TRIAL STATISTICAL ANALYSIS PLAN

c34947384-01

BI Trial No.:	1371-0003
Title:	Safety, tolerability and pharmacokinetics of single rising oral doses of BI 894416 versus placebo in healthy male Japanese subjects (single-blind, randomized, placebo-controlled within dose group) (Revised Protocol including Amendments 1-2 [c23040609-03])
Investigational Product(s):	BI 894416
Responsible trial statistician(s):	[redacted] Phone: [redacted] Fax: [redacted]
Date of statistical analysis plan:	12 FEB 2021 SIGNED
Version:	1

1. TABLE OF CONTENTS

[redacted]

[redacted]

LIST OF TABLES

2. LIST OF ABBREVIATIONS

See Medicine Glossary:
Website: http://glossary

Term	Definition / description
ALT	Alanine transaminase
AST	Aspartate transaminase
AUC_{0-tz}	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 to the last quantifiable data point
$AUC_{0-\infty}$	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity
BMI	Body mass index
CARE	Clinical data Analysis and Reporting Environment
CI	Confidence interval
C_{max}	Maximum measured concentration of the analyte in plasma
CV	Arithmetic coefficient of variation
DILI	Drug induced liver injury
gCV	Geometric coefficient of variation
gMean	Geometric mean
LLT	Lower level term
λ_z	Terminal rate constant of the analyte in plasma
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
N	Number of non-missing observations
P10	10th percentile
P90	90th percentile
po	Orally
PKS	Pharmacokinetic parameter analysis set
Q1	1st quartile
Q3	3rd quartile
qd	Once daily

Term	Definition / description
RAGe	Report Appendix Generator system
REP	Residual effect period
SD	Standard deviation
SOC	System organ class
TS	Treated set
ULN	Upper limit of normal
WHO-DD	World Health Organization Drug Dictionary

3. INTRODUCTION

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

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

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

Pharmacokinetic (PK) parameters will be calculated using Phoenix WinNonlin™ software (version 6.3 or higher, Certara USA Inc., Princeton, NJ, USA).

The statistical analyses will be performed within the validated working environment CARE, including SAS™ (current Version 9.4, by SAS Institute Inc., Cary, NC, USA), 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

The study was prematurely stopped after the first dose group (25mg BI 894416) due to a disadvantageous benefit risk ratio based on newly received data from another study with BI 894416.

Consequently, only a subset of the analyses planned in the CTP will be performed. Tables will be provided for disposition, demography, adverse events and standard safety analysis (including the primary endpoint) and for PK endpoints (including the secondary endpoints). For all study endpoints, listings will be provided. That means, for several variables, only listings will be provided and no descriptive analysis will be carried out. This applies to, for example, medical history, concomitant medication and non-drug procedures, laboratory data, vital signs and ECG.

As there is only one dose group available, no dose proportionality analysis will be done. Secondary endpoints ($AUC_{0-\infty}$ and C_{max} of BI 894416) will be analysed descriptively only.

5. ENDPOINTS

5.1 PRIMARY ENDPOINT

Section 2.1.2 of the CTP: *The primary endpoint for assessment of safety and tolerability of BI 894416 is the percentage [%] of subjects with drug related adverse events.*

