TRIAL STATISTICAL ANALYSIS PLAN

c34330267-01

BI Trial No.:	1445-0001
Title:	Safety, tolerability and pharmacokinetics of single rising oral doses of BI 1595043 (single-blind, partially randomised, placebo controlled, parallel (sequential) group design) in healthy male subjects Including Protocol Amendments 1 to 4 [c31692550-05]
Investigational Product(s):	BI 1595043
Responsible trial statistician(s):	[redacted] Phone: [redacted] Fax:
Date of statistical analysis plan:	16 APR 2021 SIGNED
Version:	1

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2. LIST OF ABBREVIATIONS

See Medicine Glossary:
http://glossary

Term	Definition / description
ALT	Alanine Aminotransferase
ANCOVA	Analysis of Covariance
AST	Aspartate Aminotransferase
$AUC_{0-\infty}$	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity
BLQ	Below Limit of Quantification
BMI	Body mass index
BP	Blood pressure
CI	Confidence Interval
C_{max}	Maximum measured concentration of the analyte in plasma
CV	Arithmetic Coefficient of Variation
DILI	Drug induced liver injury
ECGPCS	ECG Pharmacokinetic Concentration Set
gCV	Geometric Coefficient of Variation
gMean	Geometric Mean
HR	Heart rate
LLOQ	Lower limit of quantification
LLT	Lower Level Term
Max	Maximum
Min	Minimum
N	Number non missing observations
P10	10^{th} percentile
P90	90^{th} percentile
[redacted]	[redacted]
PKS	PK parameter analysis set
PR	Pulse rate
Q1	1^{st} quartile
Q3	3^{rd} quartile
RAGe	Report Appendix Generator system

Term	Definition / description
REP	Residual Effect Period
SD	Standard Deviation
[redacted]	[redacted]
TS	Treated Set
ULN	Upper Limit of Normal

3. INTRODUCTION

As per ICH E9 (1), the purpose of this document is to provide a more technical and detailed elaboration of the principal features of the analysis described in the protocol, and to include detailed procedures for executing the statistical analysis of the primary and secondary variables and other data.

This trial statistical analysis plan (TSAP) assumes familiarity with the Clinical Trial Protocol (CTP), including Protocol Amendments. In particular, the TSAP is based on the planned analysis specification as written in CTP Section 7 "Statistical Methods and Determination of Sample Size". Therefore, TSAP readers may consult the CTP for more background information on the study, e.g., on study objectives, study design and population, treatments, definition of measurements and variables, planning of sample size, randomisation.

Study data (including data entered in the RAVE EDC system and external data provided by suppliers) will be stored in a Clinical Data Repository (CDR).

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

The statistical analyses will be performed within the validated working environment CARE, including SAS® (current Version 9.4, by [redacted] and a number of SAS™-based tools (e.g., macros for the analyses of AE data or laboratory data; Report Appendix Generator system (RAGe) for compilation/formatting of the CTR appendices).

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

All analyses will be performed as planned in the CTP and are described in more detail in this TSAP.

5. ENDPOINTS(S)

5.1 PRIMARY ENDPOINT(S)

Section 2.1.2 of the CTP*: The primary endpoint for assessment of safety and tolerability of BI 1595043 is the percentage of subjects with drug-related adverse events.*

5.2 SECONDARY ENDPOINT(S)

5.2.1 Key secondary endpoint(s)

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

5.2.2 Secondary endpoint(s)

Section 2.1.3 of the CTP:
The following pharmacokinetic parameters will be determined for BI 1595043 if feasible:

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

[redacted]

Safety and tolerability:

Section 2.2.2.1 of the CTP: *Safety and tolerability of BI 1595043 will be assessed based on:*

- *AEs (including clinically relevant findings from the physical examination and ophthalmological examination)*

