TRIAL STATISTICAL ANALYSIS PLAN

c34936497-01

BI Trial No.:	1447-0001
Title:	Safety, tolerability, pharmacokinetics and pharmacodynamics of single rising oral doses of BI 1569912 in healthy male subjects (single-blind, partially randomized within dose groups, placebo-controlled, parallel-group design) with an additional relative bioavailability/ food effect part (open-label, randomized, three-way crossover design) Revised Protocol #08
Investigational Product:	BI 1569912
Responsible trial statistician:	[redacted] Phone: [redacted] Fax: [redacted]
Date of statistical analysis plan:	05-Dec-2021 SIGNED
Version:	Final

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2. LIST OF ABBREVIATIONS

Term	Definition / description
AE	Adverse Event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
$AUC_{0-\infty}$	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity
AUC_{0-tz}	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 to the last quantifiable data point
BI	Boehringer Ingelheim
C_{max}	Maximum measured concentration of the analyte in plasma
COVID	Coronavirus disease
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
CV	Arithmetic coefficient of variation
ECG	Electrocardiogram
gCV	geometric coefficient of variation
gMean	Geometric mean
HR	Heart rate
ICH	International Conference On Harmonisation
IPD	Important protocol deviations
LLOQ	Lower limit of quantification
MedDRA	Medical Dictionary For Regulatory Activities
On-trt	On-treatment
PD	Pharmacodynamics
PK	Pharmacokinetics
PKS	Pharmacokinetic parameter analysis set
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

Term	Definition / description
	electrocardiogram
QTcB	QT interval, heart rate corrected according to Bazetts formula
QTcF	QT interval, heart rate corrected according to Fridericias formula
RAGe	Report appendix generator
RPM	Report Planning Meeting
RR interval	ECG interval from the peak of the R wave to the peak of the subsequent R wave
SAE	Serious adverse event
SD	Standard Deviation
SOC	System Organ Class
TS	Treated set
TSAP	Trial Statistical Analysis Plan
ULN	Upper limit of normal range

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 revised CTP, and to include detailed procedures for executing the statistical analysis of the primary variables and other data.

This TSAP assumes familiarity with the CTP and its 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, randomisation.

Study data will be stored in a trial database within Medidata Rave system.

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]).

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

Section 7.3.3 of the CTP states that "dose proportionality will be explored for the further pharmacokinetic endpoints specified in Section 2.2.2.2". The analysis of dose proportionality is not reasonable for all 12 further PK endpoints specified in the CTP. Therefore, this TSAP specifies that this analysis of further PK endpoints will be conducted for further PK endpoint [redacted] of BI 1569912.

Section 7.5.1 of the CTP states that the "relationship between plasma concentrations and ECG endpoints will be investigated in an exploratory manner" in the 30 mg BI dose group. Against the background of the steep PK profile observed for this drug in this trial, it was decided that the time differences observed between plasma samples and ECG measurements were too big to be acceptable (partly due to study procedures with extensive measurements performed at time points). Plasma concentrations and ECG measurements would not relate with each other. It was decided not to perform this analysis in this trail.

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

5. ENDPOINTS

5.1 PRIMARY ENDPOINT

Primary endpoint in the SRD part is the percentage of subjects with treatment-emergent drug-related adverse events.

Primary endpoints in the BA/FE part are $AUC_{0\text{-}tz}$ and C_{max} of BI 1569912 in plasma.

5.2 SECONDARY ENDPOINTS

5.2.1 Key secondary endpoints

Not applicable.

5.2.2 Secondary endpoints

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

SRD-Part:

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

BA/FE-Part:

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

5.3 FURTHER ENDPOINTS

5.3.1 Safety parameters

Safety and tolerability of BI 1569912 will be assessed based on further safety parameters defined in **Section 2.2.2.1 of the CTP**:

- *AEs (including clinically relevant findings from the physical examination)*
- *Safety laboratory tests*
- *12-lead ECG*
- *Continuous ECG monitoring (SRD-Part, only)*
- *Vital signs (blood pressure, pulse rate, respiratory rate, body temperature)*
- *Columbia-Suicide Severity Rating Scale (C-SSRS)*
- *Standardized physical/ neurological assessment* [only as part of AE analysis]
- *Assessment of dissociative symptoms ([…] CADSS)*
- *Electroencephalogram (EEG)* [i.e, safety EEG, abnormal or normal]

CADSS

CTP: *The CADSS is a clinician administered measure of perceptual, behavioural and attentional alterations during active dissociative experiences. The scale contains 23 subjective items, each rated from 0 (not at all) to 4 (extremely).*

The total score of the CADSS is the sum of the 23 item scores, ranging from 0 to 92. Statistical analysis of the CADSS will be based on the total score.