5.2 SECONDARY ENDPOINTS

5.2.1 Key secondary endpoints

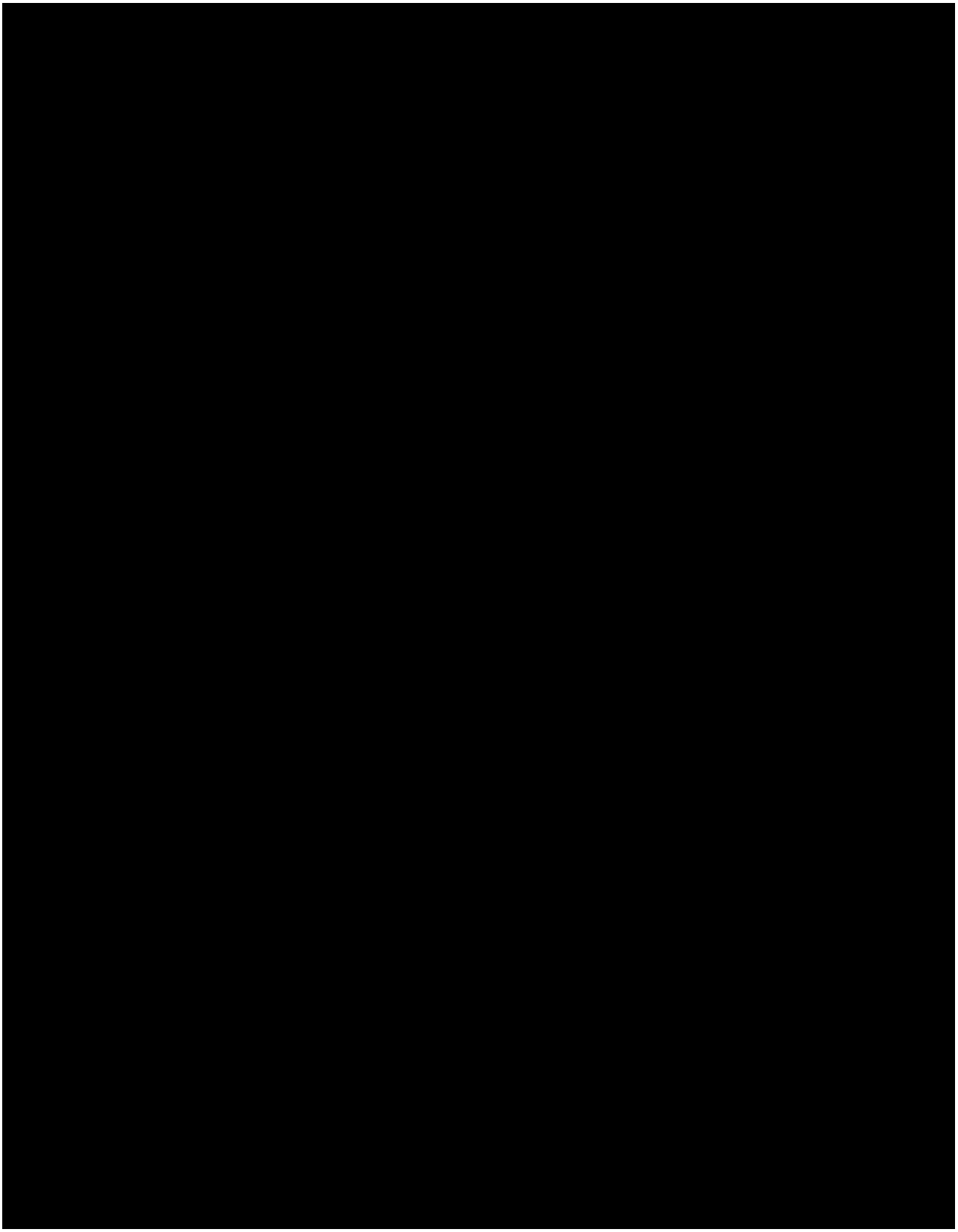
This section is not applicable as no key secondary endpoints have been defined in the CTP.

5.2.2 Secondary endpoints

Section 2.1.3 of the CTP:

The following pharmacokinetic parameters will be determined for BI 894416, 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)*



6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENTS

For basic study information on investigational products, assignment of treatments and selection of doses, please see CTP, Section 4.

The study was performed as a single-blind, randomised, placebo-controlled study in healthy male Japanese subjects. It was planned that 24 subjects will be treated with a single dose of BI 894416 or Placebo. The study comprises 3 dose groups. Each dose group was planned to consist of 8 subjects randomised to active treatment or Placebo (6 on active treatment, 2 on Placebo).

Table 6.1: 1 Treatments and labels used in the analysis

Dose group	Treatment	Short label
P*	Placebo, tablet, qd	Placebo
A	25mg BI 894416 tablet, po, qd	BI 25mg
B	50mg BI 894416 tablet, po, qd	BI 50mg
C	70mg BI 894416 tablet, po, qd	BI 70mg

*The placebo control group will include all subjects that were treated with placebo, regardless of the groups they were treated.

The study was prematurely stopped after the first dose group (25mg BI 894416). Therefore, all analyses will be performed for this dose group only (Placebo n=2, BI 25mg n=6).

Section 1.2.2 of CTP:

The Residual Effect Period (REP (...)) of BI 894416 has not been defined yet. (...)