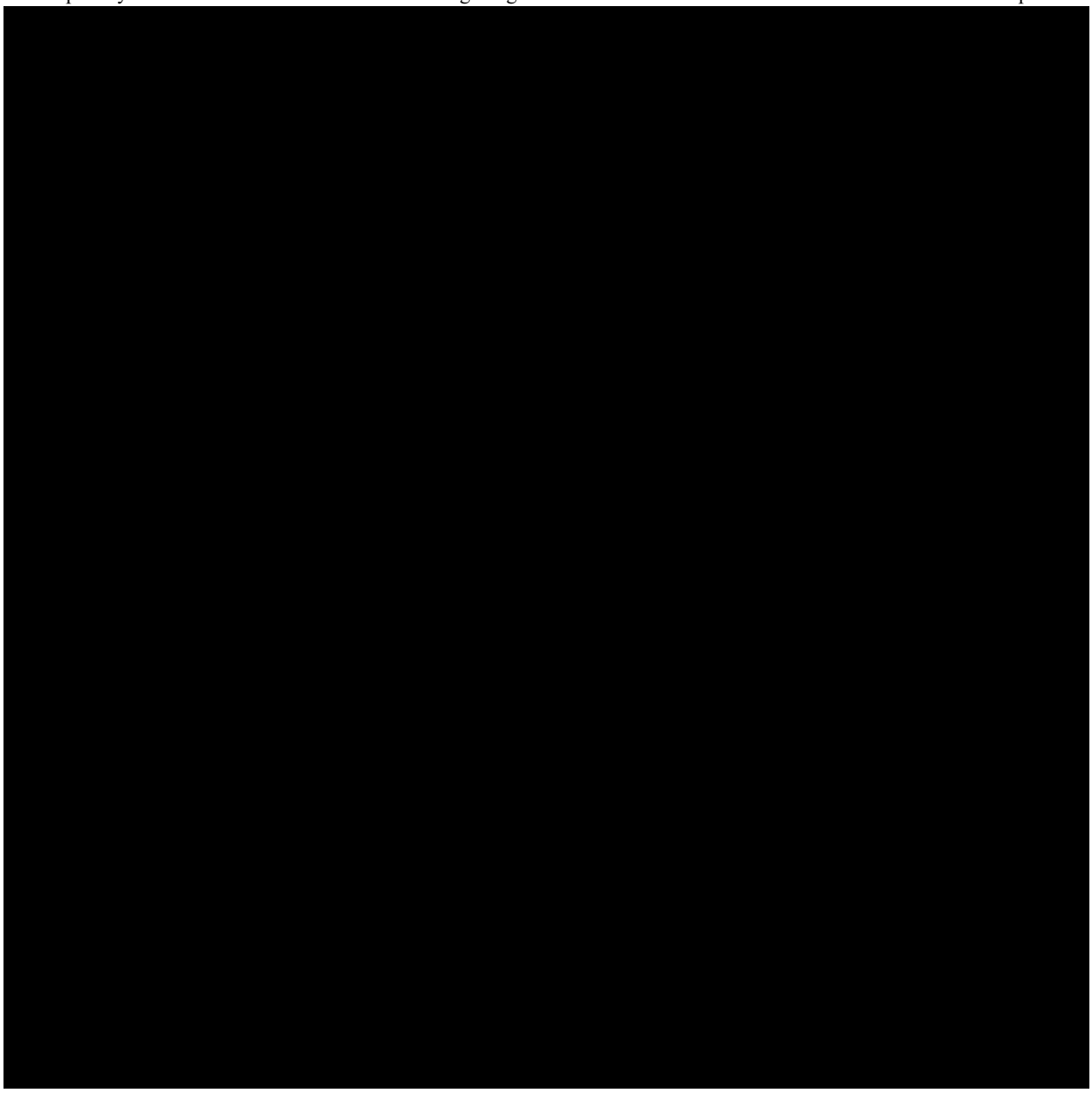
[redacted]

Details on ECG measurements and endpoints:

12-lead ECG endpoints

For the definition of baseline and a summary of time points scheduled for ECG recording and central evaluation please refer to Section 6.7.

[redacted]



6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENT(S)

It was planned that 64 healthy male subjects will enter the study (8 per dose group, 6 on active and 2 on placebo).

For details of dosage and formulation see Table 6.1:1 below.

Table 6.1: 1 Labels for treatments for use in the CTR

Treatment		Short label
P	Placebo, oral solution, po, qd*	Placebo
A	BI 1595043, 0.4 ml solution, po, qd	BI 1mg
B	BI 1595043, 1.2 ml solution, po, qd	BI 3mg
C	BI 1595043, 2.4 ml solution, po, qd	BI 6mg
D	BI 1595043, 4.8 ml solution, po, qd	BI 12mg
E	BI 1595043, 10 ml solution, po, qd	BI 25mg
F	BI 1595043, 20 ml solution, po, qd	BI 50mg
G	BI 1595043, 36 ml solution, po, qd	BI 90mg
K	BI 1595043, 64 ml solution, po, qd	BI 160mg

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

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

- **Screening** (ranging from 0:00 h on day of informed consent until administration time of study drug)
- **On treatment**
  Separately for each treatment, ranging from the time of first administration of BI / Placebo until 0:00h on the day after trial termination date

All AEs until end of trial examination will be considered on treatment.

Displays of AEs will be presented separately for the treatments described in Table 6.1: 1 above.

The following AE displays will be provided in the report:

Section 15.3 and Appendix 16.1.13.1.8 (for ClinicalTrials.gov and EudraCT) of the CTR displays:

In these displays, the on treatment phase will be analysed by dose group (labelled with the name of the study treatment (short label)). Screening will not be included in this analysis. The following total will be provided in addition:

- a total over all on treatment phases included in this analysis ("**Total on treatment**"; in 16.1.13.1.8)
- a total over all BI treated phases ("**BI Total on treatment**")

AEs during screening will be listed in Section 16.2, but not tabulated.

Tables of vital signs, laboratory values, and ECG values will present results by the above mentioned screening and on treatment phase.

More details on the technical implementation of these analyses are provided in the Technical TSAP ADS (analysis data set) plan and Data Reviewers guide.

6.2 IMPORTANT PROTOCOL DEVIATIONS

Data discrepancies and deviations from the CTP will be identified for all treated subjects.

Consistency check listings (for identification of deviations of time windows) and a list of protocol deviations (e.g. deviations in drug administration, in blood sampling times, etc.) will be provided to be discussed at the Report Planning Meeting (RPM). At this meeting, all manual deviations identified at the sites by the CRAs and deviations too complex to program will be reviewed by the trial team to decide which are considered important. For definition of important protocol deviations (iPD), and for the process of identification of these, refer to the Boehringer Ingelheim (BI) SOP "Identify and Manage Important Protocol Deviations (iPD)" (2).

Handling of iPDs in analysis is included in the DV domain specifications and stored within the TMF in EDMS.

If any iPDs are identified, they are to be summarised into categories and will be captured in the decision log (3).

Protocol deviations will be summarised and listed.

6.3 SUBJECT SETS ANALYSED

- Treated set (TS):
  The treated set includes all subjects who were randomised and treated with at least one

dose of study drug. The treatment assignment will be determined based on the first treatment the subjects received.
This is the full analysis set population in the sense of ICH-E9 (1). It is used for safety analysis. The ECG analyses are performed on the TS, except for the exposure-response analyses, which are performed on the ECGPCS defined below.