12-lead ECG endpoints

For the definition of baseline and a summary of time points please refer to Section 6.7.

Quantitative ECG endpoints:

The following quantitative ECG endpoints will be determined for the ECG variables QTcF, QT, HR, PR, QRS, RR and QTcB derived as described in Section 10.1:

- absolute values (per time point)
- changes from baseline (per time point)
- percent changes from baseline (per time point; for HR, PR, QRS)

Categorical ECG endpoints

The following categorical ECG endpoints will be determined based on the quantitative ECG endpoints.

- New onset (meaning that this or a higher category was not present at baseline) of maximum QTcF interval > 450 to 480 msec, > 480 to 500 msec, or > 500 msec on treatment. For assignment of a particular subject to one of the above categories, all time points on-treatment (refer to Table 6.7: 4 and Table 6.7: 5) will be considered.
- Maximum change from baseline in QT interval of ≤ 60 msec, or > 60 msec on treatment
- Maximum change from baseline in QTcF interval of ≤ 30 msec, > 30 to ≤ 60 msec, or > 60 msec on treatment

The occurrence of any of the following in the 30 mg dose group (with semi-automatic measurement of RR and QT intervals) will be viewed as "notable findings". Notable findings will not be defined for any of the other treatments (with automatic measurements, exclusively).

- New onset (not present at baseline) of uncorrected QT interval > 500 msec at any time on treatment
- New onset of QTcF interval > 500 msec at any time on treatment
- Change from baseline of QTcF > 60 msec at any time on treatment
- Percent change from baseline of HR ≥ 25%, when corresponding on-treatment value of HR is > 100 beats/min, or percent change from baseline of HR ≤ - 25%, when corresponding on-treatment value of HR is < 50 beats/min, at any time on treatment

For a detailed description of ‘new onset’, refer to Section 10.3.

[redacted]

6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENTS

For basic study information on treatments to be administered, assignment of treatment groups, and selection of doses, cf. Section 4 of the CTP.

Subjects were planned to be treated with

SRD part:

- either a single oral dose of 0.25, 0.75, 2, 5, 10, 20 or 30 mg of BI 1569912 (test treatments)
  or
- a single oral dose of placebo (reference treatment)

All placebo subjects will be analysed in one pooled placebo group (i.e. no distinction between dose groups will be made for placebo subjects).

BA/FE part:

- single oral dose of 5 mg BI 1569912 administered as tablet in fed state (test treatment T1) and in fasted state (test treatment T2) and administered as oral solution in fasted state (reference treatment R) with a wash-out period of at least 5 days between treatments

Subjects were randomly assigned to the six treatment sequences.

For statistical analysis of AEs, the following analysis phases are defined for each subject. Analysis phases for active treatments are defined separately for the SRD and BA/FE part.

Table 6.1: 1 Analysis phases for statistical analysis of AEs, and actual treatment for analysis of laboratory data and vital signs for SRD part

Study analysis phase	Label	Start	End
Screening[1]	**Screening**	Date of informed consent	Date/time of administration of study drug
On treatment	**Placebo,** **0.25 mg BI,** **0.75 mg BI,** **2 mg BI,** **5 mg BI,** **10 mg BI,** **20 mg BI,** or **30 mg BI,** respectively	Date/time of administration of study drug	Date/time of administration of study drug + residual effect period (36 h) or 12:00 a.m. on day after last contact date (whichever occurs first)
Follow-up	**F/U Placebo,** **F/U 0.25 mg BI,** **F/U 0.75 mg BI,** **F/U 2 mg BI,** **F/U 5 mg BI,** **F/U 10 mg BI,** **F/U 20 mg BI, or** **F/U 30 mg BI,** respectively	Date/time of administration of study drug + 36 h	12:00 a.m. on day after last contact date

[1] See Section 6.7 for definition of baseline, which will be used in the statistical analyses of safety laboratory data, ECG and vital signs.

