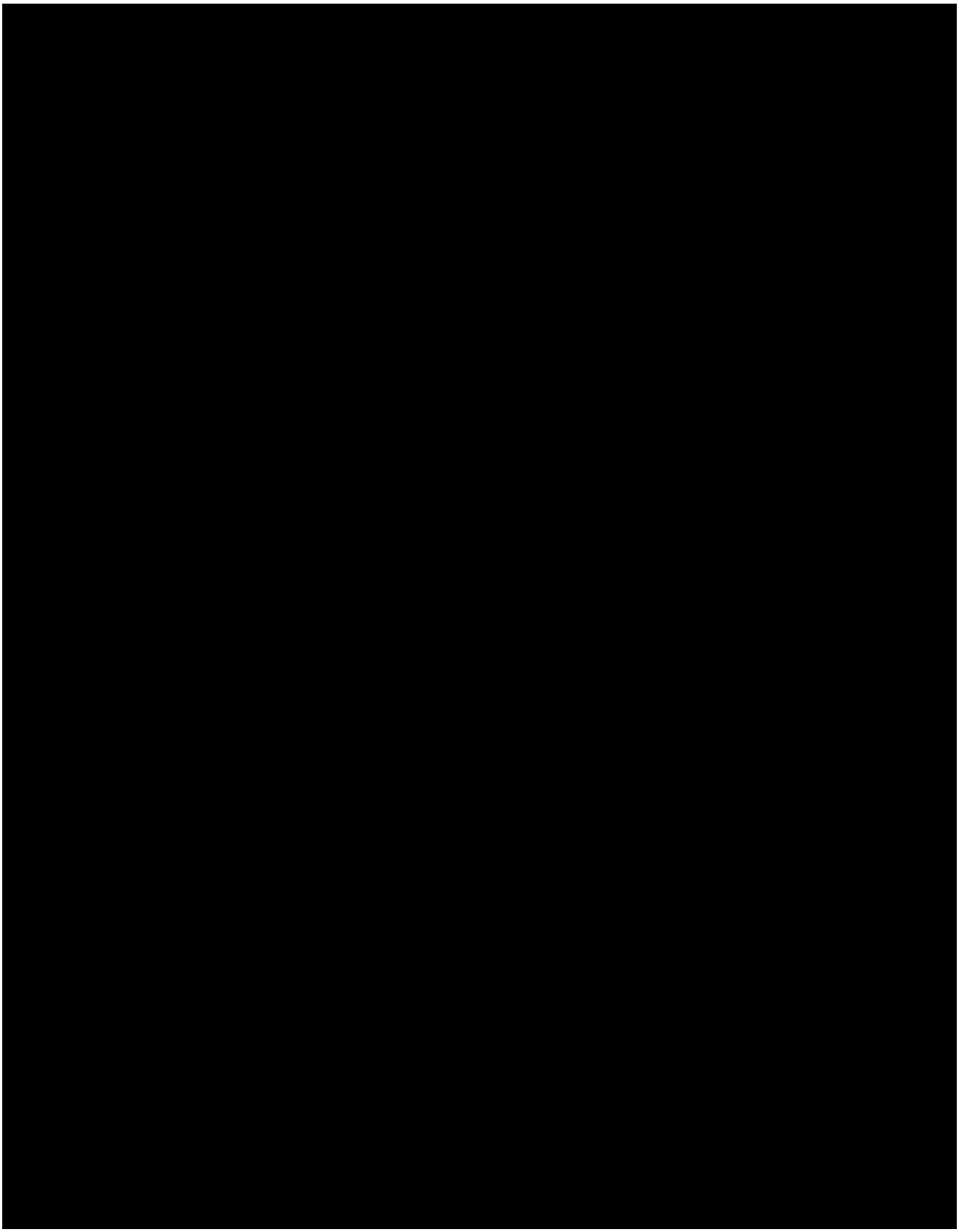
Listing of pharmacogenomic endpoints might be prepared in the CTR. PK analysis by genotyping data will be performed and reported in the CTR as needed.