- PK parameter analysis set (PKS):
  This set includes all subjects in the treated set (TS) who provide at least one PK endpoint that was not excluded due to a protocol deviation relevant to the evaluation of PK or due to PK non-evaluability. Thus, a subject will be included in the PKS, even if he contributes only one PK parameter value for one period to the statistical assessment. Descriptive and model based analyses of PK parameters will be based on the PKS.

The descriptive analysis of PK concentrations will be based on the ADS ADPC as described at the beginning of Section 7.

Section 7.3 of the CTP: *Plasma [redacted] concentration data and parameters of a subject will be included in the statistical pharmacokinetic (PK) analyses if they are not flagged for exclusion due to a protocol violation relevant to the evaluation of PK (to be decided no later than in the Report Planning Meeting) or due to PK non-evaluability (as revealed during data analysis, based on the criteria specified below). Exclusion of a subject's data will be documented in the CTR.*

Relevant protocol violations may be

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

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

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

If a pre-dose concentration value is greater than 5% of C_{max}, the subject's pharmacokinetic data will be not included in any statistical evaluations, in accordance with international guidances. The individual pharmacokinetic parameters of such a subject will be calculated and listed separately. If a pre-dose concentration is above BLQ, but less than or equal to 5% of the subject's C_{max} value, the subject's data without any adjustments will be included in all pharmacokinetic measurements and calculations.

- 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 of BI 1595043 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 database lock.

Table 6.3: 1 Analysis sets for endpoints/data description

	Analysis set			
Endpoint/data description	TS	PKS		ECGPCS
Primary endpoint / Safety assessments (incl. ECG)	X			
Secondary and further PK endpoints		X		
ECG endpoints and plasma concentrations used in exposure-response analysis				X
Demographic/baseline data	X			
Important Protocol Deviations	X			
Disposition	X			

[redacted]

6.5 POOLING OF CENTRES

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

6.6 HANDLING OF MISSING DATA AND OUTLIERS

Handling of missing data and outliers will be performed as described in the CTP, Section 7.5.

The only exception where imputation might be necessary for safety evaluation is AE dates. Missing or incomplete AE dates are imputed according to BI standards (see 001-MCG-156_RD-01 (4)).

Missing data and outliers of PK data are handled according to BI standards (see 001-MCS-36-472_RD-01) (5).

If single cardiac cycles of an ECG (out of the generally four) are missing, the arithmetic mean for this single ECG will be computed with the reduced (1, 2 or 3) number of cardiac cycles.

If replicate ECG recordings are missing, the arithmetic means per time point will be computed with the reduced number (1 or 2) of recordings.

For the classification of the on-treatment QTc/QT intervals into “no new onset” / “new onset” categories, the handling of missing values is described in Appendix Section 10.3.

For placebo subjects the missing plasma concentration values will be replaced by 0 for the exposure response analysis. For subjects on active drug, missing plasma concentration values with ‘BLQ’ in the comment field will be replaced by ½ LLOQ.

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

For the analysis of vital signs the baseline value is defined as the last measurement before trial drug administration.

For laboratory analysis the baseline is defined as the last measurement before trial drug administration.

Unscheduled measurements of laboratory data or vital signs 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.

Section 6.1 of the CTP: *Exact times of measurements outside the permitted time windows will be documented. The acceptable time windows for screening and end of trial examination are given in the* CTP *Flow Chart.*

Study measurements and assessments scheduled to occur 'before' trial medication administration on Day 1 are to be performed and completed within a 3 h-period prior to the trial drug administration (including blank values for PK [redacted]

The acceptable deviation from the scheduled time for vital signs, ECG, and laboratory tests will be ± 15 min for the first 4 h after trial drug administration, ± 30 min thereafter, Starting from 48 h post-dose a deviation from the scheduled time for vital signs, ECG and laboratory test of ± 120 min is acceptable.

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

There will be a centralised evaluation of the 12-lead ECG recordings at the time points and for the ECG recordings specified in Table 6.7: 1 below:

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

Visit	Day	Planned time [hh:mm] (relative to drug administration)	Study phase	Central evaluation
1	-28 to -1		Screening	Not applicable
2	1	-01:00 -00:45 -00:30	Baseline	first single ECG of each of the 3 triplicates
		00:30	On treatment	first single ECG of the triplicate
		01:00		first single ECG of the triplicate
		01:30		first single ECG of the triplicate
		02:00		first single ECG of the triplicate
		02:30		first single ECG of the triplicate
		03:00		first single ECG of the triplicate
		04:00		first single ECG of the triplicate
		06:00		first single ECG of the triplicate
		08:00		first single ECG of the triplicate
		12:00		first single ECG of the triplicate
	2	24:00		first single ECG of the triplicate
		34:00		first single ECG of the triplicate
	3	48:00		first single ECG of the triplicate
	5	96:00		Not applicable
	7	144:00		Not applicable
3	10 to 15			Not applicable

Three triplicate ECGs will be recorded as the baseline before the first drug administration, but only the first ECG of each of the 3 triplicates will be transferred to the database. At all other time points, 1 triplicate ECG will be recorded, but only the first single ECG of the triplicate will be transferred to the database. The baseline value of an ECG variable is defined as the mean of the transferred baseline ECG measurements prior to drug administration.

For the exposure response analyses, pairs of ECG variables and corresponding plasma concentrations will be built using the same planned time points, e.g., the HR change from baseline and the plasma concentration measured at planned time 2:00 will build one pair. Whether a time deviation between PK blood sampling time and corresponding ECG recording is too big and the pair has to be excluded from the analysis will be decided no later than at the RPM.

7. PLANNED ANALYSIS

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

Safety analysis (refer to Section 7.8) will be performed by [redacted] and will be presented in Sections 15.1 to 15.4 of the CTR and in Appendix 16.2 and 16.1.13.1.