Table 6.1: 2 Analysis phases for statistical analysis of AEs, and actual treatment for analysis of laboratory data and vital signs for BA/FE part

Study analysis phase	Label	Start	End
Screening[1]	**Screening**	Date of informed consent	Date/time of first administration of BI drug
On treatment	**BI tab fed,** **BI tab fasted,** **BI sol fasted**	Date/time of administration of study drug of respective treatment period	Date/time of administration of study drug + REP (36 h) or date/time of administration of study drug in next period or 12:00 a.m. on day after last contact date (whichever occurs first)
Follow-up	**F/U BI tab fed,** **F/U BI tab fasted,** **F/U BI sol fasted**	Date/time of respective treatment administration of BI drug + REP (36 h)	Date/time of administration of study drug of next treatment period or 12:00 a.m. on day after last contact date

[1] See Section 6.7 for definition of baseline, which will be used in the statistical analyses of safety laboratory data, ECG and vital signs.

AE summary tables will present results for the on-treatment phase only. All AEs will be listed.

In AE tables in CTR Section 15.3 (but not in Appendix 16.1.13.1.8.1 and Appendix 16.1.13.1.8.2 AE tables), the following total will be provided in addition:

SRD part:

- "**Total BI SRD**", defined as the total over all on-treatment phases of the SRD part involving BI
- "**Total on-trt SRD**", defined as the total over all on-treatment phases of the SRD part, including placebo

BA/FE part:

- "**Total BI BA/FE**", defined as the total over all on-treatment phases of the BA/FE part involving BI

Safety laboratory data, ECG, qEEG, safety EEG, ERP, CADSS, [redacted] and vital signs will be analysed based on treatment groups (SRD part: Placebo, 0.25 mg BI, 0.75 mg BI, 2 mg BI, 5 mg BI, 10 mg BI, 20 mg BI, 30 mg BI) or on treatments in the respective treatment period (BA/FE part: BI tab fed, BI tab fasted or BI sol fasted) with clear differentiation between baseline (cf. Section 6.7) and post-baseline measurements. Follow-up laboratory measurements will be listed, but will not be used in descriptive summaries.

More details on the technical implementation of these analyses are provided in the ADS Plan of this TSAP.

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. 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).

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 template. If the data show other IPDs, the definition in the DV domain template will be supplemented accordingly by the time of the Report Planning Meeting.

IPDs will be summarized and listed. Which kind of IPDs could potentially lead to exclusion from which analysis set is specified in the DV domain template. The decision on exclusion of subjects from analysis sets will be made at the latest at the Report Planning Meeting, after discussion of exceptional cases and implications for analyses. If the data show other IPDs, this table will be supplemented accordingly by the time of the Report Planning Meeting.

Non-important COVID-19 related PDs will only be listed.

6.3 SUBJECT SETS ANALYSED

The treated set (TS) and pharmacokinetic parameter analysis set (PKS) will be used as defined in Section 7.3 of the CTP. In addition, the following subject set will be used.

[redacted]

[redacted]

Table 6.3: 1 Subject sets analyzed

	Subject set		
Class of endpoint	TS	PKS	[redacted]
Primary endpoint (SRD part)	X		
Primary endpoint (BA/FE part)		X	
Secondary PK endpoints		X	
[redacted]		[redacted]	
[redacted]			[redacted]
Safety parameters	X		
Demographic/baseline characteristics	X		
Treatment 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

CTP: "*If a subject is removed 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 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: "*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).

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 per 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 value is described in Section 10.3.

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

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

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

In all analyses (except for analyses of PD endpoints and analyses of ECG variables), the last available off-treatment value determined prior to the dosing of the respective study drug will be defined as baseline. This means that a separate baseline is defined for each study treatment of the BA/FE part. Off-treatment in this context means that a value measured within an on-treatment phase, as defined in Table 6.1: 2, will not be used as baseline for any study treatment.

