TRIAL STATISTICAL ANALYSIS PLAN

c38064615-01

BI Trial No.:	1367.1
Title:	An open label, Phase Ia/Ib dose finding study with BI 894999 orally administered once a day in patients with advanced malignancies with repeated administration in patients with clinical benefit Revised protocol version 12.0 [c03063854-14]
Investigational Product(s):	BI 894999
Responsible trial statistician(s):	[redacted] Phone: [redacted] Fax: [redacted]
Date of statistical analysis plan:	19 JAN 2022 SIGNED
Version:	Revised

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2. LIST OF ABBREVIATIONS

Term	Definition / description
ADS	Analysis Dataset
AE	Adverse Event
AESI	Adverse Event of Special Interest
ATC	Anatomical, Therapeutic, Chemical
AUC	Area Under the Curve
BI	Boehringer Ingelheim
BIcMQ	Boehringer Ingelheim customised MedDRA Query
BIRDS	Boehringer Ingelheim Regulatory Documents for Submission
BLRM	Bayesian logistic regression model
BOR	Best Overall Response
BRPM	Blinded report planning meeting
C	Concentration
CR	Complete Response
CRF	Case Report Form
CT	Concomitant Therapy
CTCAE	Common Terminology Criteria for Adverse Events
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
DBL	Database Lock
DC	Disease Control
DLT	Dose Limiting Toxicity
ECG	Electrocardiogram
ECGS	ECG Set
EoT	End of Text
[redacted]	[redacted]
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
ICH	International Conference on Harmonisation
IPV	Important Protocol Violation
LVEF	Left Ventricular Ejection Fraction
MedDRA®	Medical Dictionary for Regulatory Activities

Term	Definition / description
MQRM	Medical Quality Review Meeting
MTD	Maximum Tolerated Dose
MTDS	MTD Set
NHL	Non-Hodgkin Lymphoma
OR	Objective Response
OS	Overall Survival
PD	Progressive Disease
PFS	Progression-Free Survival
PGS	Pharmacogenomics Set
PK	Pharmacokinetics
PKS	Pharmacokinetics analysis Set
PR	Partial Response
PSA	Prostate-Specific Antigen
PT	Preferred Term
PV	Protocol violation
Q1	Lower quartile
Q3	Upper quartile
RECIST	Response Evaluation Criteria in Solid Tumours
REP	Residual Effect Period
RPM	Report Planning Meeting
SAE	Serious Adverse Event
ScS	Screened Set
SD	Stable Disease
SDL	Subject Data Listing
SS	Steady State
SSC	Special Search Category
StD	Standard deviation
SMQ	Standardised MedDRA query
SOC	System Organ Class
TBD	To Be Determined
ToC	Table of contents
TS	Treated Set

Term	Definition / description
TSAP	Trial statistical analysis plan
ULN	Upper Limit of Normal
UPROZ	Urine Protein
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, randomization.

SAS® Version 9.4 will be used for all analyses.

R Version 4.0.2 and JAGS Version 4.3.0 or the latest versions will be used for the BLRM analyses.

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

Due to the decision to discontinue the development of BI 894999 without expected out-licensing activities, an Abbreviated Report will be written. The analyses on safety will be conducted as stated in CTP, and an abbreviated set of tables and listings will be provided for other parts. Below are the main changes to the statistical methods described in the CTP and subsequent amendments are detailed in this TSAP:

- For the analysis of secondary efficacy endpoint objective response, only frequency tables including the corresponding percentages will be calculate for each cohort. The Bayesian hierarchical modelling analysis for Phase Ib part for the shrinkage estimators of response rate endpoints will not be carried out.
- [redacted]
- Further efficacy analyses will not be conducted.
- Where considered appropriate, the potential impact of Coronavirus Disease 2019 (COVID-19) on the study will be assessed by producing additional subject data listing of protocol deviations.
- The collected urine samples for the pharmacokinetic analysis will not be further analysed. Only information on urine intervals sampling times, urine volumes and urine concentrations of BI 894999 (if within their stability period) will be presented in subject data listing format.

The detailed changes to the pre-planned analyses are provided in Sections 5 and 7 below.

5. ENDPOINTS(S)

The Phase Ia/Ib trial consists of dose escalation part (Phase Ia) and expansion part (Phase Ib).

The main objective of the dose escalation part of the trial is to determine the maximum tolerated dose (MTD) of BI 894999 using three different schedules (Schedule A with continuous dosing, Schedule B with two weeks on treatment and one week off in 3-week cycles, Schedule C with a loading dose on Day 1 followed by a maintenance dose on the six next days and a week off, repeated every two weeks in 4-week cycles) in patients with solid tumours and to determine the MTDs using Schedules B and C in patients with diffuse large B-cell lymphoma (DLBCL) and provide safety data in terms of drug-related adverse events (AEs) for the recommendation of the dose and schedule of treatment for the expansion Phase Ib of this trial.

The main objective of the expansion part is to further collect safety information at the dose recommended by the data monitoring committee (DMC) for Phase Ib in patients with colorectal cancer (CRC), metastatic castrate resistant prostate cancer (mCRPC), small cell lung cancer (SCLC) and NUT carcinoma (NC) in Schedule B; and in patients with NC in Schedule C.

Please refer to Section 5.1 and 7.3 in the CTP for more details on the endpoints for this study.

5.1 PRIMARY ENDPOINT(S)

5.1.1 Phase Ia

- Number of patients with DLT (defined in Section 5.3.6.1 of the CTP) observed during the first treatment cycle (the first 21 days for Schedules A and B, the first 28 days for Schedule C) for each schedule in patients with solid tumours and for the Schedules B and C in the DLBCL cohort.

The MTD is defined as the highest dose of BI 894999 with less than 25% risk of the true DLT rate being above 33% during the MTD evaluation period (i.e., the first treatment cycle). The MTD determination will be based on the treated set population in Phase Ia excluding patients that have to be replaced for analysis of the MTD.

5.1.2 Phase Ib

- Number of patients with DLTs observed during the entire treatment period (as assessed approximately every 3 weeks, at the end of each new cycle after Cycle 2 for Schedule B, every 4 weeks for Schedule C in the NC cohort) for patients enrolled and treated in the Phase Ib part, i.e., SCLC patients, mCPRC patients, CRC patients, Schedule B in NC patients and Schedule C in NC patients.

5.2 SECONDARY ENDPOINT(S)

5.2.1 Key secondary endpoint(s)

No key secondary endpoint is defined for this study.

5.2.2 Secondary endpoint(s)

For Phase Ia only

- Number of patients with DLTs observed during all treatment cycles for each of the schedules (A, B and C) in patients with solid tumours and for the Schedules B and C in the DLBCL cohort

For Phases Ia and Ib

- Pharmacokinetic (PK) parameters after single dose and at steady state (C_{max}, AUC_{0-24}, $C_{max,ss}$ and $AUC_{\tau,ss}$) measured during the first cycle

- Objective response (OR)

  OR is defined as best overall response (BOR) of complete response (CR) or partial response (PR) with tumour assessment during treatment period for each schedule. For DLBCL patients, a minor response according to RECIL 2017 is not part of an objective response.

  BOR is determined from first treatment administration until the earliest of disease progression, death or last evaluable tumour assessment before start of subsequent anti-cancer therapy, loss to follow-up or withdrawal of consent, according to the following criteria depending on the type of cancer:

  - Based on tumour assessment of CT and/or MRI according to Response Evaluation Criteria In Solid Tumours (RECIST) version 1.1 (2) in patients with solid tumours including mCRPC patients with measurable disease, every 2 cycles

  - Based on bone scan and PSA level according to Prostate Cancer Clinical Trials Working Group 3 (PCWG3) in mCRPC patients of Phase Ib without measurable disease according to RECIST 1.1, every 4 cycles

  - Based on FDG-PET/CT scans according to Response Evaluation Criteria In Lymphoma 2017 (RECIL 2017) in DLBCL patients, every 2 cycles

For Phase Ib only

- Progression-free survival (PFS) defined as the time from date of start of BI 894999 to the date of objective disease progression (PD) or death, whichever is earlier for SCLC patients, CRC patients, mCRPC patients with measurable disease by RECIST 1.1 and NC patients, with tumour assessment every 2 cycles according to RECIST 1.1 during treatment period

  Or

  Radiological PFS with tumour assessment by bone scan every 4 cycles for mCRPC patients with non-measurable disease by RECIST 1.1

  For patients with ‘event’ as an outcome for PFS:

- PFS [days] = date of outcome – date of first treatment administration + 1.

For patients with 'censored' as an outcome for PFS:

- PFS (censored) [days] = date of outcome – date of first treatment administration + 1.

The censoring rules for PFS outcome (event or censored) along with the date of outcome are given in Table 5.2.2: 1. Clinical disease progression will not be considered for determination of a PFS event, unless the outcome of the progression is death.