Inferential statistical analyses of PK endpoints (refer to Section 7.5.2) will also be performed by [redacted] and will be presented in Section 15.5 of the CTR and in Appendix 16.1.13.3.

Descriptive data analysis of PK parameters and concentrations will be performed by the department of [redacted] at [redacted] and will be presented in Section 15.6 of the CTR.

Descriptive data analysis of PD parameters and concentrations will be performed by the department of [redacted] at [redacted] and will be presented in Section 15.7 of the CTR.

The format of the listings and tables will follow the standards defined in the BI corporate guideline “Reporting of Clinical Trials and Project Summaries” [001-MCG-159] (6) with the exception of those generated for PK and PD calculations.

The individual values of all subjects will be listed, sorted by treatment group, subject number, and visit. The listings will be included in Appendix 16.2 of the CTR.

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

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

For analyte concentrations, 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:

CV	arithmetic coefficient of variation
gMean	geometric mean
gCV	geometric coefficient of variation
P10	10th percentile

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

The data format for descriptive statistics of concentrations will be identical 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 (%) for each treatment group/sequence. Percentages will be rounded to one decimal place and will be based on all subjects in the respective subject set whether they have non-missing values or not. The category 'missing' will be displayed only if there are actually missing values.

Units of variables should be given in the titles or column/row descriptors in square brackets (e.g. [mg]).

Exclusion of PK parameters

The ADS ADPP (PK parameters) contains column variables APEXC and APEXCO indicating inclusion/exclusion (APEXC) of a PK parameter and an analysis flag comment (APEXCO). All analyses based on the PKS will include parameters if they are not flagged for exclusion; that is APEXC is equal to “Included”.

Exclusion of PK concentrations

The ADS ADPC (PK concentrations per time-point or per time-interval) contains column variables ACEXC 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 (and, as a consequence, any calculation that relies on λ_z) only; the value is included for all other analyses.

Further details are given in “Noncompartmental Pharmacokinetic / Pharmacodynamic Analyses of Clinical Studies” [001-MCS-36-472_RD-01] (5) and “Description of Analytical Transfer Files and PK/PD Data Files” [001-MCS-36-472_RD-03] (7).

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Only descriptive statistics are planned for this section of the report, based on the TS.

7.2 CONCOMITANT DISEASES AND MEDICATION

Frequency tables are planned for this section of the report, based on the TS.

Concomitant diseases will be coded using the coding system of the Medical Dictionary for Drug Regulatory Activities (MedDRA). Medications will be coded using the World Health Organization Drug Dictionary (WHO-DD). The coding version number will be displayed as a footnote in the respective output.

The diagnoses and medications will be listed. Subjects without any concomitant diagnoses or concomitant therapies should be marked with a "No" in the respective column.

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

7.3 TREATMENT COMPLIANCE

Section 4.3 of the CTP: *Compliance will be assured by administration of all trial medication in the study centre under supervision of the investigating physician or a designee. The measured plasma concentrations and/or urinary excretion of trial medication will provide additional confirmation of compliance.*

It is not intended to list the compliance separately. Any deviations from complete intake will be addressed in the RPM (cf. TSAP Section 6.2) and described in the CTR.

7.4 PRIMARY ENDPOINT(S)

7.4.1 Primary analysis of the primary endpoint(s)

Refer to TSAP Section 7.8 for a description of the analysis of safety and tolerability of BI 1595043.

7.4.2 Sensitivity analysis, subgroup analysis, exploratory analysis of the primary endpoint(s)

Refer to TSAP Section 7.8 for a description of the analysis of safety and tolerability of BI 1595043.

7.5 SECONDARY ENDPOINT(S)

7.5.1 Key secondary endpoint(s)

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

7.5.2 (Other) Secondary endpoint(s)

Pharmacokinetics

Descriptive statistics of plasma concentrations and PK endpoints will be done by department [redacted] at [redacted] and will be presented in Section 15.6 of the CTR.

Assessment of dose proportionality

Dose proportionality of the PK endpoints $AUC_{0-\infty}$ and C_{max} of BI 1595043 in plasma as a further analysis will be explored using the power model that describes the functional relationship between dose and PK endpoints. The basic model consists of a regression model applied to log-transformed data (log-transformation refers to using the natural logarithm). The corresponding ANCOVA (Analysis of Covariance) model includes the logarithm of the dose as a covariate.

Section 7.3.2 of the CTP: *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,*
x_{km}	*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,…,8,*
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.

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.

A regression plot will be performed, where the logarithm of dose is depicted versus logarithm of PK endpoint, including the estimated regression line from the power model and reference line of perfect proportionality (β=1).

7.7 EXTENT OF EXPOSURE

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

7.8 SAFETY ANALYSIS

All safety analyses will be performed on the TS.

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

The safety data for treated subjects who failed to complete the study (dropouts or withdrawals) will be reported as far as their data are available. All withdrawals will be documented and the reason for withdrawal recorded.

7.8.1 Adverse Events

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

Unless otherwise specified, the analyses of AEs will be descriptive in nature. All analyses of AEs will be based on the number of subjects with AEs and not on the number of AEs.

For details on summarization of AE data, please refer to (9).

Section 5.2.7.1.4 of the CTP: *The following are considered as AESIs:*

- *Hepatic injury*

  A hepatic injury is defined by the following alterations of hepatic laboratory parameters:

  - An elevation of AST (aspartate transaminase) and/or ALT (alanine transaminase) ≥3-fold ULN combined with an elevation of total bilirubin ≥2-fold ULN measured in the same blood sample, or

- Aminotransferase (ALT, and/or AST) elevations ≥10 fold ULN

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.