Table 6.7: 1 Baseline for [redacted] and ERP endpoints

Post-baseline value		Corresponding baseline value	
Planned time	**Clock time**	**Planned time**	**Clock time**
4:00	12:00	-20:00	12:00
24:00	08:00	-24:00	8:00
48:00	08:00	-24:00	8:00
72:00	08:00	-24:00	8:00

Table 6.7: 2 Baseline for qEEG endpoints

Post-baseline value		Corresponding baseline value	
Planned time	**Clock time**	**Planned time**	**Clock time**
0:45	08:45	-23:00	09:00
1:15	09:15	-23:00	09:00
3:00	11:00	-21:00	11:00
8:00	16:00	-16:00	16:00
24:00	08:00	-23:00	09:00
48:00	08:00	-23:00	09:00
72:00	08:00	-23:00	09:00

Table 6.7: 3 Baseline for additional analysis of qEEG endpoints, using first value after drug administration as baseline

Post-baseline value		Corresponding baseline value	
Planned time	**Clock time**	**Planned time**	**Clock time**
1:15	09:15	0:45	08:45
3:00	11:00	0:45	08:45

A centralised evaluation of 12-lead ECG recordings is performed at the time points specified in Table 6.7: 4 for the SRD part and in Table 6.7: 5 for the BA/FE part.

Table 6.7: 4 Time schedule of 12-lead ECG recordings with centralised evaluation (SRD part)

Visit	Day	Planned time [hh:mm] - relative to first drug administration	Study phase
2	-1	-25:00	Baseline
	1	00:30	On-treatment
		01:10	
		01:30	
		02:00	
		03:00	
		04:00	
		06:00	
		08:00	
		12:00	
	2	24:00	
		34:00	
	3	48:00	Follow-up
	4	72:00	

Table 6.7: 5 Time schedule of 12-lead ECG recordings with centralised evaluation (BA/FE part)

Visit	Day	Planned time [hh:mm] - relative to first drug administration	Study phase
2/3/4	-1	-25:00	Baseline
	1	00:30	On-treatment
		01:05	
		02:00	
		04:00	
		08:00	
	2	24:00	
	3	48:00	Follow-up
	4	72:00	

Three triplicate ECGs will be recorded as the baseline before the first drug administration within each treatment period. Within each triplicate, the mean of ECG variables will be calculated. The mean over the three triplicates will be used as baseline for ECG variables.

For subjects from 30 mg dose group, only the first ECG of each of the 3 baseline triplicates of that period will be transferred to the database. The mean over the three triplicates will be used as baseline for ECG variables in this dose group.

Additional (unscheduled) ECGs may be recorded for safety reasons. These ECGs are assigned to the prior scheduled time point in the sponsor's database. 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.

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

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 or sequence group, 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 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 PK parameters the following descriptive statistics will additionally be calculated:

P10	10^{th} percentile
Q1	1^{st} quartile
Q3	3^{rd} quartile
P90	90^{th} 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 CRF 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 one decimal place. 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.

[redacted]

7.2 CONCOMITANT DISEASES AND MEDICATION

Concomitant diseases 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. Concomitant non-drug therapies will be coded according to the most recent version of MedDRA.

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

CTP: *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 dose 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.

[redacted]

7.4 PRIMARY ENDPOINTS

7.4.1 Primary analysis of the primary endpoints

SRD part:

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 in the SRD part.

BA/FE part:

CTP: *The statistical model used for the analysis of the primary endpoints will be an analysis of variance (ANOVA) model on the logarithmic scale. That is, phamacokinetic endpoints will be log-transformed (natural logarithm) prior to fitting the ANOVA model. This model will include effects accounting for the following sources of variation: sequence, subjects within*

sequences, period and treatment. The effect 'subjects within sequences' will be considered as random, whereas the other effects will be considered as fixed. The model is described by the following equation:

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

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

μ = *the overall mean,*

ζ_i = *the ith sequence effect, i = 1, ... , 6*

s_{im} = *the effect associated with the mth subject in the ith sequence, m = 1, 2, ..., ni*

π_j = *the jth period effect, j = 1, 2, 3*

τ_k = *the kth treatment effect, k = 1, 2, 3*

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

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

Point estimates for the ratios of the geometric means (T1/ T2 and T2/ R) for the primary endpoints (see Section 2.1) and their two-sided 90% confidence intervals (CIs) will be provided.

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

The analysis of primary endpoints of the BA/FE part will be based on the PKS.

Exclusion of PK parameters

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

CTP: *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.*

Exclusion of plasma concentrations

The ADS ADPC (PK concentrations per time-point or per time-interval) contains column variables ACEXC or ACEXCO indicating inclusion/exclusion (ACEXC) of a concentration and an analysis flag comment (ACEXCO). Exclusion of a concentration depends on the analysis flag comment ACEXCO. For example, if ACEXCO is set to "ALL CALC", the value will be excluded for all types of analyses based on concentrations. If ACEXCO is set to "DESC STATS" the value will be excluded from descriptive evaluations per planned time point/time interval. If ACEXCO contains the addition "TIME VIOLATION" or "TIME DEVIATION", the value can be used for further analyses based on actual times. If ACEXCO is set to "HALF LIFE", the value will be excluded from half-life calculation 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 PK/PD Analyses of Clinical Studies"(4) and "Description of Analytical Transfer Files and PK/PD Data Files" (5).