If patients would have their radiological examinations over a number of days, i.e. target lesions assessed on day x, non-target lesions assessed on day y and new lesion (if applicable) on day z, the earliest date of the multiple assessments should be considered.

Table 5.2.2: 1 Censoring rules for PFS

Situation	**Outcome (event or censored)**	**Date of outcome**
No baseline radiological assessment (no death before second scheduled radiological assessment)	censored	Date of first treatment administration
Death with no radiological assessment performed post-baseline (1st scenario takes precedence)	event	Date of death
No radiological assessment performed post-baseline, vital status is unknown or patient is known to be alive	censored	Date of first treatment administration
Progressed according to radiological assessment (irrespective of missed radiological assessments)	event	Date of radiological assessment of progression
Death without progression	event	Date of death
Alive and not progressed (irrespective of missed radiological assessments)	censored	Date of last radiological assessment
Subsequent anti-cancer therapy before progression or death (check interval between start of new medication and earliest of subsequent PD or death)		
Interval <= 7 days	event	Earliest date of radiological assessment of progression or death
Interval > 7 days	censored	Date of last radiological assessment before initiation of subsequent anti-cancer therapy

- Best overall response (BOR)
- Prostate-specific antigen (PSA) response in patients with mCRPC

  PSA response is defined as a decline in PSA value ≥50% from baseline (which is confirmed by a second value 3 to 4 weeks apart).

- Overall survival (OS) in patients with NC.

  OS is defined as the time from first administration of BI 894999 until death from any cause in patients with NC. The analysis of OS is limited for NC patients after approval of protocol version 11.0 and who gave consent to the collection of OS.

  For patients with 'event' as an outcome for OS:

  - OS [days] = date of outcome – date of first treatment administration + 1.

  For patients with 'censored' as an outcome for OS:

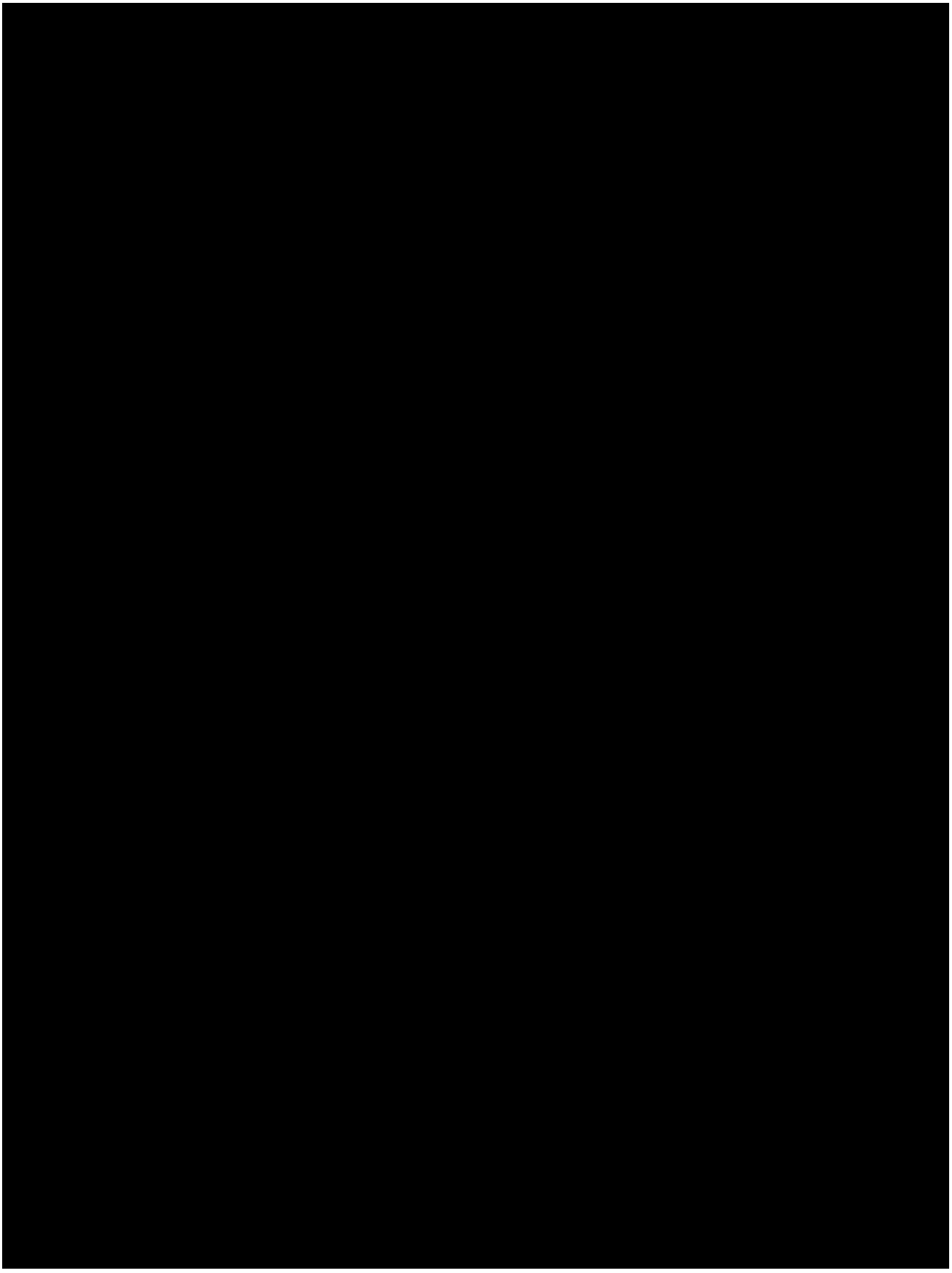
  - OS (censored) [days] = date of outcome – date of first treatment administration + 1.

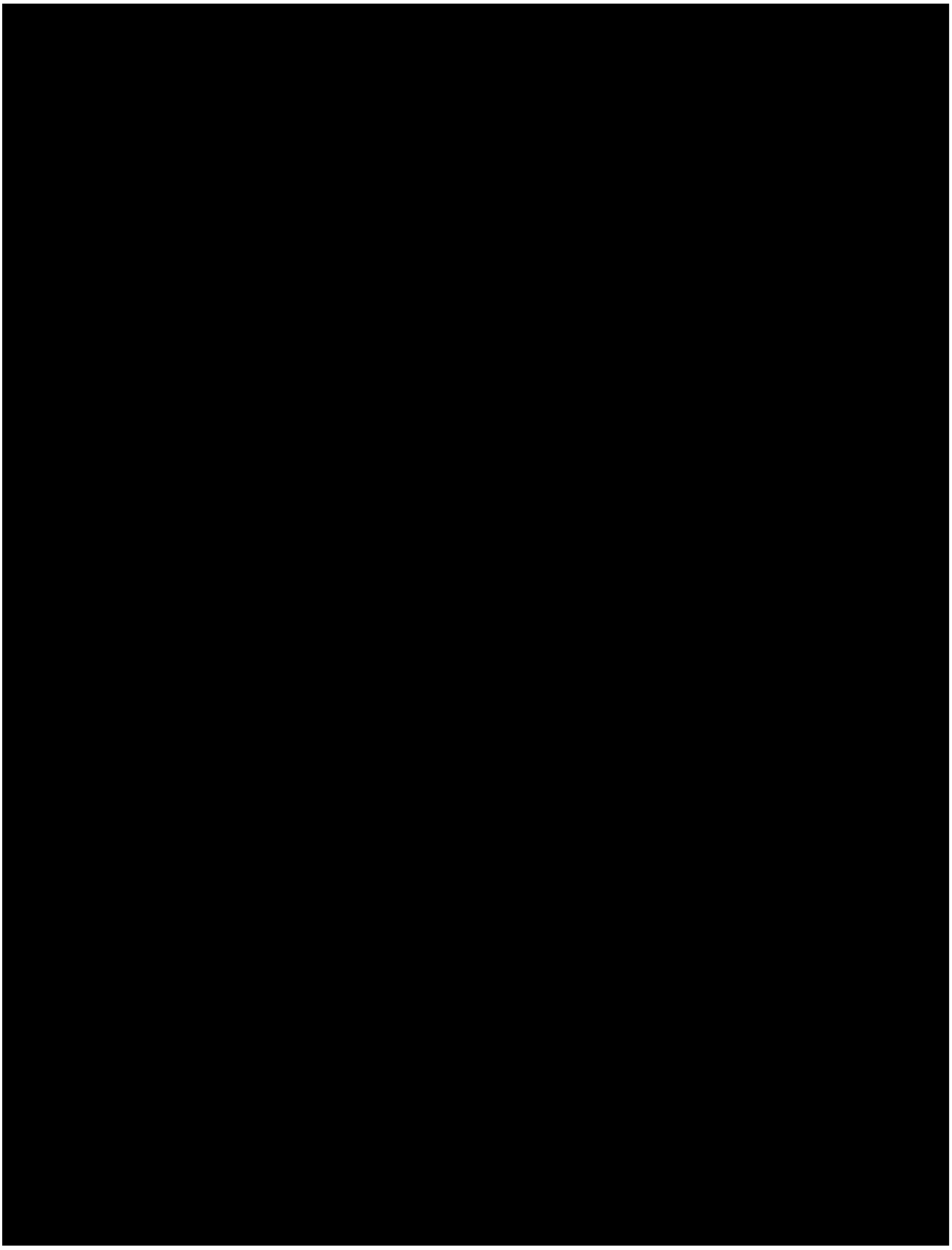
  The censoring rules for OS (i.e. outcome and date of outcome) are given in Table 5.2.2: 2.