According to ICH E3 (10), in addition to Deaths and Serious Adverse Events, 'other significant' AEs need to be listed in the clinical trial report. These will be any non-serious adverse event that led to an action taken with study drug (e.g. discontinuation or dose reduced or interrupted).

An overall summary of AEs (including AESIs) will be presented.

The frequency of subjects with AEs will be summarized by treatment, primary system organ class (SOC) and preferred term (PT). Separate tables will be provided for subjects with serious AEs, for subjects with drug-related AEs, for subjects with drug-related serious adverse events and for subjects with AESIs. Furthermore, tables will be provided for AEs of at least moderate severity and AEs leading to treatment discontinuation.

The SOC and PTs will be sorted by frequency (within SOC). The MedDRA version number will be displayed as a footnote in the respective output.
In addition, frequencies of subjects with non-serious AEs that had an incidence of > 5% for at least one treatment will be summarised by treatment, primary SOC and PT.

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

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

7.8.2 Laboratory data

The analyses of laboratory data will be descriptive in nature and will be based on BI standards [001-MCG-157] (11).

Laboratory data will be analysed qualitatively via comparison of laboratory data to their reference ranges. Values outside the reference range as well as values defined as possible clinically significant will be flagged in the data listings.

It is the investigator's responsibility to decide whether a lab value is clinically significant abnormal or not (at the RPM at the latest).

7.8.3 Vital signs

Descriptive statistics over time including change from baseline will be performed for vital signs (blood pressure and pulse rate). Descriptive statistics will be calculated by planned time point based on the last value of the patient at that planned time point (or assigned to that planned time point).

7.8.4 ECG

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

Continuous safety ECG monitoring (by investigator)

Clinically relevant abnormal findings will be reported as adverse events.

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

12-lead ECG

The descriptive evaluation of ECG data will be based on the TS, except the exposure-response analyses, which are based on the ECGPCS set.

Listing of individual data

For all quantitative endpoints, listings of individual data will be shown in Appendix 16.2. For QTcB and RR only listings will be provided. Occurrences of notable findings will be flagged.

Comments regarding the ECGs will be listed.

Categorical endpoints

For the categorical endpoints, frequency tables will be provided.

For all subjects with any notable finding in ECG intervals, a separate listing will be created as end-of-text display (based on the same display template as in Appendix 16.2), and the corresponding time profiles will be shown.

Quantitative endpoints

Descriptive statistics (N, mean, SD, min, median, max) will be provided for the absolute values and changes from baseline over time of QTcF, QT, HR, PR and QRS. The time profiles of mean and SD for the changes from baseline on treatment will be displayed graphically by treatment.

For QTcF and HR changes from baseline, the relationship to the corresponding plasma concentrations will be evaluated using a random coefficient model. For subjects in the

ECGPCS, all time points with available ECG endpoints and valid time-matched drug plasma concentrations will be included. For the handling of missing values, see Section 6.6.

The response variable will be the change from baseline in QTcF (ΔQTcF). The placebo subjects will be included in the analysis, setting their plasma concentrations to zero.

As a first step, it is investigated if there is a potential delayed or accelerated (e.g. due to metabolites) effect of the drug on QTcF. A general visual impression is 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 active treatment group (presented in the End-of-Text part of the CTR).

The relationship between BI 1595043 plasma concentrations and QTcF changes from baseline will be investigated in an exploratory manner using a random coefficient model to estimate the difference in means between BI 1595043 and placebo of QTcF change from baseline and its 90% confidence interval at the geometric mean of the C_{max} for each dose. Additionally, the estimated overall slope with its 90% confidence interval will be provided. The used random coefficient model is based on a white paper from Garnett et al. (12) with ΔQTcF as response variable, centered baseline QTc and plasma concentration as continuous covariates, treatment and time 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 stadanrd errors and estimate denominator degrees of freedom. For more details refer to Section 10.4.

For visualization, a scatterplot of the BI 1595043 plasma concentration against the following individual QTcF values will be provided: For each subject on active treatment and each time point, subtract the mean value of all individual observed ΔQTcF values from the placebo group for this time point from the individual observed ΔQTcF value for this subject and time point. This results in estimates for “individual ΔΔQTcF” values, which should only be used for plotting purposes. The corresponding regression line and its pointwise confidence bands as well as and the geometric mean of C_{max} 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 Garnett et al. (12)) and residual plots. In case of non-linearity or if there is evidence for a delayed effect, further models will be explored in order to better characterise the PK-ECG relationship (e.g. effect compartment models, non-linear models, etc.).

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

Appropriateness of heart rate correction methods of QT interval

To evaluate the appropriateness of the heart rate correction methods, the slope of the relationship of QTcF interval versus RR interval (values log-transformed using the natural logarithm) will be estimated by applying the random coefficient model described in Section 10.2 using all time points. 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