Conservatively, a minimum period of 14 days after last administration of BI 894416, or placebo, has been selected as the REP. Therefore, the individual subject's end of trial will be 14 days following last dosing with BI 894416, or placebo, at the earliest.

All adverse events (AE) reported between administration of trial medication and the individual subject's end of trial will be counted as on-treatment AEs.

The following study phases will be defined for the analysis:

- **Screening** (ranging from 0:00 h on day of informed consent until time of administration of trial medication (BI 894416 or Placebo))

- **On treatment** (ranging from the time of administration of trial medication until 336 hours (14 days) after time of administration)

- **Follow-up (F/U)** (ranging from 336 hours (14 days) after administration of trial medication until 0:00 h on day after trial termination date)

Section 7.3.4 of the CTP: *Note that AEs occurring after the last per protocol contact but entered before final database lock will be reported to Pharmacovigilance only and will not be captured in the trial database.*

The following AE displays will be provided in the report:

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

In these displays, the on-treatment phase will be analysed (labelled with the name of the study treatment (short label)). Screening and Follow up phases will not be included in this analysis. As the study was prematurely discontinued after one dose group, no additional totals will be provided.

In Section 15.4 and Appendix 16.2 (Listings) of the CTR displays, screening and follow-up periods will be included.

For detailed information on the handling of the treatments refer to Technical TSAP ADS (analysis data set) plan and Analysis Data Reviewers guide.

6.2 IMPORTANT PROTOCOL DEVIATIONS

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

Section 7.3 of the CTP: *Important protocol deviation (IPD) categories will be specified in the TSAP, IPDs will be identified no later than in the Report Planning Meeting, and the IPD categories will be updated as needed.*

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).

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 Table 6.2: 1. 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, the definition below will be supplemented accordingly by the time of the Report Planning Meeting and will be documented in the decision log and in the iPD specification file (3).
The iPDs will be listed in the CTR.

Table 6.2: 1 Important protocol deviations

Category/ Code		Description
A		**Eligibility Criteria**
	A1	Critical inclusion/exclusion criteria violated
	A2	Withdrawal criteria as defined in the protocol met, but subject was not withdrawn
B		**Informed Consent**
	B1	Required informed consent not available/not done
C		**Trial Medication and Randomization**
	C1	Randomisation order not followed
	C2	Critical trial medication procedure violated
D		**Concomitant medication**
	D1	Improper medication washout
	D2	Prohibited medication use
	D3	Mandatory medication not taken/insufficient
E		**Critical Study Procedure/Assessment**
	E1	Improper primary endpoint assessment
	E2	Improper key secondary endpoint assessment
F		**Safety Procedures/SAE Reporting**
	F1	Critical safety procedure not followed
G		**Privacy/Data Protection**
	G1	Privacy and/or data protection violated
Q		**Non-important COVID-19 Related**
	Q1	Missed examination
	Q2	Missed visit
	Q3	Drug shipment

6.3 SUBJECT SETS ANALYSED

Section 7.3 of the CTP:

- *Treated set (**TS**): The treated set includes all subjects who were randomized and treated with at least one dose of investigational medicinal product. The treatment assignment will be determined based on the first treatment the subjects received. The treated set will be used for safety analyses.*

- *Pharmacokinetic parameter analysis set (**PKS**): This set includes all subjects in the treated set (TS) who provide at least one PK endpoint that was not excluded due to a protocol violation relevant to the evaluation of PK or due to PK non-evaluability (as specified in the following subsection 'Pharmacokinetics'). Thus, a subject will be included in the PKS, even if he contributes only one PK parameter value for one period to the statistical assessment. Descriptive […] analyses of PK parameters will be based on the PKS.*

(…)

Pharmacokinetics

Plasma and urine concentration data and parameters of a subject will be included in the statistical 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 and urine concentrations and/or parameters of a subject will be considered as non-evaluable, if for example

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

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

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

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

Table 6.3: 1 Subject sets analysed

	Subject set	
Class of endpoint	TS	PKS
PK endpoints		X
Safety parameters	X	
ECG endpoints	X	
Demographic/baseline parameters	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 exceptions where imputation might be necessary for safety evaluation are AE dates. Missing or incomplete AE dates are imputed according to BI standards (see BI-KMED-BDS-HTG-0035) (4).

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

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

The baseline value is defined as the last measurement before trial medication administration.