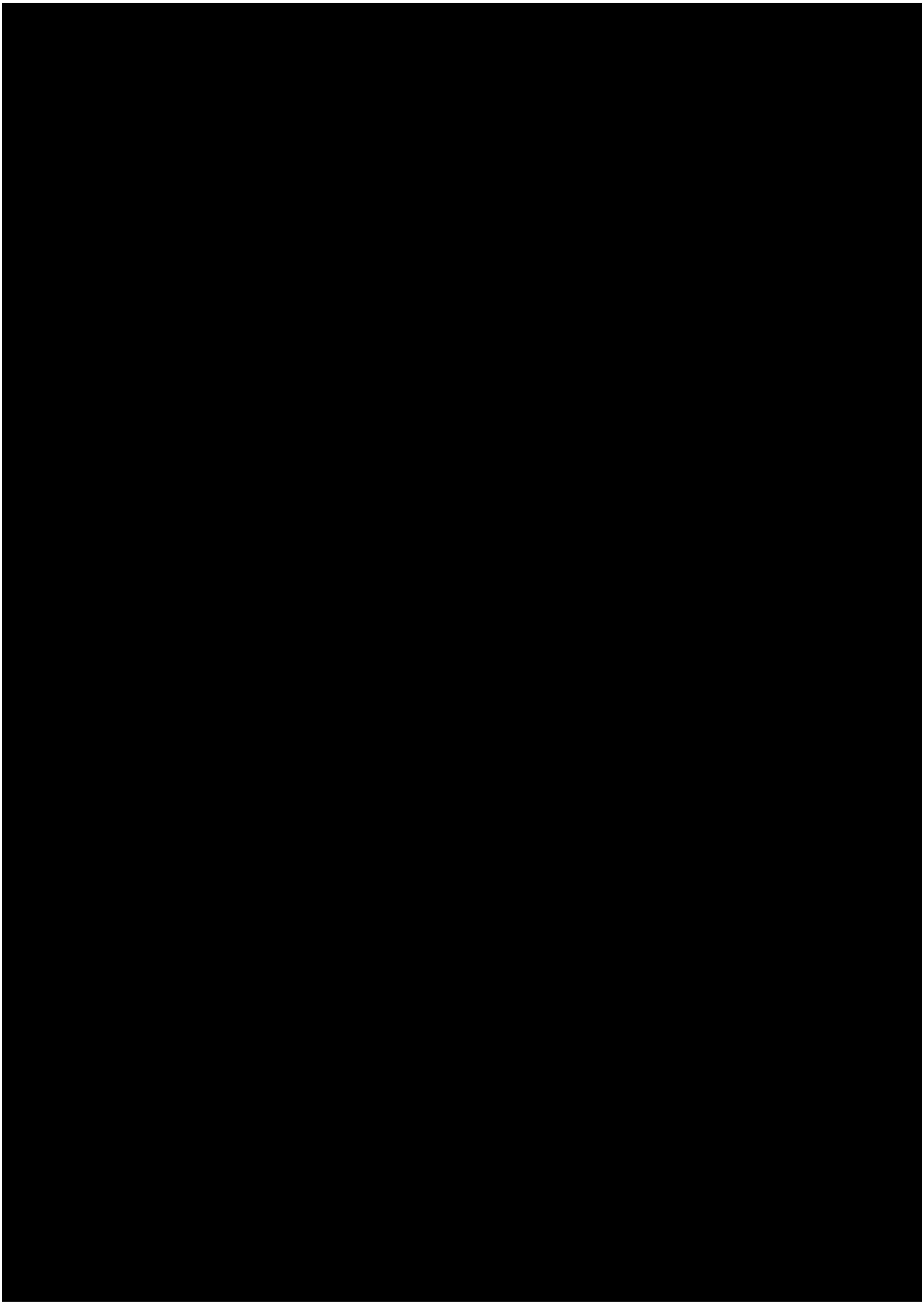
  Table 5.2.2: 2 Censoring rules for OS

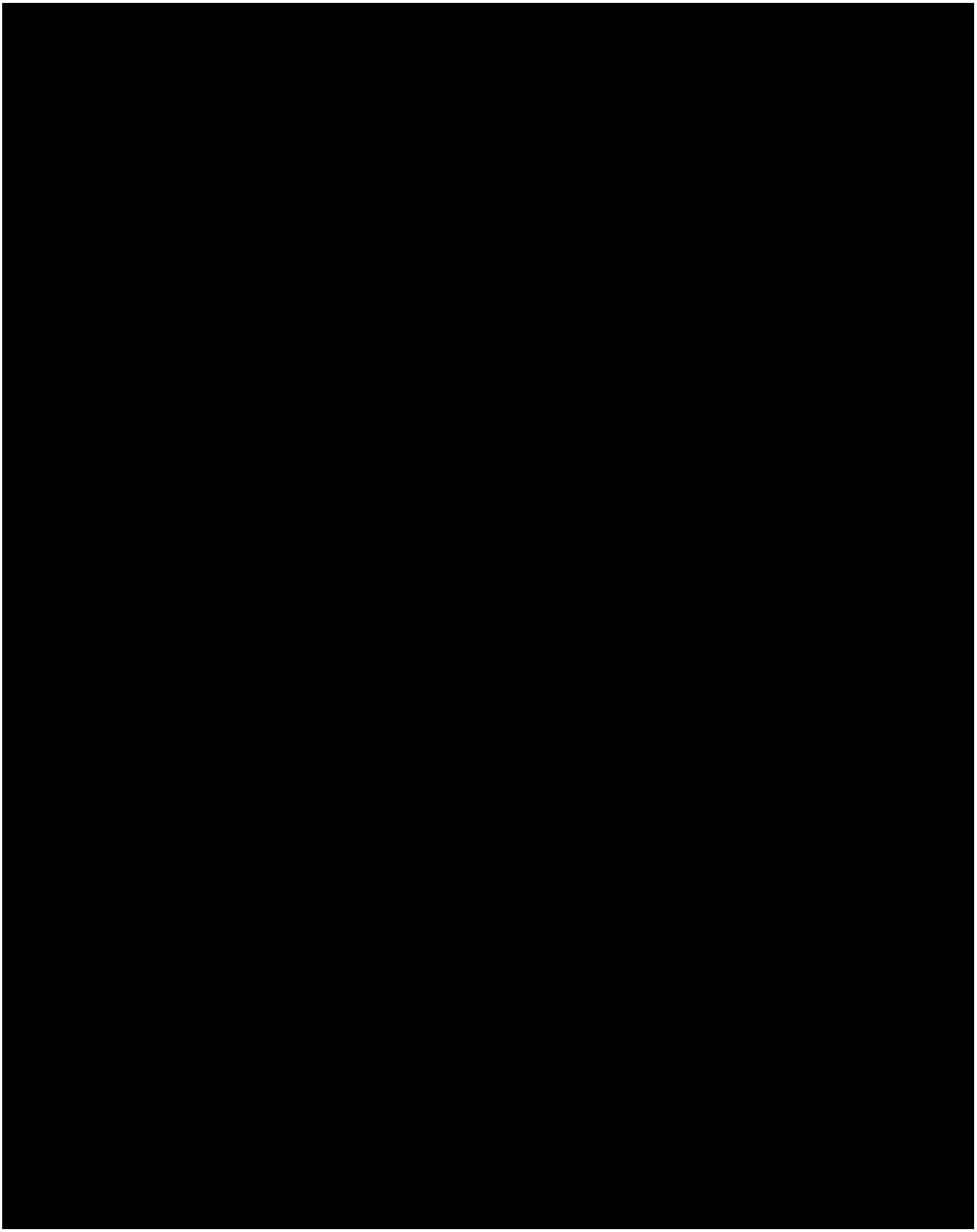
Status at time of analysis	**Outcome (event or censored)**	**Date of outcome**
Patient died and the date of death is known	event	Date of death
Patient died and date of death is unknown	event	Date of last contact when the patient is known to be alive + 1 day
Patient alive	censored	Date of last contact when the patient is known to be alive
Unknown	censored	Date of last contact when the patient is known to be alive