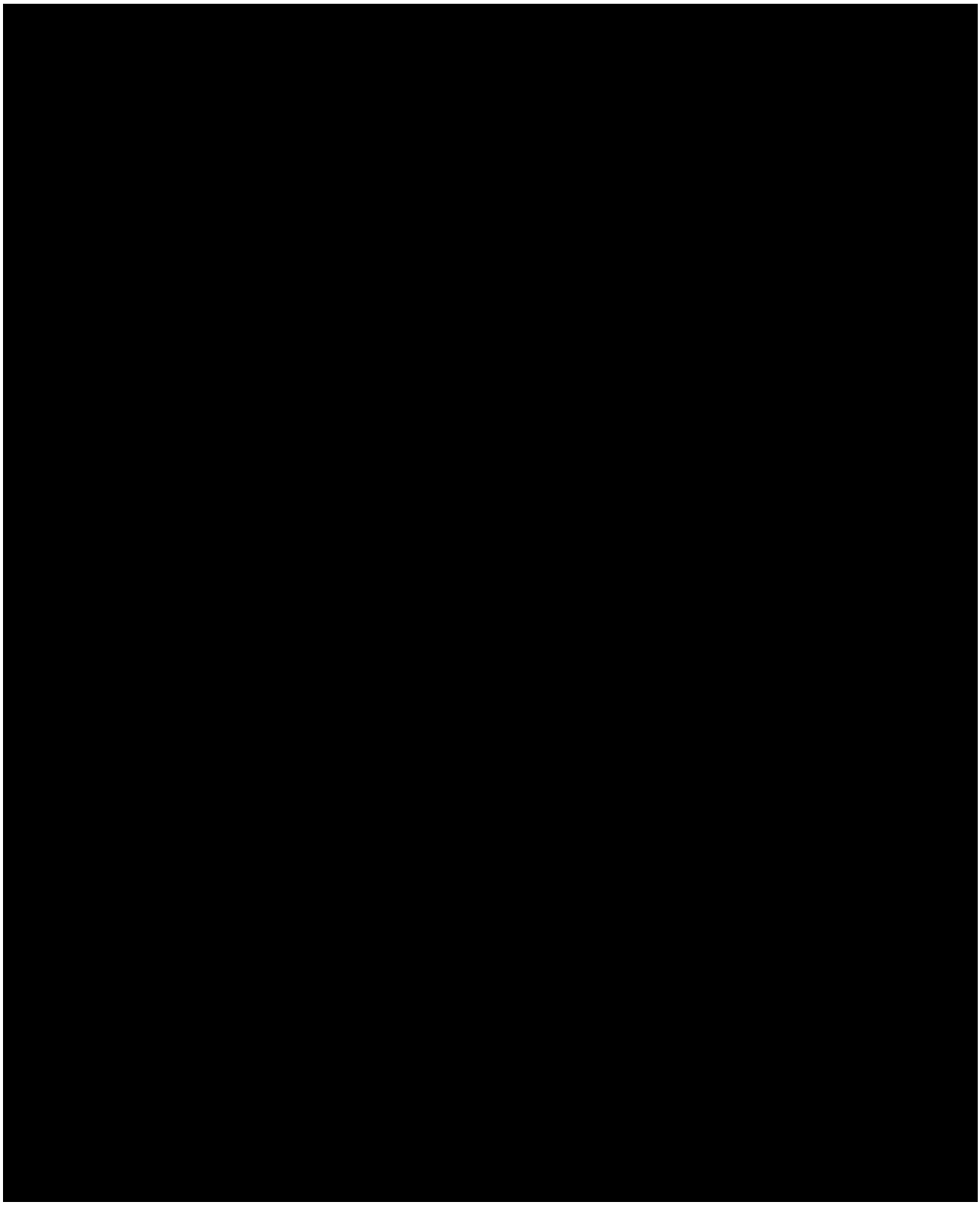
Physical / ophthalmological examination findings will be reported as relevant medical history/baseline condition (i.e., a condition already existent before intake of study drug) or as AE and will be summarised as such.
No separate listing or analysis of physical / ophthalmological examination findings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