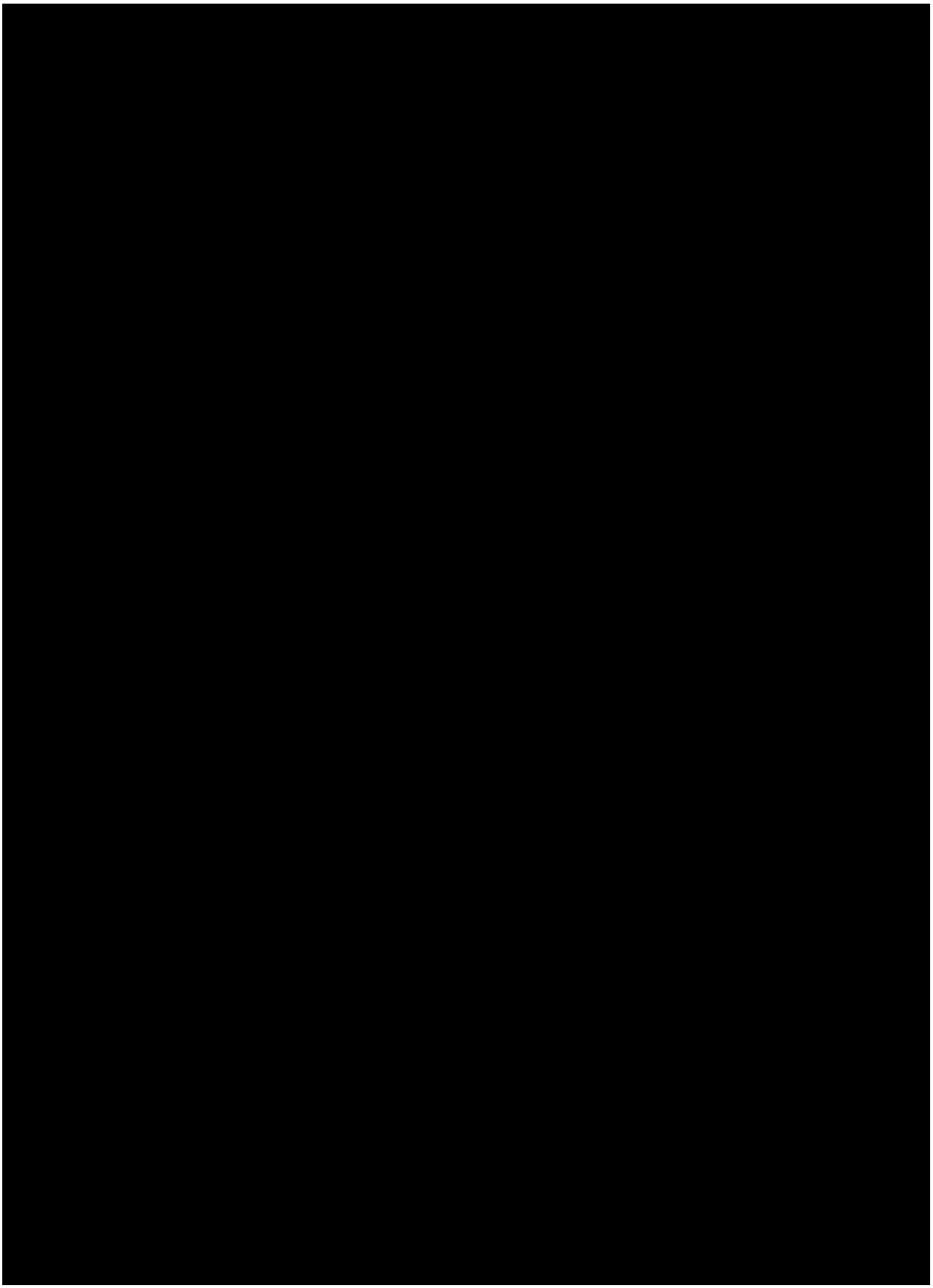
8. TIMEPOINT OF RELEASE OF TREATMENT INFORMATION

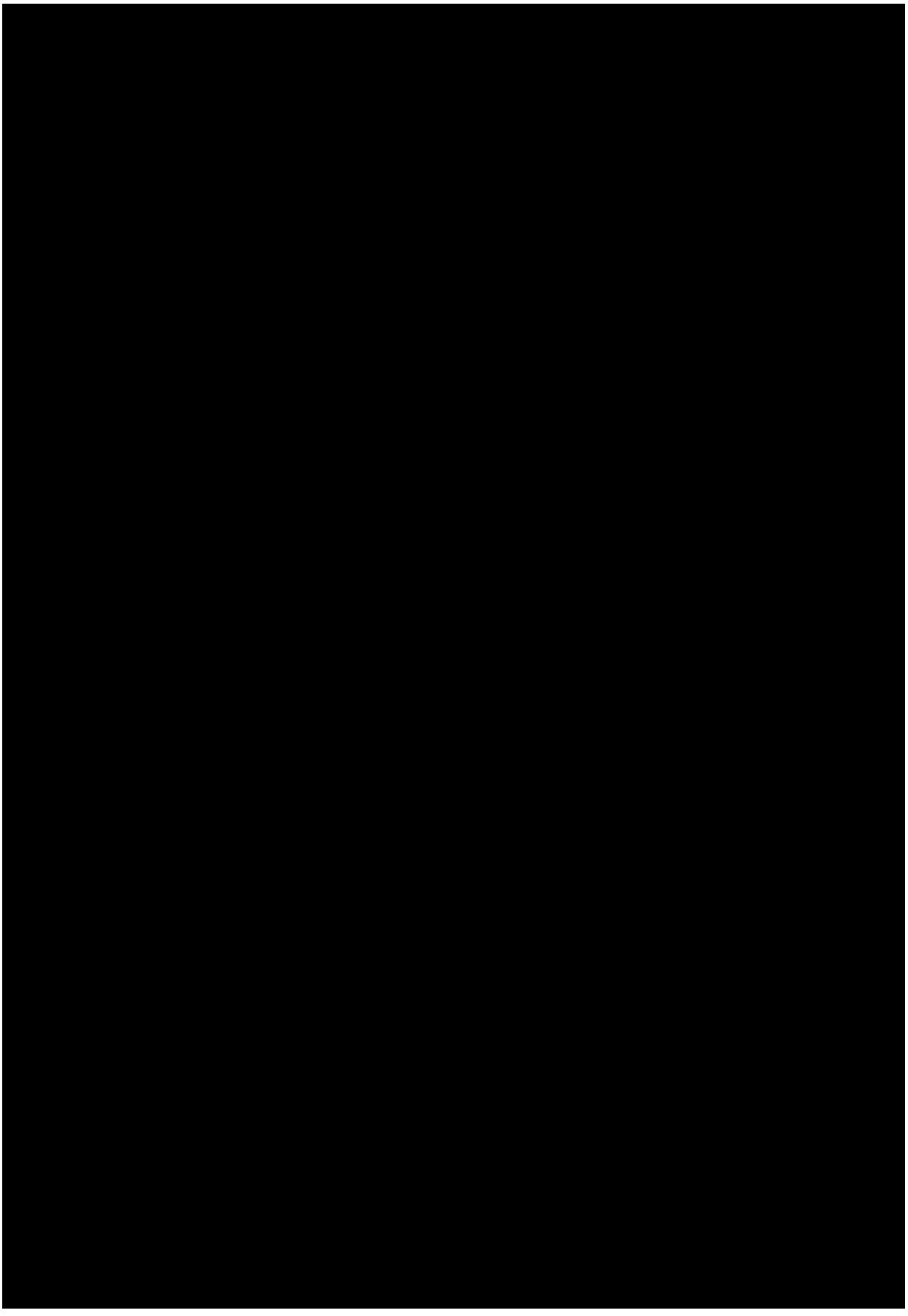
The treatment information has been released to unblind the trial database during the conduct of the trial and was handled open-label (see CTP section 4.1.5.1).