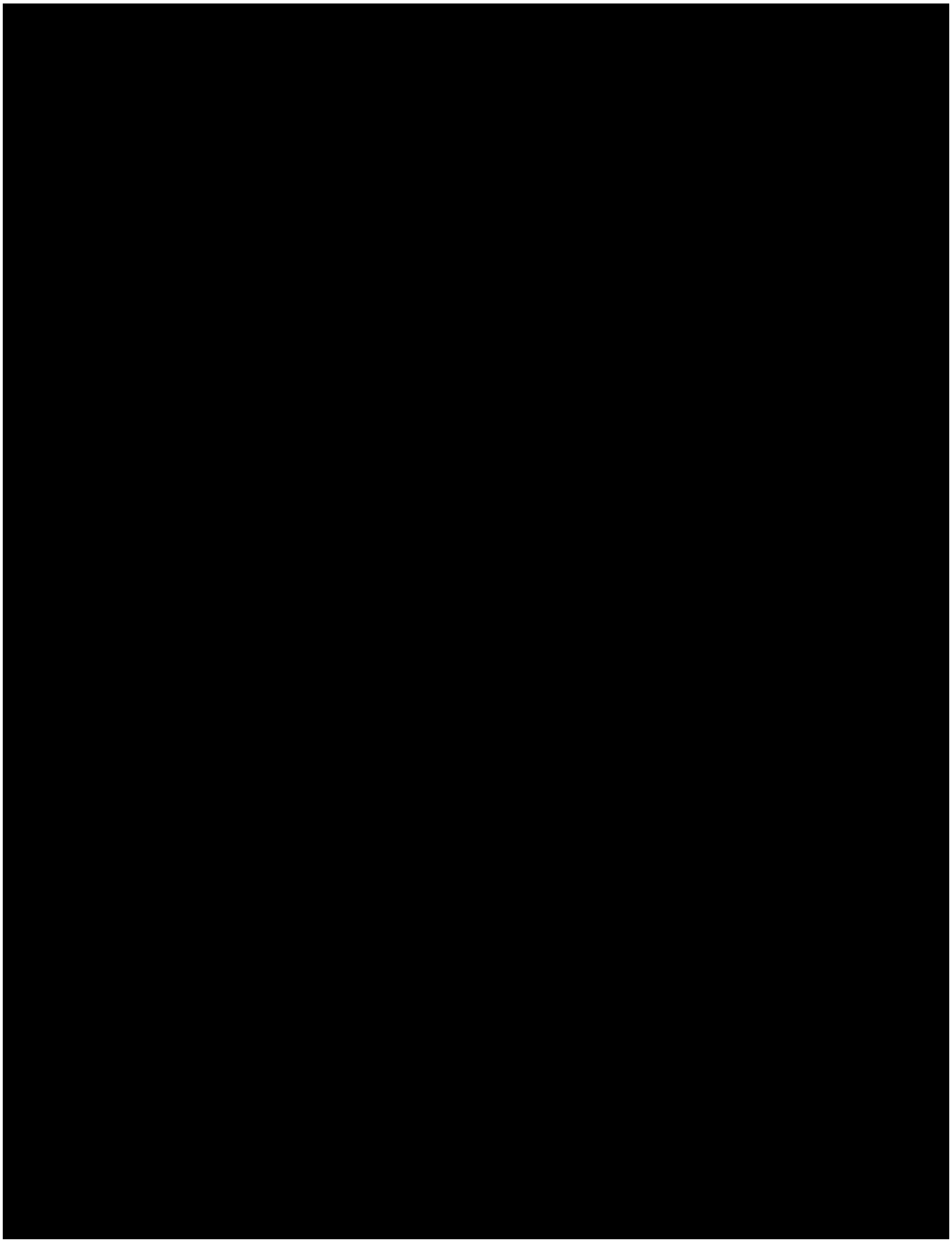
[redacted]

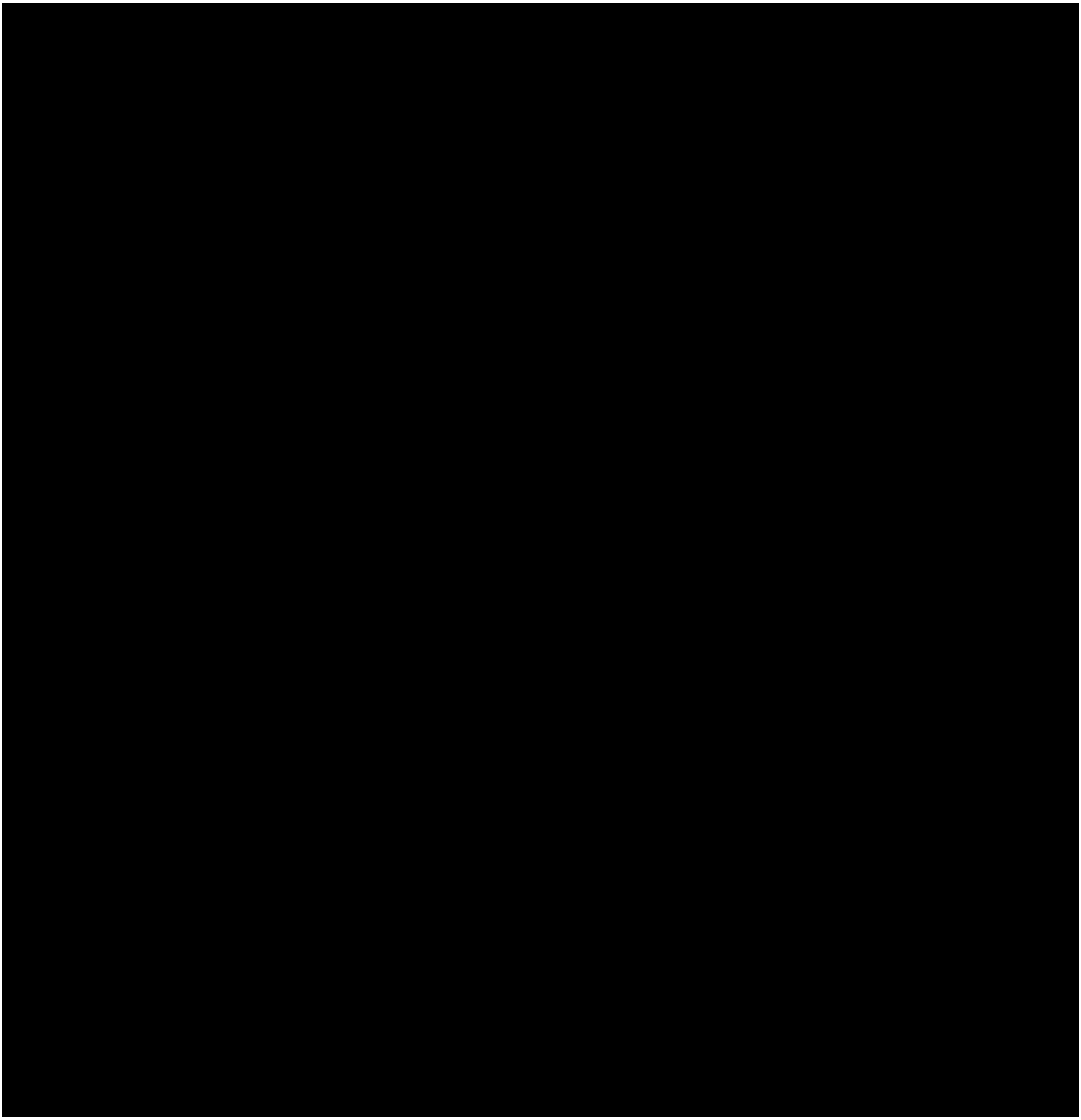












6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENT(S)

This is an open label, non-randomised study with a dose escalation Phase Ia and an expansion Phase Ib. For basic study information on treatments to be administered, assignment of treatment groups, selection of doses, refer to CTP Section 4.

Patients will be analysed by the initial study treatment administered on the first day of the first treatment cycle. The following "analysing treatment" (see Table 6.1: 1) will be used for reporting treatment emergent adverse events (AEs) and safety laboratory variables and the inequalities start date ≤ onset date of AE≤ stop date will determine if an AE will be assigned to the "analysing treatment" or not.

For the on-treatment and follow-up periods, AE frequency tabulations will contain a "total" column, representing all doses of BI 894999 combined. Subject data listings of AEs will not have a "total" column. The data will be presented for each dose cohort separately. To justify the MTD determination, DLTs occurring during the MTD evaluation period will be presented separately from those occurring during the entire on-treatment period.

Table 6.1: 1 Definition of analysing treatment periods for safety analysis

Analysing Treatment Period	**Start Date**	**Stop Date**
Screening	Date of informed consent	Date of the first administration of study treatment – 1 day
On-treatment	Date of the first administration of study treatment	For discontinued patients: date of the last administration of study treatment + 30 days, or death, whichever comes first. For on-going patients: DBL date
Follow-up (Post-treatment)	Last day of on-treatment period + 1 day Note: on-going patient have no follow-up period	Date of the last contact, or death, or DBL date, whichever comes first
MTD evaluation period*	Date of the first administration of study treatment	Date of the first administration of study treatment + 21 days (Schedule A and B) / + 28 days (Schedule C), or DBL date, or the start date of the second

		treatment cycle – 1 day, whichever is earlier

Note: a 30-day residual effect period (REP) is defined for this study. DBL = database lock. *The MTD evaluation period is only applied to patients in the dose escalation Phase Ia of the trial.