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 the end of trial examination are provided in the* CTP *Flow Chart.*

Trial measurements and assessments scheduled to occur 'before' trial medication administration at Day 1 are to be performed and completed within a 2 h-period prior to the investigational medicinal product administration (including blank values for PK). A blank urine sample for PK will be collected within 3 h before drug administration.

The acceptable deviation from the scheduled time for vital signs and ECG will be ± 10 min for the first 4 h after investigational medicinal product administration and ± 30 min thereafter. For laboratory test, the acceptable deviation is ± 30 min.

(...)

The acceptable deviation from the scheduled time for neurological tests is ± 45 min on Day 1 and ± 90 min for other days.

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

Unscheduled measurements of laboratory data and vital signs data will be assumed to be repeat measurements of the most recent scheduled measurement (e.g. for follow-up or confirmation of a particular value). Therefore, unscheduled measurements will be assigned to the planned time point of the previous scheduled measurement.

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

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

Visit	Day	Planned time [hh:mm] (relative to drug administration)	Study phase	Central evaluation
1	-28 to -1		Screening	NA
2	-1	-24:00	Pre-dose	Three triplicate ECGs**
	1	-01:00	Baseline	Triplicate ECG*
		00:30	On treatment	Triplicate ECG*
		01:00	On treatment	Triplicate ECG*
		01:30	On treatment	Triplicate ECG*
		02:00	On treatment	Triplicate ECG*
		02:30	On treatment	Triplicate ECG*

		03:00	On treatment	Triplicate ECG*
		04:00	On treatment	Triplicate ECG*
		06:00	On treatment	Triplicate ECG*
		08:00	On treatment	Triplicate ECG*
		12:00	On treatment	Triplicate ECG*
	2	24:00	On treatment	Triplicate ECG*
		34:00	On treatment	NA
	3	48:00	On treatment	NA
	4	72:00	On treatment	NA
3	15 to 17		End of trial examination	NA

* Central ECG lab evaluation will be performed for the first ECG of triplicate ECGs at every time point
** Will not be used for ECG analyses

Three triplicate ECGs will be recorded on Day -1 -24:00, but only the first triplicate will be transferred to the database. These values will not be used for the ECG analyses.
At all other time points, triplicate ECGs will be recorded, but only the first ECG of the triplicate will be transferred to the data base. The baseline value of an ECG variable is defined as the first single ECG of the triplicate at Day 1 prior to drug administration (-1:00).

7. PLANNED ANALYSIS

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

PK evaluation will be performed by [redacted] and monitored by the [redacted] and the descriptive statistics of PK endpoints and plasma concentrations will be presented in Section 15.6 of the CTR. Inferential statistical analyses of PK endpoints will not be applied in this trial due to the premature discontinuation.

The format of the listings and tables will follow BI standards (see BI-KMED-BDS-HTG-0045 (7)) with the exception of those generated for PK evaluations following BI standards for PK/PD analysis (8).

The individual values of all subjects will be listed, sorted by treatment, subject number and visit. The listings of PK and other than PK will be included in Appendices 16.1.13.5 and 16.2 of the CTR, respectively.

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

N	number 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 to 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 (%). Percentages will be rounded to one decimal place and will be based on all subjects in the respective subject set whether they have non-missing values or not. The category 'missing' will be displayed only if there are actually missing values.

Exclusion of PK parameters

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

Exclusion of PK concentrations

The ADS “ADPC” (PK concentrations per time-point or per time-interval) contains column variables ACEXC and ACEXCO indicating inclusion/exclusion (ACEXC) of a concentration and an analysis flag comment (ACEXCO). Exclusion of a concentration depends on the analysis flag comment ACEXCO. For example, if ACEXCO is set to ‘ALL CALC’, the value will be excluded for all types of analyses based on concentrations. If ACEXCO is set to ‘DESC STATS’ the value will be excluded from descriptive evaluations per planned time point/time interval. If ACEXCO contains the addition ‘TIME VIOLATION’ or ‘TIME DEVIATION’ the value can be used for further analyses based on actual times. If ACEXCO is set to ‘HALF LIFE’, the value will be excluded from half-life calculation (and, as a consequence, any calculation that relies on λ_z) only; the value is included for all other analyses.

Further details are given in *BI-KMED-TMCP-MAN-0014* “Noncompartmental Pharmacokinetic / Pharmacodynamic Analyses of Clinical Studies” (6) and *BI-KMED-TMCP-MAN-0010*: “Description of Analytical Transfer Files and PK/PD Data Files” (9).