[redacted]

7.5 SECONDARY ENDPOINTS

7.5.1 Key secondary endpoints

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

7.5.2 Secondary endpoints

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

7.5.2.1 Secondary endpoint analysis

SRD part:

The PK endpoints will be assessed descriptively. Analyses will be performed for the parent drug and for metabolites. The analysis of standard PK parameters is performed according to BI standards (4). Exclusion of PK parameter and exclusion of plasma concentrations are handled as described in Section 7.4.1.

BA/ FE-Part:

CTP: *The secondary endpoints (refer to Section 2.1.3) will be* […] *assessed statistically using the same methods as described for the primary endpoints.*

[redacted]

7.8 SAFETY ANALYSIS

All safety analyses will be performed on the TS.

7.8.1 Adverse Events

AEs will be coded with the most recent version of MedDRA.

The analyses of AEs will be descriptive in nature. 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 phases as defined in Section 6.1. AEs will be analysed based on actual treatments, as defined in Table 6.1: 1 and Table 6.1: 2.

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

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*

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. AEs which were considered by the investigator to be drug related will be summarised separately. Separate tables will also be provided for subjects with SAEs and subjects with AESIs. AEs will also be summarized by maximum intensity.

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.

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 baseline and on-treatment 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 subject 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 will be highlighted in the listings.

Clinically significant abnormal laboratory values are only those identified either in the Investigator's comments or at the Report Planning Meeting at the latest. It is the Investigator's responsibility to decide whether a lab value is clinically significant abnormal or not. Standard or project-specific rules for flagging clinically significant values in an automated manner will

not be applied in this study. Clinically relevant findings in laboratory data will be reported as baseline conditions (prior to first administration of study treatment) or as AEs (after first administration of study treatment) if judged clinically relevant by the investigator, and will be analyzed as such.

7.8.3 Vital signs

The analyses of vital signs (blood pressure, pulse rate, respiratory rate, 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 time point based on the last value of the subject 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).
If the time of measurement is missing for an unscheduled measurement, this measurement will be listed but will be ignored for the calculation of descriptive statistics.

Clinically relevant findings in vital signs data will be reported as baseline conditions (prior to first administration of study treatment) or as AEs (after first administration of study treatment) if judged clinically relevant by the investigator, and will be analyzed as such.

7.8.4 ECG

Abnormal findings will be reported as baseline conditions (prior to first study drug administration) or as AEs (from first study drug administration onwards) if judged clinically relevant by the investigator.

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

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. 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 quantitative ECG recordings, 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 of QTcF, QT, HR, PR and QRS will be presented in figures.

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.

Absolute values and changes from baseline (per time point) of QTcB and RR will only be listed, i.e., no statistical summaries will be provided for these quantitative endpoints.

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

7.8.5 Others

7.8.5.1 Physical examination

Physical examination 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 Standardized neurological assessment

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 separate listing or analysis of neurological examination findings will be prepared.

7.8.5.3 Suicidality assessment (C-SSRS)

Suicidality monitoring will be performed as described in Section 5.2.6 of the CTP, results will be listed. Additionally, frequency of subjects categorized by any question answered with

'Yes' (or all answered with 'No' or missing) will be presented. Results for subjects who answered any question with 'Yes' will additionally be listed. Findings will also be reported as AEs.

7.8.5.4 Assessment of dissociative symptoms (CADSS)

Frequency of subjects categorized by CADSS total score '0' or '>=1' will be presented by treatment (or treatment sequence) and time point. In addition, subjects with a total score >0 will be listed.

7.8.5.5 Assessment of safety electroencephalogram (EEG)

Abnormal findings will be reported as baseline conditions (at screening) or AEs (during the trial), if judged clinically relevant by the investigator.

Frequency of subjects categorized by EEG abnormalities will be presented by treatment and day.