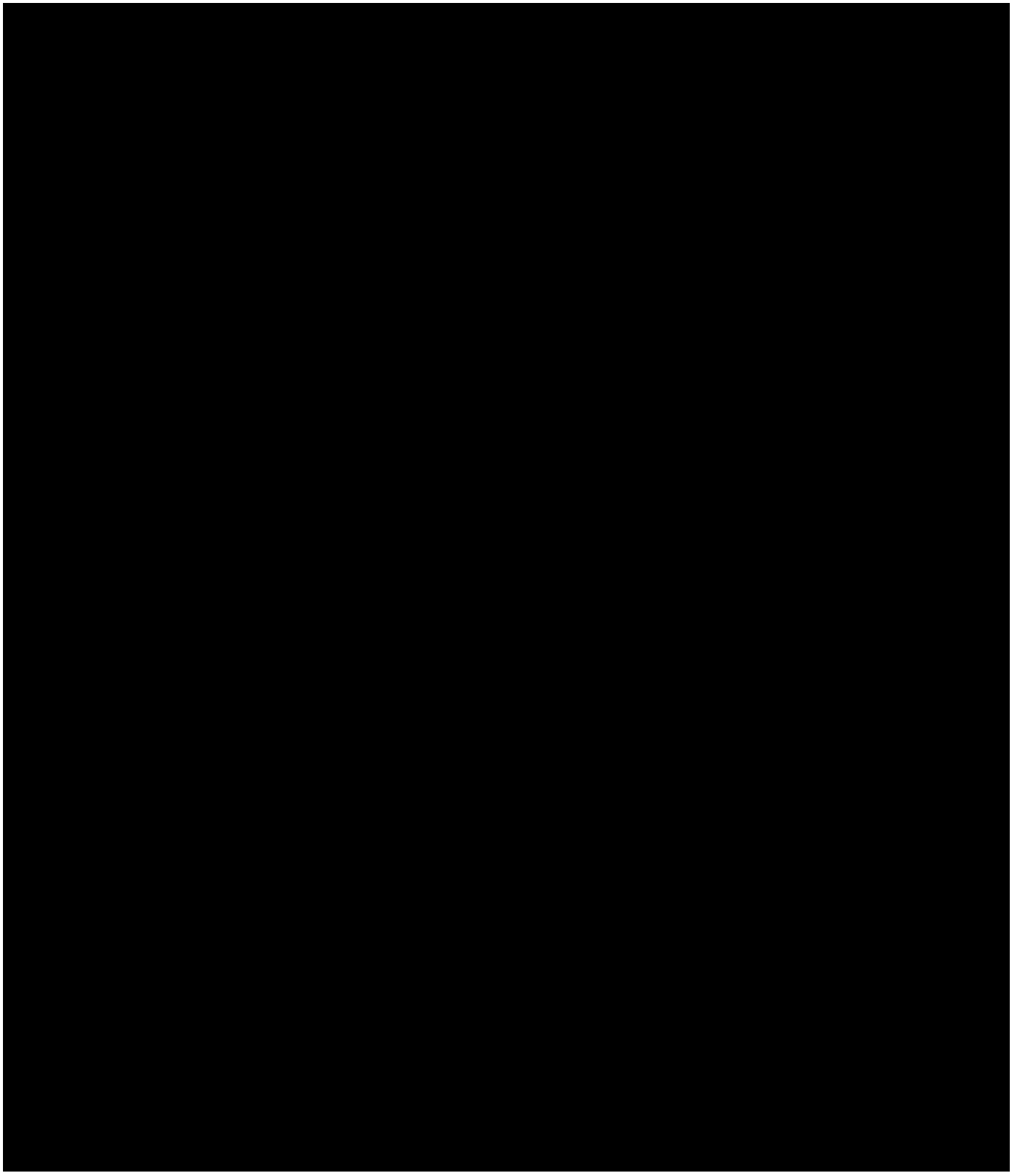
8. TIMEPOINT OF RELEASE OF TREATMENT INFORMATION

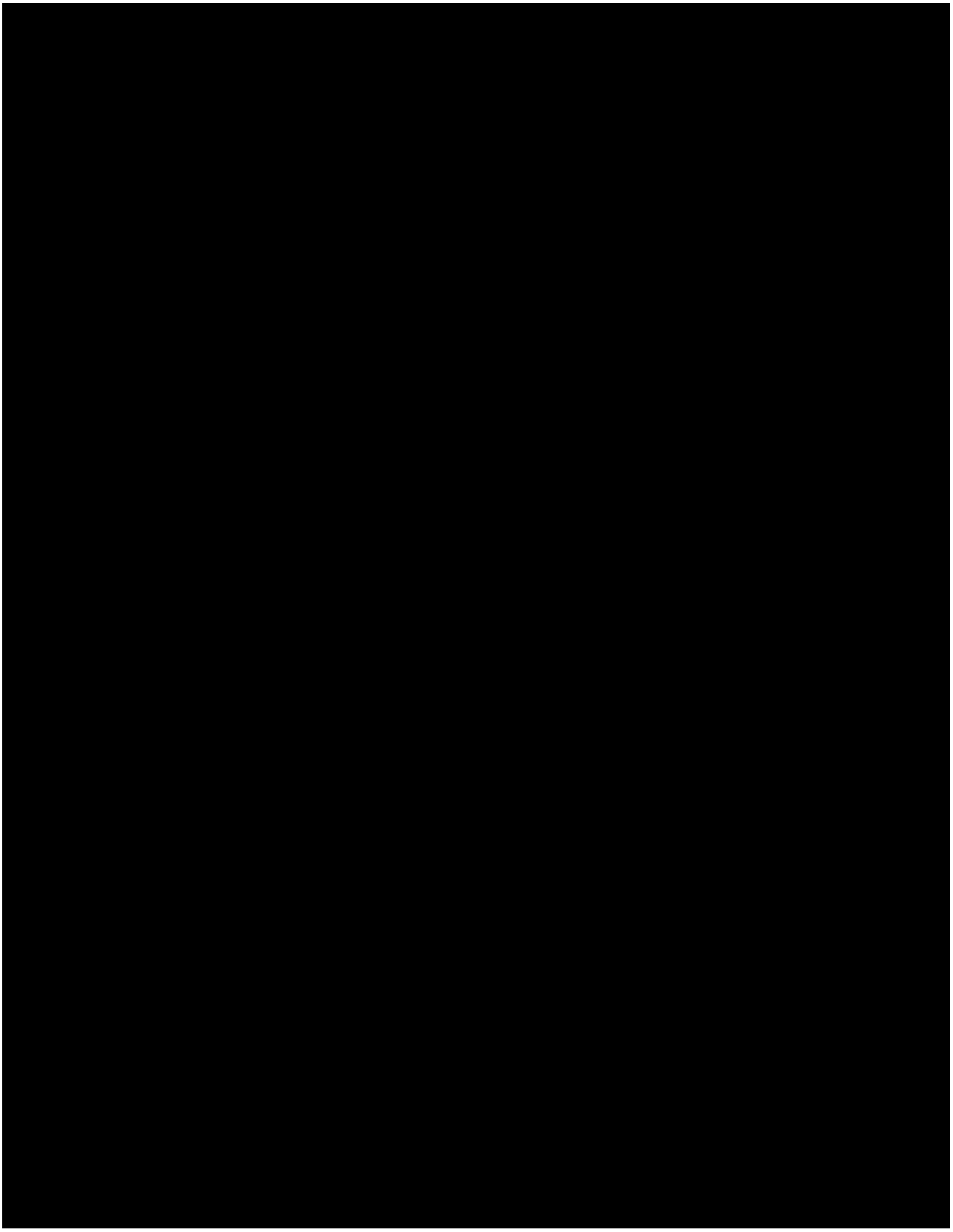
The treatment information will be loaded into the trial database after completion of enrolment, i.e. the randomization has been completed.