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Only descriptive statistics for demographics are planned for this section of the report, based on the TS.
The data will be summarised by treatment and in total.

7.2 CONCOMITANT DISEASES AND MEDICATION

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

The diagnoses and medications will be listed. 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 trial 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

Refer to TSAP Section 7.8 for a description of the analysis of safety and tolerability of BI 894416.

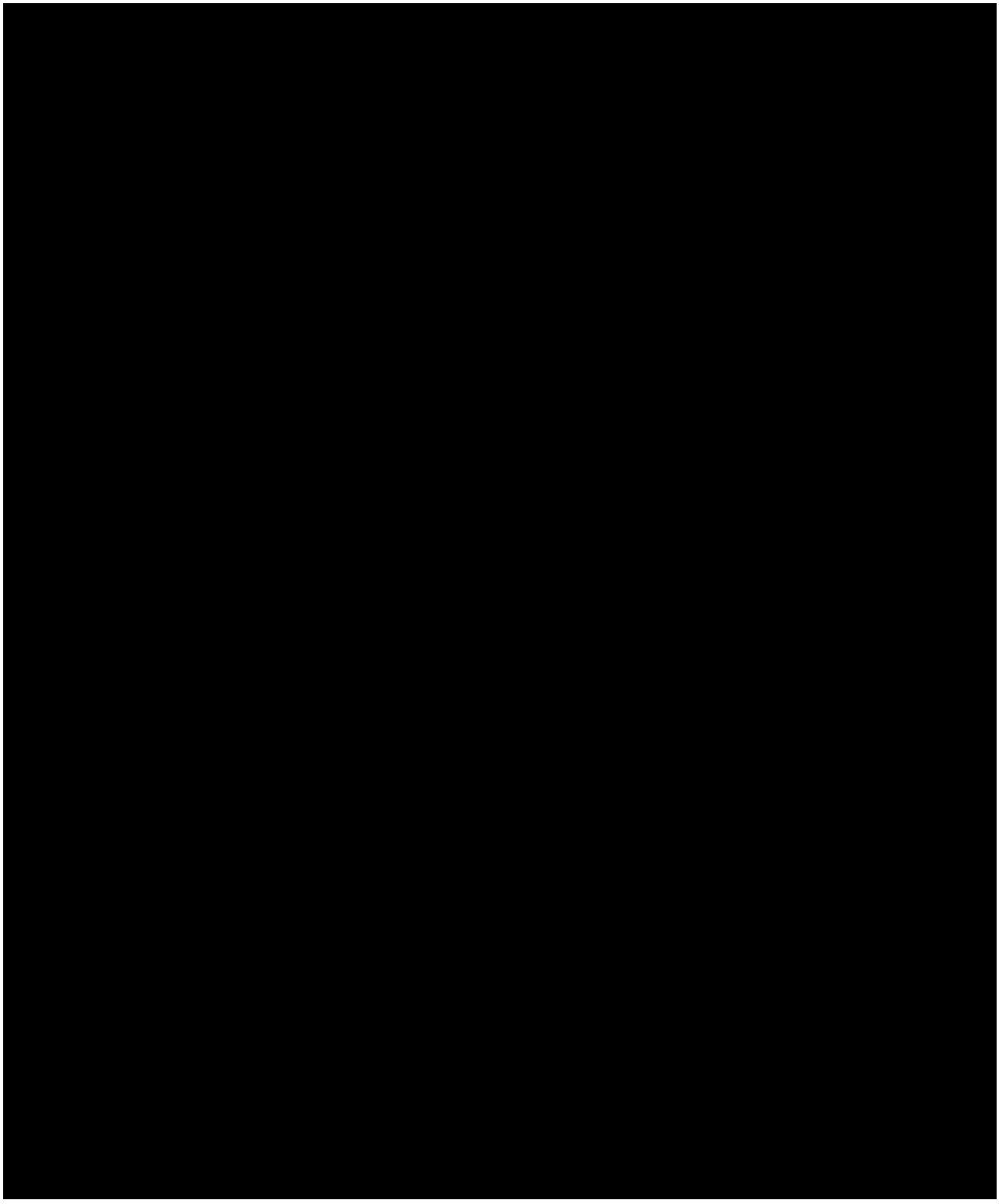
7.5 SECONDARY ENDPOINTS

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 endpoint

Section 7.3.2 of the CTP: *The secondary endpoints (refer to* CTP *Section 2.1.3) will be analysed descriptively. Analyses will be performed for the parent drug.*



7.7 EXTENT OF EXPOSURE

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.