7.8.5.6 Body weight

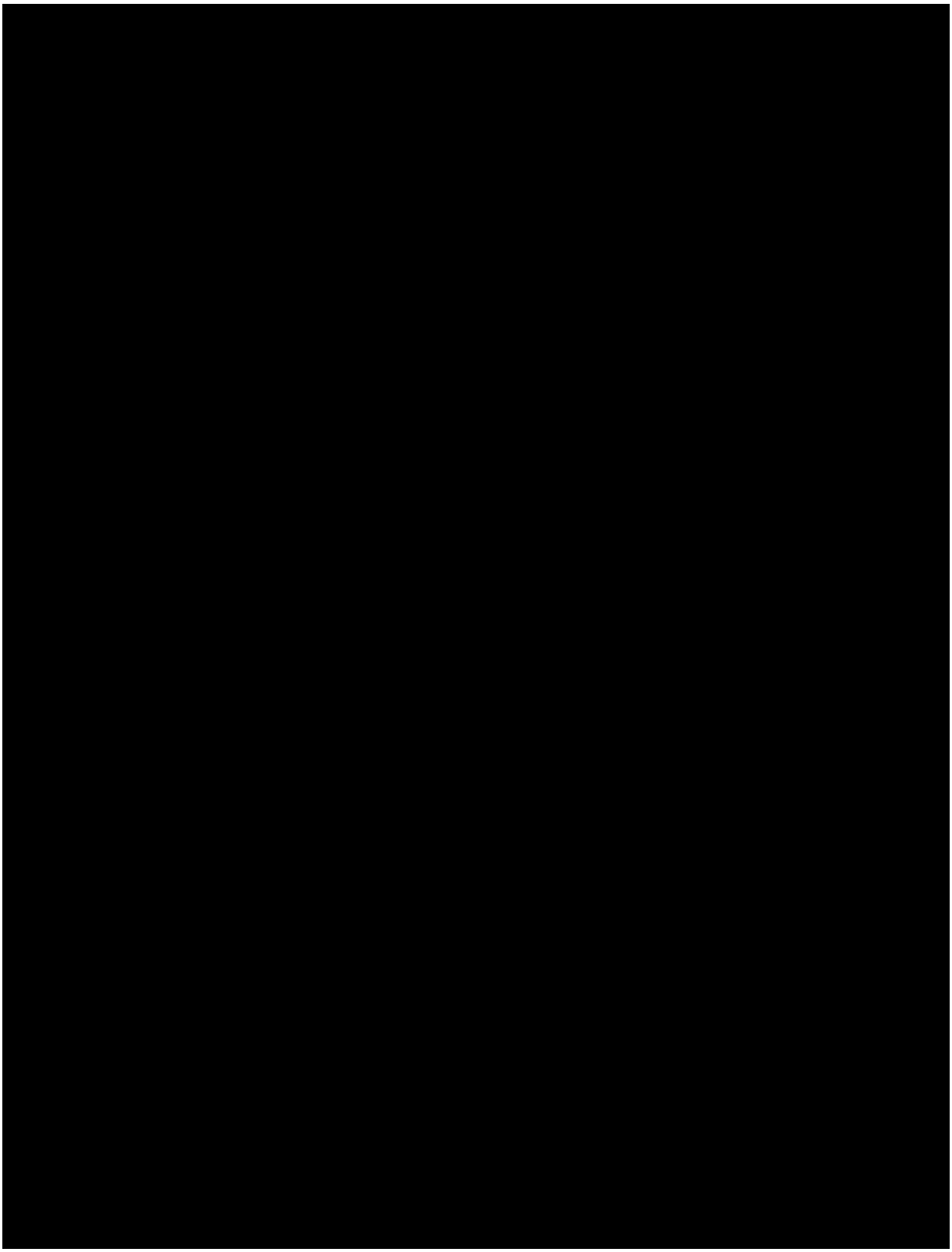
Body weight will be analyzed descriptively, by visit.