6.2 IMPORTANT PROTOCOL DEVIATIONS

Data discrepancies and deviations from the CTP will be identified for all patients in the database (i.e., enrolled patients). Consistency check listings (for identification of violations of time windows) and a list of protocol deviations will be provided to be discussed at the Medical Quality Review Meetings (MQRMs) and report planning meetings (RPMs). At this meeting, it will be decided whether a discrepant data value can be used in analyses or whether it must be queried in the clinical database. Each protocol deviation must be assessed to determine whether it is an important Protocol Deviation (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)" (3). Table 6.2: 1 contains the categories which are considered to be iPDs in this trial.

If any iPDs are identified, handling of iPDs in analysis will be documented in the meeting minutes of MQRMs and RPMs. The final list of iPDs and the decision whether a patient will be excluded from the analysis will be confirmed at the final RPM before DBL. No per protocol set is defined for this phase I study, but patients with an iPD will be identified and reported in the CTR.

Table 6.2: 1 Important protocol deviations

Category/ Code	Description	Comments	Excluded from
A	**Entrance criteria violated** #		
A1	Inclusion criteria not met		None
A2	Exclusion criteria met		None
B	**Informed consent** #		
B1	Informed consent not available/not done		
B1.1	Informed consent not available/not done	Informed consent date missing	All
B1.2	Pharmacogenomics informed consent not available/not done	Patient consented to the main study but not consented to the pharmacogenomic part	PGS
B2	Informed consent too late	Informed consent (main consent and/or pharmacogenomics consent) date was after screening visit date	None
C	**Trial medication**		

C1	Incorrect trial medication taken	Medication kit assigned not matching IRT assignment	None
C2	Dose adjustment		
C2.1	Dose reduction not following the protocol	Refer to Section 4.1.4 of the CTP	None
C2.2	Intra-patient dose escalation		None
C3	Treatment discontinuation		
C3.1	Continuation of treatment although criteria for re-treatment not met	Refer to Section 4.1.4 of the CTP	None
C3.2	Discontinuation of trial medication not following the protocol	Refer to Section 3.3.4 of the CTP	None
C3.3	Withdrawal of patient not according to the protocol	Refer to Section 3.3.4 of the CTP	None
C4	Non-compliance with study medication		
C4.1	Wrong dosage/dosing schedule	Incorrect daily dose taken leading to overdose (not intra-patient dose escalation) or under dose (>2 tablets away from planned daily dose)	None
C4.2	Non-compliance	Number of tablets taken out of 80-120% medication compliance range not due to AE	None
D	**Concomitant medication**		
D1.1	Prohibited medication use	Refer to Section 4.2.2.1 of the CTP	None
D1.2	Administration of non-protocol investigational anti-cancer treatment during treatment period	Refer to Section 4.2.2.1 of the CTP	None
E	**Missing data**		
E1	Critical safety procedures not done		None
G	**Other protocol deviations** #		
G1	Negative pregnancy test result not obtained for women of child bearing potential	Negative pregnancy test result not obtained at screening or EOT	None

PD will be detected by automatic programming.

To assess the the potential impact of Coronavirus Disease 2019 (COVID-19) on the study, additional subject data listing of protocol deviations related to COVID-19 will be produced. The start date for COVID-19 having an impact on the trial will be taken as the earliest date of a COVID-19 related protocol deviation, discontinuation due to COVID-19, onset of a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) related AE or COVID-19 related global BI recruitment hold (17 MAR 20).

6.3 SUBJECT SETS ANALYSED

- Screened Set (ScS): includes all patients who have signed the informed consent form and will be used for patient disposition.

- Treated Set (TS): includes all patients who were dispensed study treatment and were documented to have taken at least one dose of the study treatment. The TS is used for both efficacy and safety analyses, and for summary of demographics, baseline characteristics, disease history, and concomitant therapies.

  The following subsets within TS are defined for specific analyses:

  - MTD Evaluation Set (MTDS): includes all patients in the TS who were not replaced for the MTD determination. The MTD Evaluation Set is used for the primary analyses of DLTs and MTD determination. Rules for replacement of patients are defined in the CTP Section 3.3.4. The list of replaced patients will be provided by the Clinical Trial Leader (CTL) no later than the last RPM and should be documented in the RPM minutes.

  - Solid Tumour Schedule A in Phase Ia dose escalation (Solid A): includes all solid tumour patients in the TS who were treated in Phase Ia with Schedule A and are evaluable for MTD.

  - Solid Tumour Schedule B in Phase Ia dose escalation (Solid B): includes all solid tumour patients in the TS who were treated in Phase Ia with Schedule B and are evaluable for MTD.

  - Solid Tumour Schedule C in Phase Ia dose escalation (Solid C): includes all solid tumour patients in the TS who were treated in Phase Ia with Schedule A and are evaluable for MTD.

  - DLBCL Schedule B in Phase Ia dose escalation (DLBCL B): includes all DLBCL patients in the TS who were treated in Phase Ia with Schedule B and are evaluable for MTD.

  - DLBCL Schedule C in Phase Ia dose escalation (DLBCL C): includes all DLBCL patients in the TS who were treated in Phase Ia with Schedule C and are evaluable for MTD.

  - Treated Set in Phase Ib dose expansion (TS PhIb): includes all patients in the TS who were treated in Phase Ib. TS PhIb is used for analyses of progression-free survival (PFS), best overall response (BOR).

  - SCLC Schedule B in Phase Ib dose expansion (SCLC): includes all SCLC patients in the TS who were treated in Phase Ib with Schedule B

  - CRC Schedule B in Phase Ib dose expansion (CRC): includes all CRC patients in the TS who were treated in Phase Ib with Schedule B

- mCRPC Schedule B in Phase Ib dose expansion (mCRPC): includes all mCRPC patients in the TS who were treated in Phase Ib with Schedule B. mCRPC B is used for PSA analyses.
- NC Schedule B in Phase Ib dose expansion (NC B): includes all NC patients in the TS who were treated in Phase Ib with Schedule B.
- NC Schedule C in Phase Ib dose expansion (NC C): includes all NC patients in the TS who were treated in Phase Ib with Schedule C.
- NC Schedules B and C in Phase Ib dose expansion (NC PhIb): includes all NC patients in the TS who were treated in Phase Ib with Schedules B and C. Patients in NC PhIb and after approval of protocol version 11.0 and gave consent to the collection of overall survival status will be used for the analysis of overall survival (OS).

- PK analysis Set (PKS): includes all patients in the TS who have at least one evaluable PK parameters and PKS is used for pharmacokinetic analyses.

[redacted]

6.5 POOLING OF CENTRES

This section is not applicable because centre / country is not included in the statistical model.

6.6 HANDLING OF MISSING DATA AND OUTLIERS

Every effort should be made to collect complete data at each visit for each patient. If not specified otherwise, missing data will not be imputed and remain missing. Potential outliers will be reported and analysed as observed.

Missing or incomplete AE dates will be handled according to the Boehringer Ingelheim (BI) guideline (4).

Missing data and outliers of PK data will be handled according to the BI standards (5).

[redacted]

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

Study days and visits will be labelled according to the CTP's flow chart.

Unless otherwise specified, baseline is defined as the time point closest to and prior to the first administration of study treatment. Note that for some study procedures (e.g. body weight, vital signs, laboratory tests) baseline may be the measurement made on the same day the study treatment was started. In such cases these measurements will be assumed to have been taken according to the protocol, i.e. prior to the first administration of study treatment.

For laboratory parameters for which not only the examination date but also the sampling time was recorded, examination time should be taken into consideration when defining baseline. That is a laboratory measurement on the same date as the first administration of study treatment is considered as baseline if and only if the examination time of this laboratory measurement is before the first administration of study treatment.

7. PLANNED ANALYSIS

In general the display format of the analysis results will follow BI guideline (6) as much as possible.

For End-Of-Text (EoT) tables, the set of summary statistics is: N / Mean / Standard Deviation (StD) / Min / Median / Max.

For tables that are provided for endpoints with some extreme data, median, quartiles and percentiles will be preferred to mean, standard deviation, minimum and maximum.

In general, means, medians, and percentiles will be presented to one more decimal place than the raw data and StDs will be presented to two more decimal places than the raw data. Minima and maxima will be presented to the same number of decimal places as the raw data.

For time-to-event analysis tables, the set of statistics is: number of patients [N (%)], number of patients with event [N (%)], <Time to event> [<unit>] followed by P25 (25th percentile), median + 95% confidence interval, P75 (75th percentile). If not specified otherwise, the duration as well as the time to event will be displayed in weeks and a final decision will be made at the last RPM.