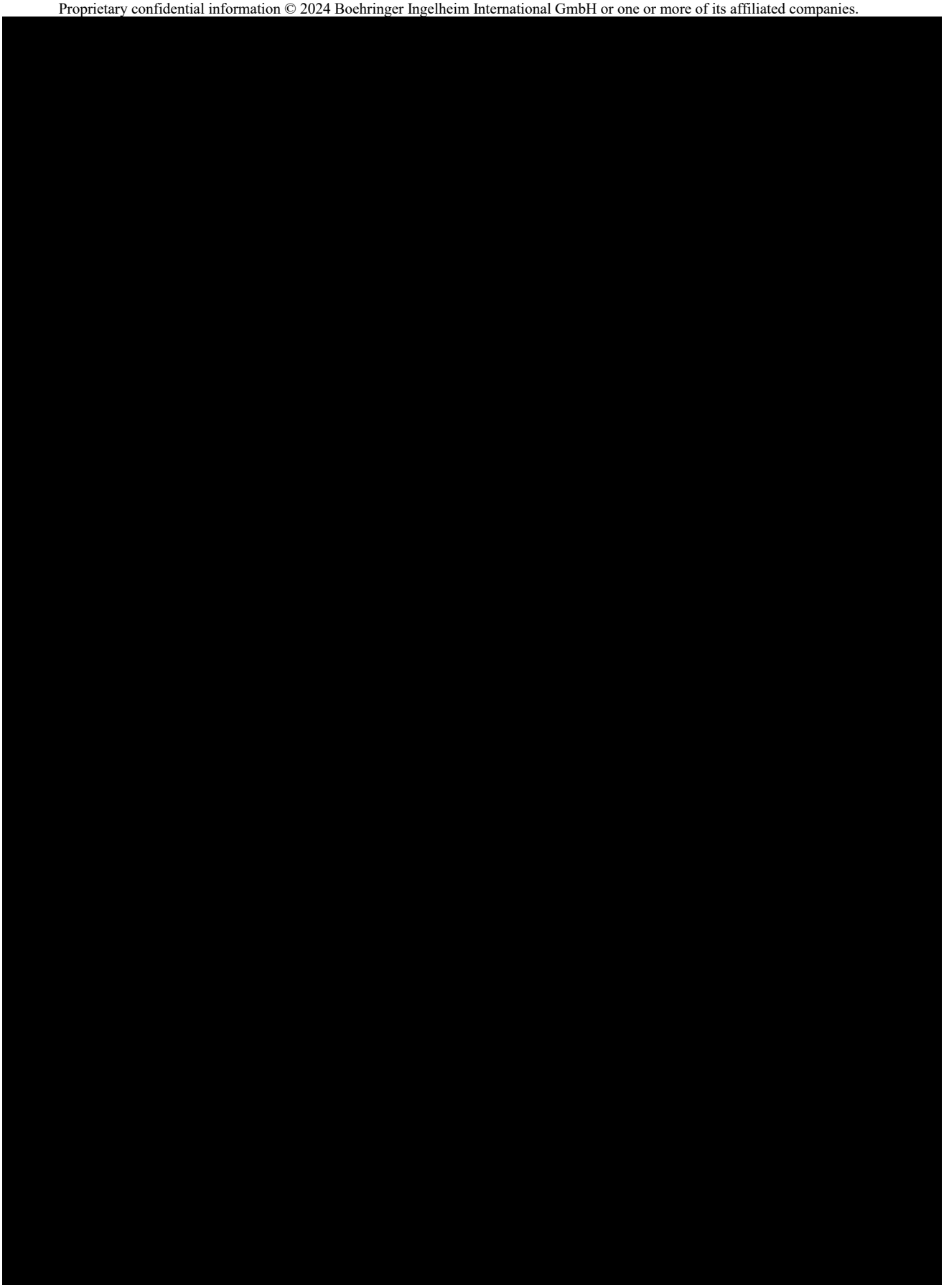
9. REFERENCES

1	*CPMP/ICH/363/96*: "Statistical Principles for Clinical Trials", ICH Guideline Topic E9; Note For Guidance on Design, Conduct, Analysis and Evaluation of Clinical Trials, current version
[redacted]	
8	*CPMP/ICH/137/95*: "Structure and Content of Clinical Study Reports", ICH Guideline Topic E3; Note For Guidance on Structure and Content of Clinical Study Reports, current version
[redacted]	
10	Garnett C, Bonate PL, Dang Q, Ferber G, Huang D, Liu J, et al. Scientific white paper on concentration-QTc modeling. J Pharmacokinet Pharmacodyn. 2018. 45(3): 383-397. [R18-0143]
[redacted]	









11. HISTORY TABLE

Table 11: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
1.0	**31-JUL-24**	[redacted]	None	This is the final TSAP.