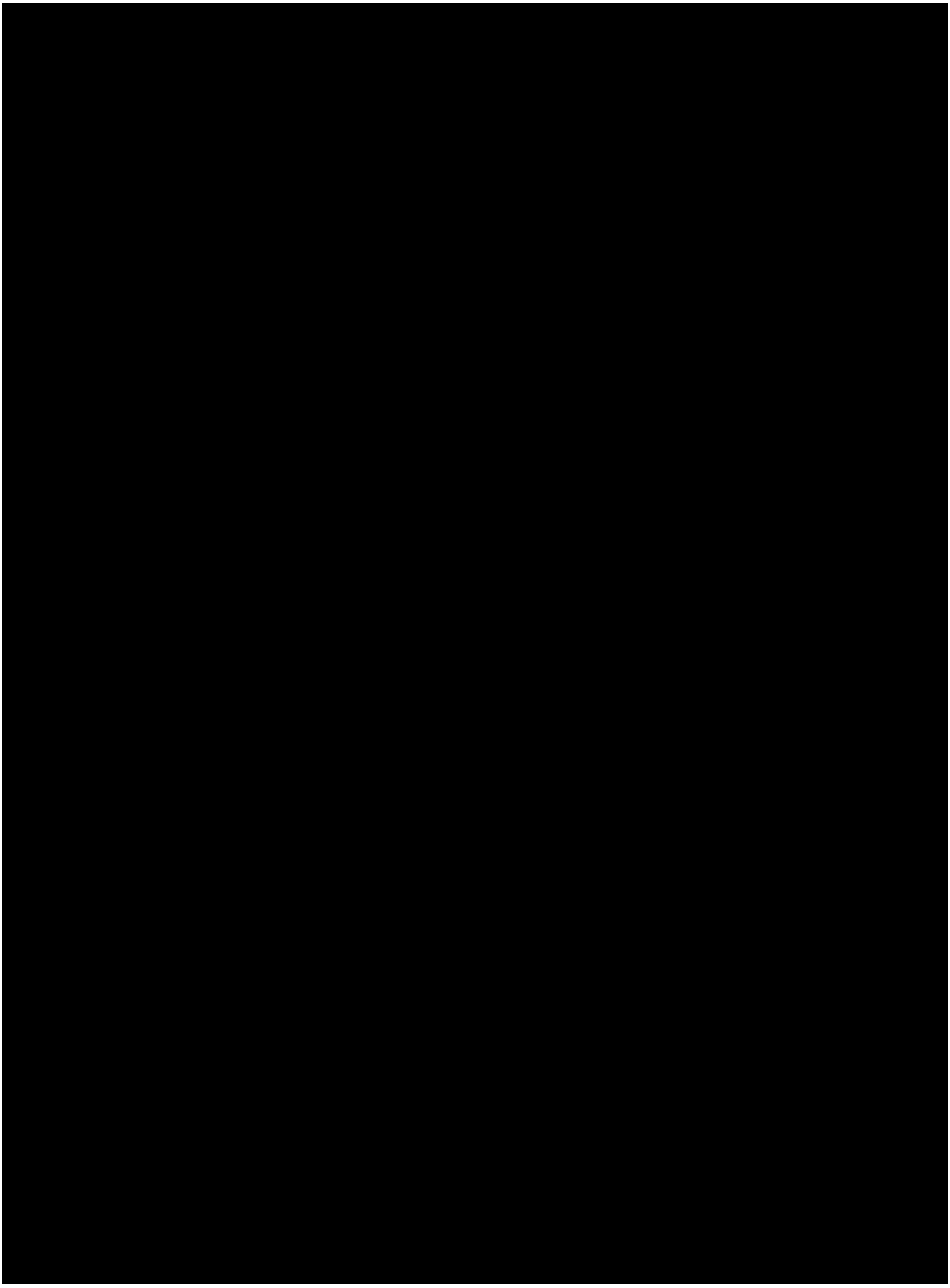
8. TIMEPOINT OF RELEASE OF TREATMENT INFORMATION

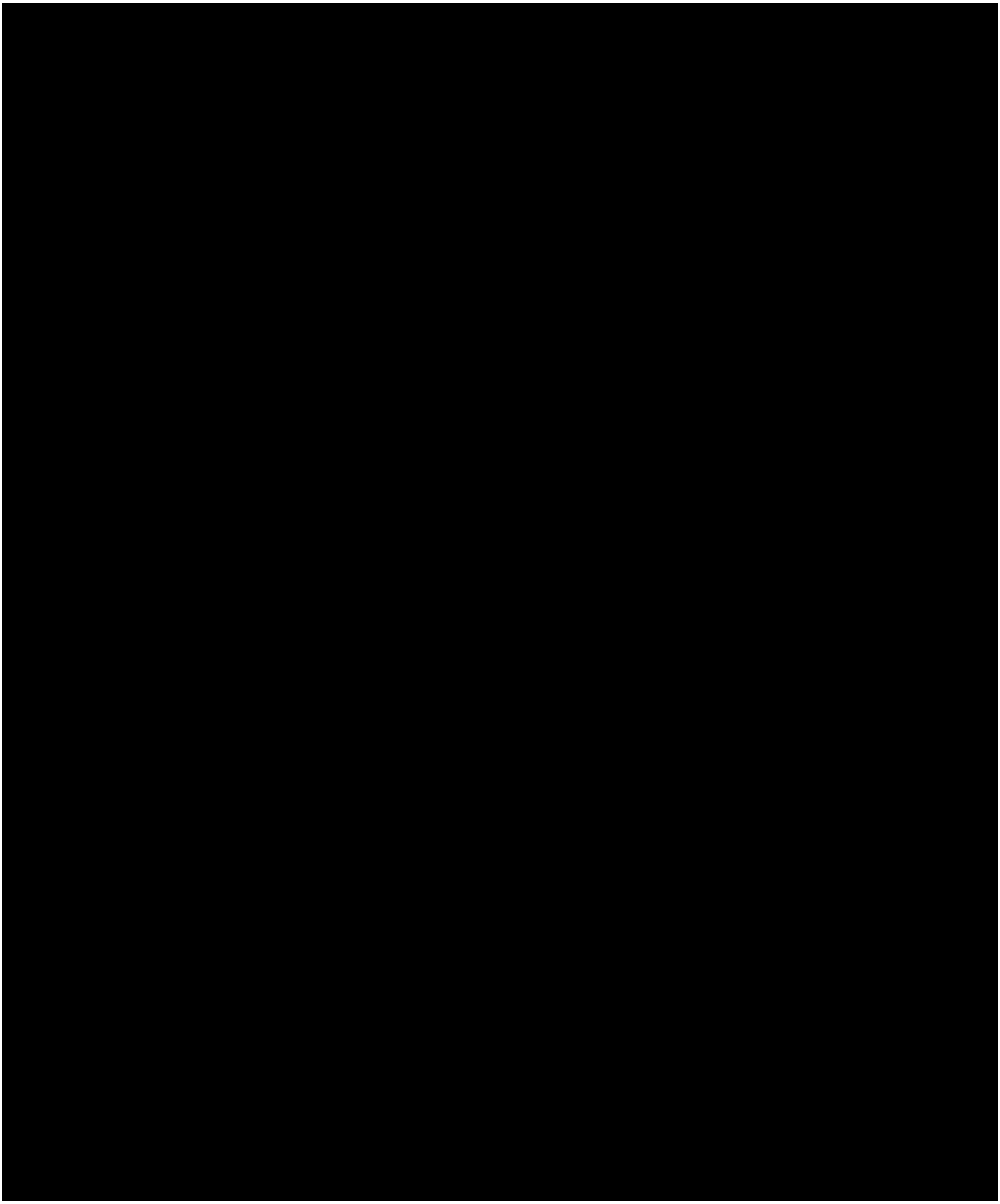
The treatment information will be loaded into the trial database at trial initiation, i.e., the database will be handled open-label in accordance with the CTP.

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
2	*001-MCS-40-413:* "Identify and Manage Important Protocol Deviations (iPD)", current version; IDEA for CON
3	*KM Asset BI-KMED-BDS-HTG-0035:* "Handling of missing and incomplete AE dates", current version; KMED
4	*KM Asset BI-KMED-TMCP-MAN -0014*: "Noncompartmental PK/PD Analyses of Clinical Studies", current version; KMED
5	*KM Asset BI-KMED-TCMP-MAN-0010:* "Description of Analytical Transfer Files and PK/PD Data Files", current version; KMED
6	*KM Asset BI-KMED-BDS-HTG-0045:* "Reporting of Clinical Trials and Project Summaries", current version; KMED
7	*KM Asset BI-KMED-BDS-HTG-0066:* "Analysis and Presentation of Adverse Event Data from Clinical Trials", current version; KMED
8	*CPMP/ICH/137/95*: "Structure and Content of Clinical Study Reports", ICH Guideline Topic E3; Note For Guidance on Structure and Content of Clinical Study Reports, current version
9	*KM Asset BI-KMED-BDS-HTG-0042:* "Handling, Display and Analysis of Laboratory Data", current version; KMED







11. HISTORY TABLE

Table 11: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
Final	**05-DEC-21**	[redacted]	None	This is the final TSAP