Tabulations of frequencies for categorical data will include all possible categories (even if there is no count in a category) and will display the number of observations in a category as well as the percentage (%) relative to the number of patients in the respective treatment group (unless otherwise specified, all patients in the respective patient set whether they have non-missing values or not). Percentages will be rounded to one decimal place. The category missing will be displayed only if there are actually missing values.

If a table presents only categorical data, "[N (%)]" will be displayed in the column headers only.

Abbreviations (e.g. Wors.) or acronyms (e.g. PD) will not be displayed in tables and Subject Data Listings (SDLs) without any explanation. They will be either spelled out or explained in footnotes.

If applicable, conversion from days to weeks, months and years will be as follows:

- Weeks = days ÷ 7
- Months = 12 × days ÷ 365.25
- Years = days ÷ 365.25.

Descriptive statistics for PK variables include: N / geometric mean / geometric coefficient of variation / arithmetic mean / arithmetic coefficient of variation / StD / Min / P10 (10th percentile) / Q1 (25th percentile) / median / Q3 (75th percentile) / P90 (90th percentile) / Max.

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Only standard descriptive statistics and summary tables are planned for this section of the report. Data will be summarised by treatment group (i.e. dose cohort and dosing schedule in Phase Ia; expansion cohort in Phase Ib) and a "total" column will be included in the summary table.

The following age categories will be used:

- ≤ 65 years
- > 65 to ≤ 75 years
- > 75 years.

7.2 CONCOMITANT DISEASES AND MEDICATION

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

Concomitant diseases will be coded similarly as AEs based on the most current Medical Dictionary for Regulatory Activities (MedDRA®) version. Concomitant therapies (CTs) will be coded according to the World Health Organization Drug Dictionary (WHO DD). CTs will be classified according to the Anatomical, Therapeutic, Chemical (ATC) classification system. The third ATC level will be used to categorise CTs by therapy type. In situations where a medical product may be used for more than one equally important indication, there are often several classification alternatives. As appropriate, patients receiving CTs with more than one possible ATC level-three category will be counted more than once; footnotes will clarify this possible double counting in tables.

7.3 TREATMENT COMPLIANCE

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

7.4 PRIMARY ENDPOINT(S)

Phase Ia

The primary objective of Phase Ia is to determine the MTD. The purpose of the primary analysis is to summarise and document the data that led to the selection of the MTD. Therefore an overall summary of the number of patients with DLT(s) which occurred during the MTD evaluation period (see definition in Table 6.1: 1) will be provided for each dose cohort and for each patient set Solid A, Solid B, Solid C, DLBCL B, DLBCL C and MTDS (see definitions in Section 6.3). Patients who were treated but replaced for the assessment of DLT and dose escalation will be excluded from the summary table. A summary of the number of patients with DLTs occurring during the entire on-treatment period will also be given by initial treatment and displayed in a similar format to the summary of DLTs occurring in the MTD evaluation period.

The dose escalation and determination of MTD is guided by a Bayesian logistic regression model (BLRM) with overdose control. The MTD is defined as the highest dose for a given dosing schedule that is expected to cause less than 25% risk of the true DLT rate being above

33% during the MDT evaluation period. Estimation of the MTD during the dose escalation phase of this study is based on the estimation of the posterior probability of the incidence of DLT in the toxicity categories during the MTD evaluation period for all evaluable patients. The BLRM used is specified in CTP Section 7.1. Results from the BLRM will be presented using the actual dose escalation information.

Phase Ib

The number of patients with DLTs observed during the entire treatment period for each cohort will be analysed descriptively. BLRM will be re-run using the number of patients with DLTs observed during the entire treatment period for Schedule B and Schedule C.

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)

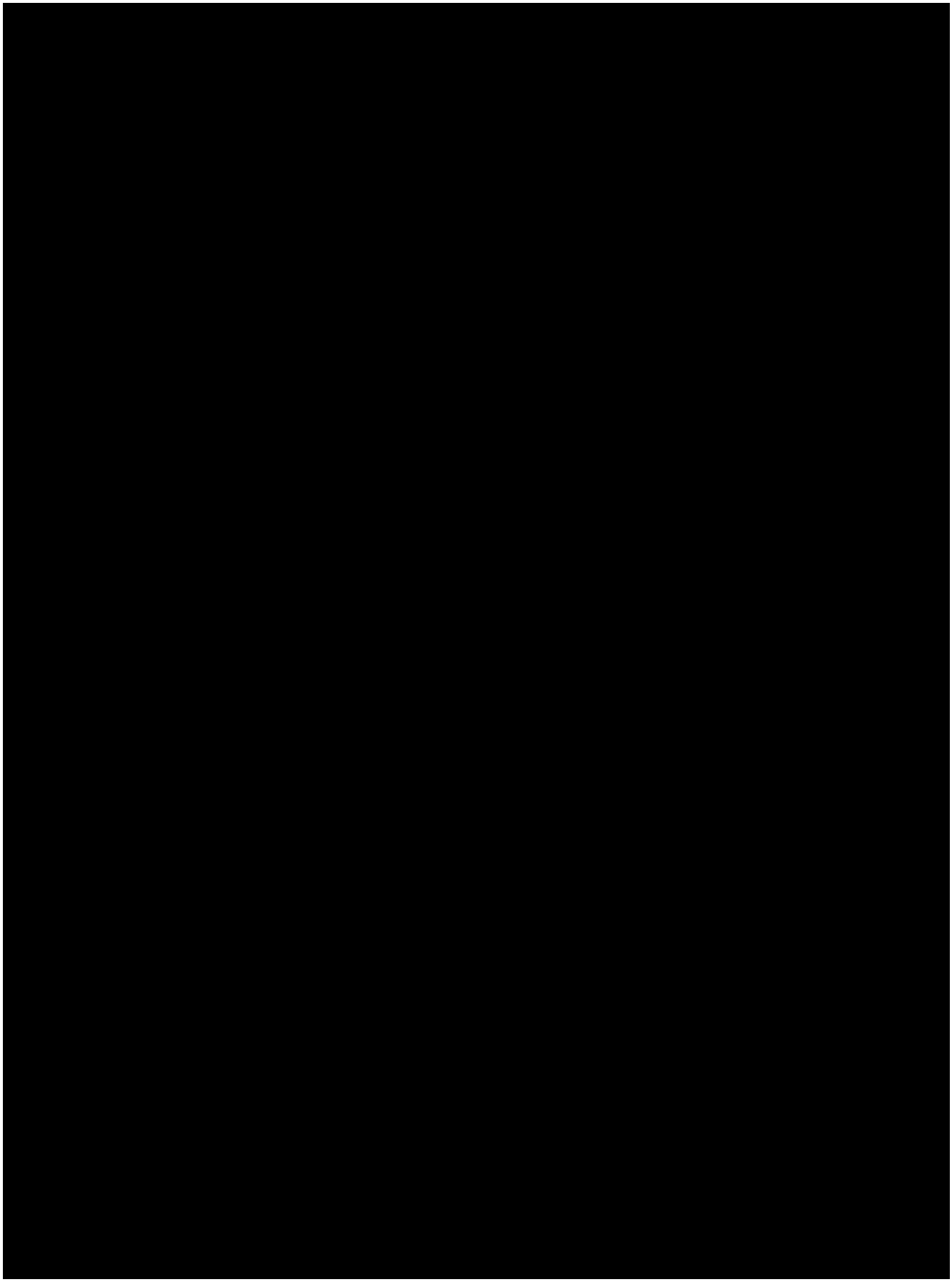
The number of patients with DLT(s) which occurred during the entire treatment period for the patient sets will be summarised for each dose cohort.