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.

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

The analysis of AEs will be based on the concept of treatment emergent AEs. That means that all AEs will be assigned to 'screening', '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.

According to the clinical study protocol, adverse events of special interest (AESI) will be analysed:

Section 5.2.6.1.4 of the CTP: *The following are considered as AESIs:*

- *Hepatic injury*
  A hepatic injury is defined by the following alterations of hepatic laboratory parameters:
  - *An elevation of AST (aspartate transaminase) and/or ALT (alanine transaminase) ≥3-fold ULN combined with an elevation of total bilirubin ≥2-fold ULN measured in the same blood sample, or*
  - *Aminotransferase (ALT, and/or AST) elevations ≥10 fold ULN*

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

An overall summary of AEs will be presented.

The frequency of subjects with AEs will be summarised by treatment, primary system organ class (SOC) and preferred term (PT). Separate tables will be provided for subjects with serious AEs, for subjects with drug-related AEs, for subjects with drug-related serious adverse events and for subjects with AESIs. In addition, the frequency of subjects with AEs will be summarised by treatment, worst intensity, primary system organ class (SOC) and preferred term (PT).

The SOCs and PTs will be sorted by frequency (within SOC). The MedDRA version number 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.

7.8.2 Laboratory data

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

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

Clinically relevant findings in laboratory data will be reported as baseline conditions (at screening) or as AEs (during the trial) if judged clinically relevant by the investigator, and will be analysed as such.
It is the investigator's responsibility to decide whether a lab value is clinically significantly abnormal or not (at the RPM at the latest).

7.8.3 Vital signs

For vital signs (blood pressure and pulse rate), listings including change from baseline will be presented by planned time point based on the last value of the subject at that planned time point (or assigned to that planned time point).

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

7.8.4 ECG

Continuous safety ECG monitoring:

ECG recordings will be checked by the investigator for pathological results. Clinically relevant abnormal findings for ECG will be listed under 'Relevant Medical History / Baseline Conditions' (if they pre-exist prior to trial inclusion) or will be reported as AEs (if they occurred on treatment), and will be analysed as such. No separate ECG monitoring listing will be provided.

12-lead ECG:

Abnormal findings will be reported as baseline conditions (at screening) or as AEs (during the trial) if judged clinically relevant by the investigator, and will be analysed as such. Additionally, a dataset of quantitative and categorical ECG endpoints will be provided to [redacted] for analysis by an ECG programmer at BI.