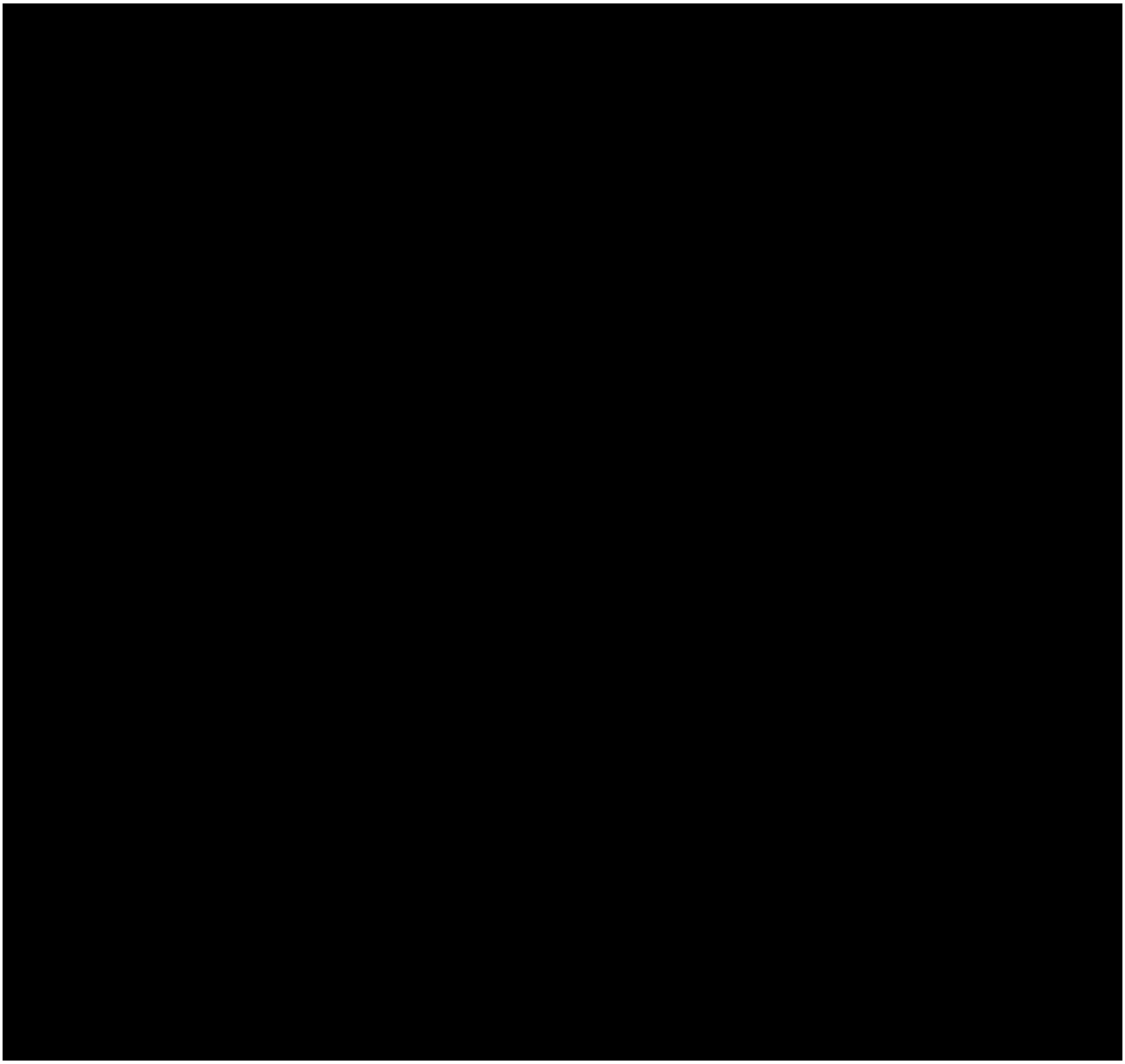
9. REFERENCES

1.	*CPMP/ICH/363/96:* "Statistical Principles for Clinical Trials", ICH Guideline Topic E9, Note For Guidance on Statistical Principles for Clinical Trials, current version.
2.	*001-MCS-40-413:* "Identify and Manage Important Protocol Deviations (iPD) ", current version, BIRDS
3.	*001-MCS-50-415_RD-03:* "Clinical Trial Analysis Decision Log", current version; IDEA for CON.
4.	*001-MCG-156_RD-01:* "Handling of Missing and Incomplete AE Dates", current version; IDEA for CON.
5.	*001-MCS-36-472_RD-01*: "Noncompartmental Pharmacokinetic/Pharmacodynamic Analyses of Clinical Studies", current version; IDEA for CON.
6.	*001-MCG-159*: "Reporting of Clinical Trials and Project Summaries", current version; IDEA for CON.
7.	*001-MCS-36-472_RD-03:* "Description of Analytical Transfer Files and PK/PD Data Files", current version; IDEA for CON.
8.	*001-MCS 36-472*: "Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics", current version; IDEA for CON.
9.	*BI-KMED-BDS-HTG-0066*: "Analysis and Presentation of Adverse Event Data from Clinical Trials", current version; KMED.
10.	*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
11.	*001-MCG-157*: "Handling, Display and Analysis of Laboratory Data", current version; IDEA for CON.
12.	Garnett C, Bonate PL, Dang Q, Ferber G, Huang D, Liu J, et al. Scientific white paper on concentration-QTc modeling. J Pharmacokin Pharmacodyn 2017 [R18-0143]
13.	BI Statistical Position Paper - Statistical Methods for PK - Reference Document 3: Regulatory recommendations for BA/BE trials and implementation instructions in clinical trial documents, version 1.0 (2017).









11. HISTORY TABLE

Table 11: 1 History table

Version	Date (DD-MMM-YYYY)	Author	Sections changed	Brief description of change
1	16-APR-2021	[redacted]		This is the final TSAP without any modification