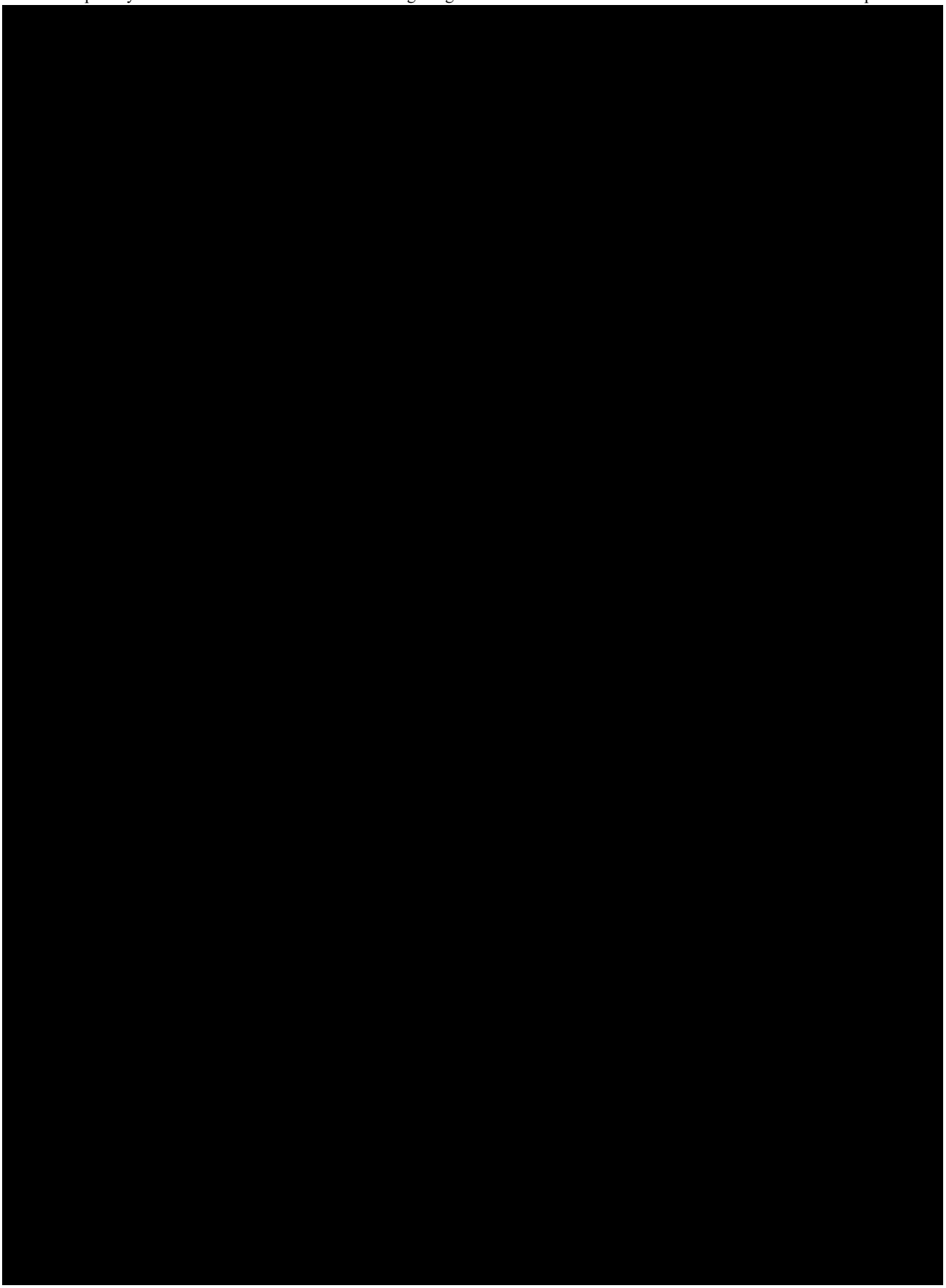
Best overall response, objective response will be summarised descriptively. The number of treated patients and the frequency of patients by best overall response category and objective response (yes / no) including the corresponding percentages will be calculated for each patient set. Percent change in PSA from baseline and PSA response for mCRPC patients will be presented in listings.

PFS based on investigator's assessment and OS will be assessed based on the Kaplan-Meier method. Point estimates together with confidence intervals (based on Greenwood's method) will be provided for median time to event and quartiles.

The analysis of standard PK parameters is performed according to (5). Descriptive statistics for PK will be given as: N, geometric mean, geometric coefficient of variation, arithmetic mean, arithmetic coefficient of variation, standard deviation, minimum, 10^{th} percentile (P10), 25^{th} percentile (Q1), median, 75^{th} percentile (Q3), 90^{th} percentile (P90) and maximum.

[redacted]





7.7 EXTENT OF EXPOSURE

Standard descriptive statistics over all treatment cycles will be calculated. This will include a summary of the variables defined in Section 5.4.1 and will comprise a mixture of frequency and percentages, as well as summary statistics.

7.8 SAFETY ANALYSIS

All safety analyses will be performed on the treated set. Patients who were replaced within the MTD evaluation period will be excluded from the determination of MTD but will be included in all other safety assessments.

7.8.1 Adverse Events

Unless otherwise specified, the analyses of AEs will be descriptive in nature. All analyses of AEs will be based on the number of patients with AEs and NOT on the number of AEs. The reporting and analyses of AEs will follow the BI guideline (7). AEs will be coded with the most recent version of MedDRA®. The severity of AEs will be scaled according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

For analysis of AE attributes such as duration, severity, etc., multiple AE occurrence data on the Case Report Form (CRF), will be collapsed into AE episodes provided that all of the following applies:

- The same MedDRA lowest level term was reported for the occurrences

- The occurrences were time-overlapping or time-adjacent (time-adjacency of 2 occurrences is given if the second occurrence started on the same day or on the day after the end of the first occurrence)
- Treatment did not change between the onset of the occurrences OR treatment changed between the onset of the occurrences, but no deterioration was observed for the later occurrence.

For further details on summarization of AE data, please refer to (4, 7).

The analysis of AEs will be based on the concept of treatment emergent adverse events. That means that all adverse events occurring between the date of the first administration of study treatment till the date of the last administration of study treatment + residual effect period will be assigned to the on-treatment period labelled with the study treatment assigned on Day 1 of the first treatment cycle. All AEs occurred before the first administration of study treatment will be assigned to 'screening' and all AEs occurred after the residual effect period will be assigned to 'follow-up' (for listings only). For details on the treatment definition, see Section 6.1.

An overall summary of AEs will be presented with an additional entry for patients with DLT(s) and will also include the number of patients with AEs by the worst CTCAE grade.

Adverse events of special interest (AESIs): see Section 5.3.6.1 of the CTP for details.

Other significant AEs according to ICH E3:

According to ICH E3 (8), AEs classified as 'other significant' needs to be reported and will include those non-serious and non-significant adverse events with
(i) 'action taken = discontinuation' or 'action taken = reduced', or
(ii) marked haematological and other lab abnormalities or lead to significant concomitant therapy as identified by the Clinical Monitor/Investigator at a MQRM.

The frequency of patients with AEs will be summarised by treatment, primary system organ class (SOC) and preferred term (PT), and will be sorted by the highest CTCAE grade. Separate tables will be provided for patients with

- DLTs during the MTD evaluation period
- DLTs during the entire treatment period
- AESIs
- serious adverse events (SAEs)
- related AEs
- serious related AEs
- other significant AEs according to ICH E3
- AEs leading to death
- AEs leading to dose reduction
- AEs leading to permanent discontinuation of study treatment.

The system organ classes will be sorted alphabetically, and preferred terms will be sorted by frequency (within system organ class).

Special Search Categories:

Special search categories (SSC) for AEs are defined in Table 7.8.1: 1. For SSC which contains sub-searches and / or two sensitivity levels (broad and narrow) all possibilities will be displayed on the SSC level in tables. The frequency of patients with AEs will also be summarised by treatment, SSC and preferred term and will be sorted by the highest CTCAE grade.

Table 7.8.1: 1 Definitions of Special Search Categories

Nr	Subject	Definition (for programmers)	Other monitoring options
1	Bone marrow suppression (all cell lines)	20000027 20000029 20000030	
2	Neutropenia	BicMQ Neutropenia BicMQ Leukopenia	
3	Thrombocytopenia	20000081	
4	Bleeding	20000040 20000039	
5	Infections, pneumonia, sepsis, febrile neutropenia	10021881 10024970 10040054	
6	Mucositis	BicMQ Mucositis	
7	Diarrhea	BicMQ Diarrhea	
8	Abdominal pain	10017926	
9	Anorexia, nausea	BicMQ Nausea	
10	Hyponatriemia	NA	Ref lab data, Review individual PTs manually
11	Hepatic enzyme elevation	20000006 BicMQ ALT BicMQ AST BicMQ ALKP BicMQ Bilirubin	
12	Hyperglycemia	Hyperglycaemia/new onset diabetes mellitus (SMQ)	SMQ code: 20000041 Only the narrow search is needed
13	Dysgeusia	NA	Review individual PTs manually
14	Skin rash	BicMQ Skin eruptions	
15	Fatigue	BicMQ Asthenic conditions	
16	Overdose: dehydration, oral ulceration, liquid stool, (ruffled fur)	NA	Review individual PTs manually
17	Decrease in urine volume and electrolyte excretion, dehydration	BicMQ Volume Depletion (Dehydration)	
18	Increased heart rate	NA	Ref vital signs, Review individual PTs manually

Nr	Subject	Definition (for programmers)	Other monitoring options
19	BW loss	BicMQ Weight loss	
20	Hypertriglyceridemia	BicMQ Triglycerides	
21	Decreases of cholesterol	NA	Ref lab data
22	Decreases of total protein (albumin & globulin)	NA	Ref lab data
23	Phototoxicity	10072982	

BicMQ – Boehringer Ingelheim customised MedDRA Query

7.8.2 Laboratory data

The analyses of laboratory data will be descriptive in nature and will follow the BI guideline (9). The same on-treatment period as defined for the analysis of AEs will be applied for the laboratory parameters. Patients having at least one post-baseline laboratory value will be displayed in the descriptive analyses.