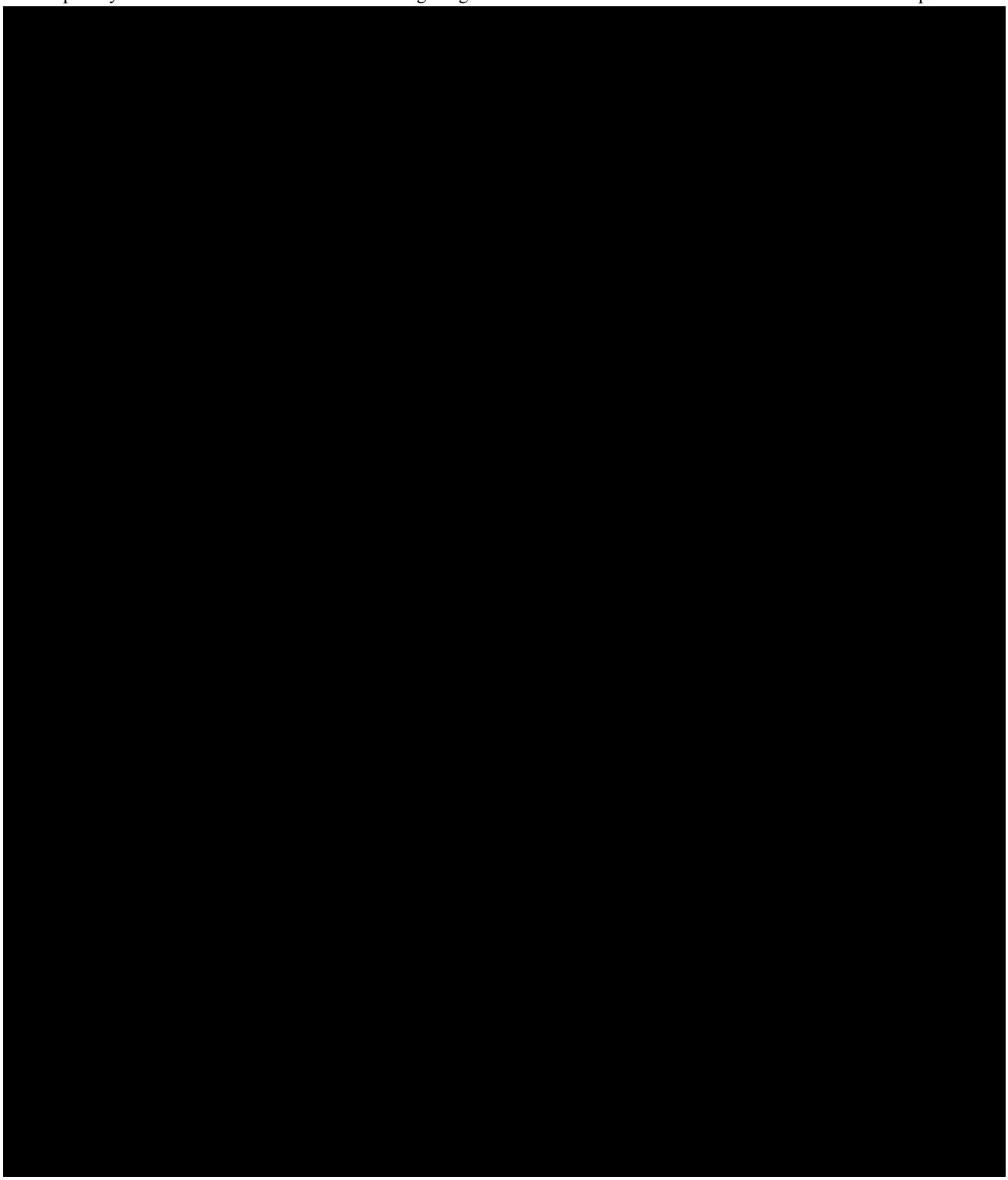
Listings of individual data of ECG endpoints will be shown in Appendix 16.2. Occurrences of notable findings will be flagged. Comments regarding the ECGs will be listed.