Descriptive statistics, including change from baseline and frequency of patients with transitions relative to the reference range, will be provided. CTCAE grades for applicable laboratory parameters will be calculated according to CTCAE version 4.03. The following outputs will be presented:

- worst CTCAE grade experienced during the on-treatment period
- transitions of CTCAE grade from baseline to worst laboratory value, from worst to last laboratory value during the on-treatment period, and from baseline to last laboratory value.

Patients with missing CTCAE grade at baseline or no baseline value but with post-baseline values will be displayed in the category “Missing CTCAE grade at baseline”.

Possible clinically significant abnormal laboratory values:

Possible clinically significant abnormal laboratory values are defined as those laboratory values that are of CTCAE Grade ≥ 2 and show an increase from baseline value by at least one CTCAE grade. For those parameters for which no CTCAE has been defined, BI standard definition will be used to determine possible clinical significance. Frequency of patients with possible clinically significant abnormal laboratory values will be provided whenever applicable. If no baseline value is available but the patient had a post-baseline laboratory value of CTCAE Grade ≥ 2 an increase from baseline will be assumed, i.e. the laboratory value considered as possible clinically significant.

Laboratory values of special interest:

Laboratory parameters of special interest are white blood cells, neutrophils, lymphocytes, platelets, CK, CK-MB, troponin T, hemoglobin, AST, ALT, ALKP, and bilirubin. However, all laboratory parameters will be displayed in the same laboratory tables.

Potential Hy’s law cases:

Special attention will be paid to patients fulfilling the criteria for potential Hy's law cases.

For patients with normal hepatic function at baseline:

- an elevation of AST and / or ALT ≥ 3 fold the Upper Limit of Normal (ULN) combined with an elevation of total bilirubin ≥ 2 fold ULN measured in the same blood draw sample,

  and / or

  marked peak aminotransferase (ALT and / or AST) elevation ≥ 10 fold ULN.

For patients with abnormal hepatic function at baseline (e.g. due to primary liver cancer or hepatic metastases)

- an elevation of AST and / or ALT > 5 fold ULN combined with an elevation of bilirubin > 2 fold ULN measured in the same blood draw sample.

The events can occur in any order, but must occur within 14 days of the previous event, i.e. the second event must occur within 14 days of the first event, and the third event must occur within 14 days of the second event, etc.

Handling of laboratory parameters with CTCAE grade -1:

For uric acid, glomerular filtration rate (GFR) and hypokalemia, the CTCAE grade cannot always be assigned by the laboratory parameter itself as two different CTCAE grades have the same laboratory constellation, but are distinguished by additional clinical parameter. In this case a CTCAE grade of "-1" will be assigned initially. For all analyses patients with a CTCAE grade of "-1" will be treated as

Grade 1 for uric acid

Grade 3 for GFR

Grade 1 for hypokalemia (Only when CTCAE version 4.03 is used).

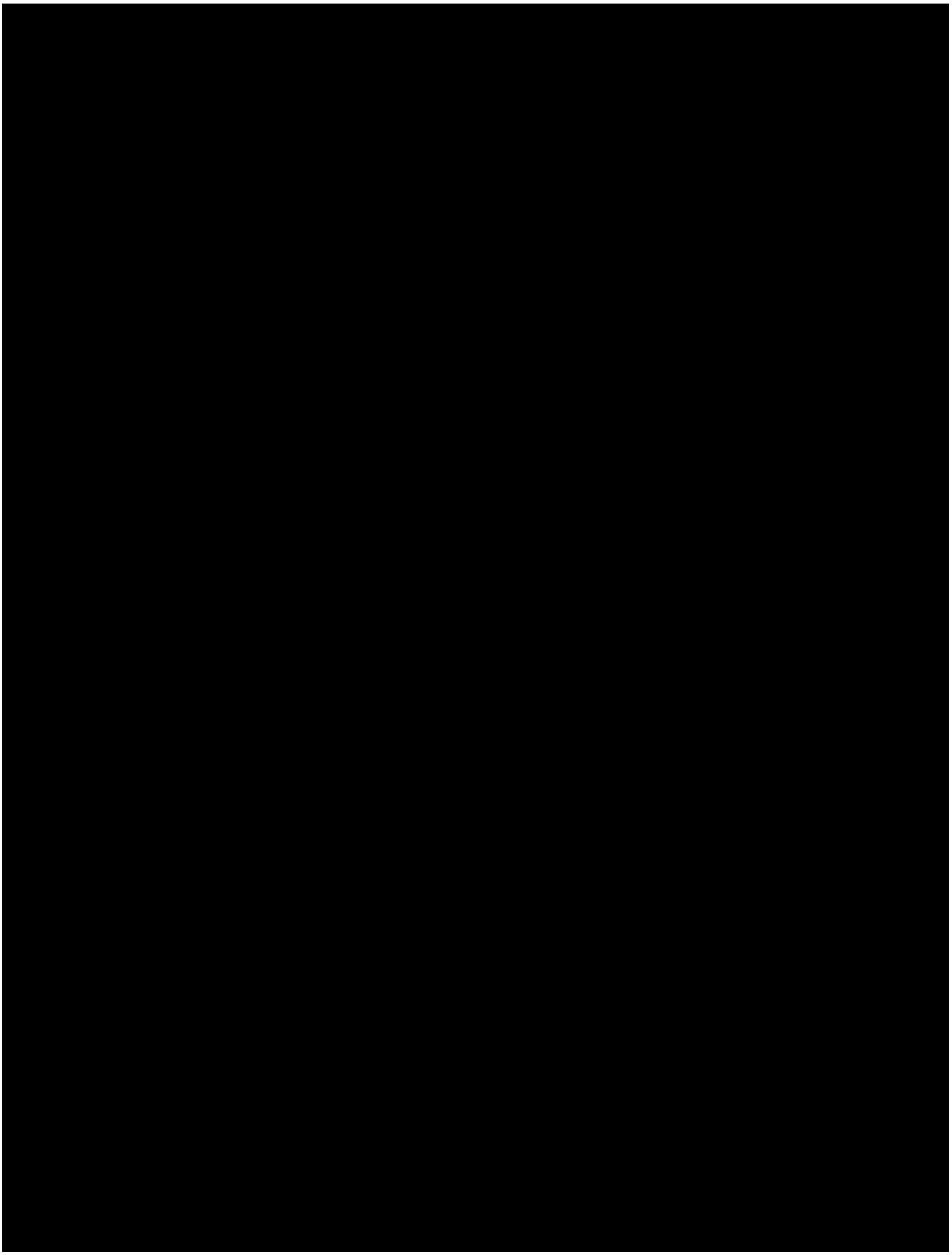
Handling of urine protein (UPROZ):

With CTCAE version 4, the CTCAE grade 3 for proteinuria is defined based on 24 hrs values [g/24 hrs] only; no dipstick definition is available based on quantitative results.

High values of UPROZ (+++, ++++; labstd = 3, 4) would therefore be assigned to CTCAE grade -9, which by default is equivalent to CTCAE grade 0. To circumvent this, high values of UPROZ (+++, ++++; labstd = 3, 4) will be assigned to CTCAE grade 2.

7.8.3 Vital signs

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



8. TIMEPOINT OF RELEASE OF TREATMENT INFORMATION

The treatment information will be loaded into the trial database after completion of enrolment.

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	R09-0262: Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer 2009; 45: 228-247.
3	*BI-KMED-COPS-HTG-0135*: "Identify and Manage Important Protocol Deviations (iPD)", current version; IDEA for CON.
4	*BI-KMED-BDS-HTG-0035:* "Handling of missing and incomplete AE dates", current version; IDEA for CON.
5	*BI-KMED-TMCP-MAN-0012*: "Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics", current version; IDEA for CON.
6	*BI-KMED-BDS-HTG-0045*: "Standards for Reporting of Clinical Trials and Project Summaries", current version; IDEA for CON.
7	*BI-KMED-BDS-HTG-0066*: "Analysis and Presentation of Adverse Event Data from Clinical Trials", current version; IDEA for CON.
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	*BI-KMED-BDS-HTG-0042*: "Handling, Display and Analysis of Laboratory Data", current version; IDEA for CON.

11. HISTORY TABLE

This is a revised TSAP including the following modifications to the final TSAP

Table 11: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
Final	**08-FEB-2017**	[redacted]	None	This is the final TSAP without any modification.
Revised	**19-JAN-2022**		All Sections	This is a revised TSAP with the following revisions: ➢ Reflect changes in CTP version 12.0, i.e., treatment groups, endpoints and analyses of solid tumours in Schedule C, DLBCL in Schedules B and C, cohorts in Phase Ib expansion part. ➢ Reflect decision of abbreviated report (details see Section 4).