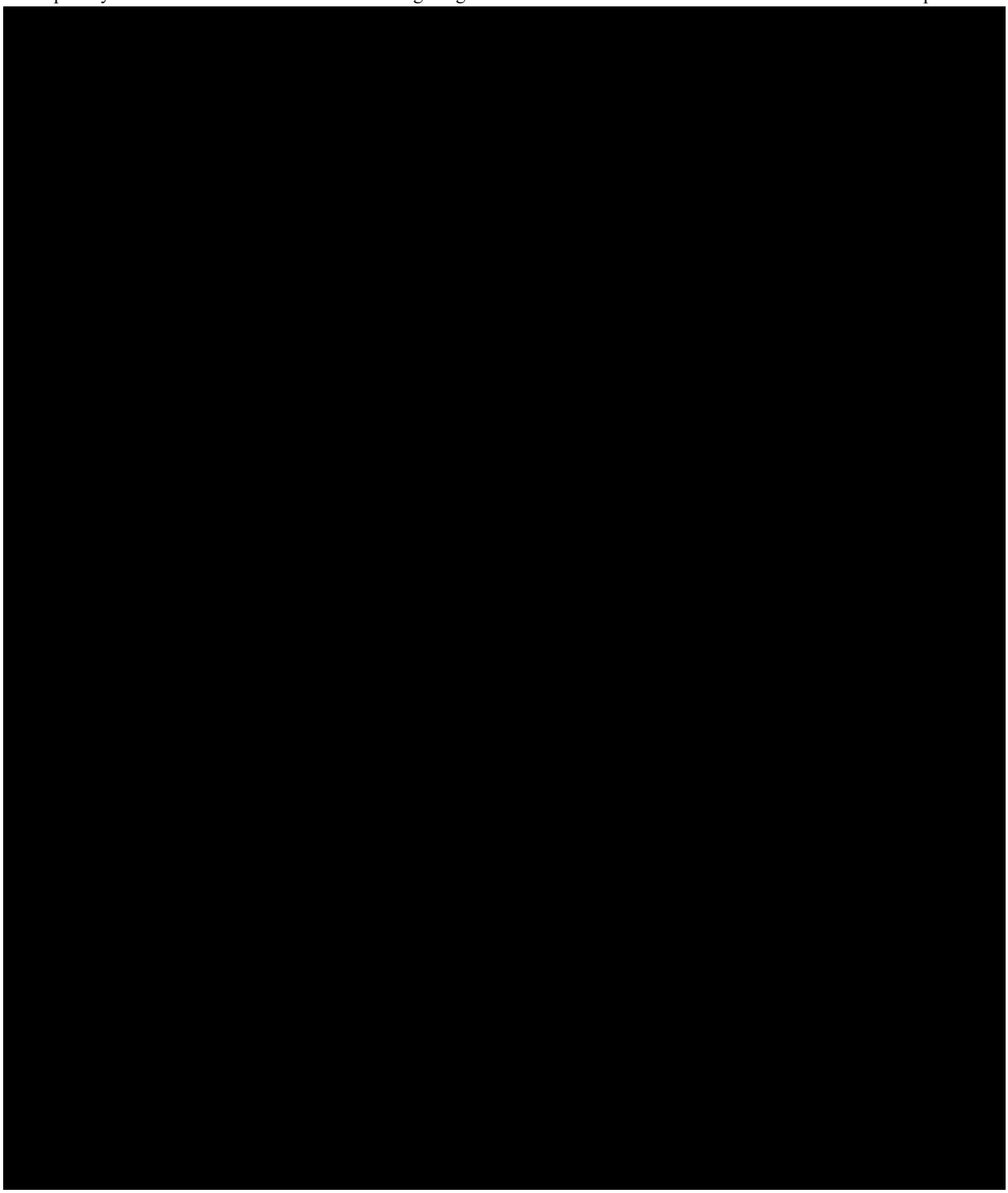
7.8.5 Others

Physical examination
Physical 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 (if they occurred on treatment) and will be summarised as such. No separate listing or analysis of physical examination findings will be prepared.

8. REFERENCES

1.	*CPMP/ICH/363/96:* "Statistical Principles for Clinical Trials", ICH Guideline Topic E9, Note For Guidance on Statistical Principles for Clinical Trials, current version.
2.	*001-MCS-40-413:* "Identify and Manage Important Protocol Deviations (iPD) ", current version, IDEA for CON.
3.	*BI-KMED-BDS-TMP-0059*: "iPD specification document (sdtm-dv-domain-specification)", template, current version, KMED.
4.	*BI-KMED-BDS-HTG-0035*: "Handling of Missing and Incomplete AE Dates", current version; KMED.
5.	*BI-KMED-TMCP-MAN-0012*: "Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics", current version; KMED.
6.	*BI-KMED-TMCP-MAN-0014*: "Noncompartmental Pharmacokinetic / Pharmacodynamic Analyses of Clinical Studies", current version; KMED.
7.	*BI-KMED-BDS-HTG-0045*: "Standards for Reporting of Clinical Trials and Project Summaries", current version; KMED.
8.	*BI*-KMED-TMCP-OTH-0003: "Graphs and Tables for Clinical Pharmacokinetics and Pharmacodynamic Noncompartmental Analyses", current version, KMED.
9.	*BI-KMED-TMCP-MAN-0010*: "Description of Analytical Transfer Files and PK/PD Data Files", current version; KMED.
10.	*BI-KMED-BDS-HTG-0041*: "Analysis and Presentation of Adverse Event Data from Clinical Trials – Display Template", current version; KMED.
11.	BI-KMED-BDS-HTG-0066: "Analysis and Presentation of AE data from clinical trials", current version; KMED.
12.	*CPMP/ICH/137/95*: "Structure and Content of Clinical Study Reports", ICH Guideline Topic E3; Note For Guidance on Structure and Content of Clinical Study Reports, current version.
13.	*BI-KMED-BDS-HTG-0042*: "Handling, Display and Analysis of Laboratory Data", current version; KMED.





10. HISTORY TABLE

Table 10: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
1	**12-FEB-2021**	[redacted]	None	This is the final TSAP