TRIAL STATISTICAL ANALYSIS PLAN

c22546283-02

BI Trial No.:	1381-0004
Title:	An open label, Phase I study of BI 754091 monotherapy and combination therapy of BI 754091 and BI 754111 in Asian patients with advanced solid tumours. Including Protocol Amendment 5 [c16323837-07]
Investigational Product(s):	Ezabenlimab (BI 754091) and BI 754111
Responsible trial statistician(s):	[redacted] [redacted] Address: [redacted] Phone: [redacted]
Date of statistical analysis plan:	15 JUN 2021 SIGNED
Version:	Final

1. TABLE OF CONTENTS

LIST OF TABLES

2. LIST OF ABBREVIATIONS

Include a list of all abbreviations used in the TSAP

Term	Definition / description
ATC	Anatomical Therapeutic Chemical
AE	Adverse event
BOR	Best overall response
CR	Complete response
CTC	Common Terminology Criteria
CT	Concomitant therapy
CTP	Clinical Trial Protocol
DBL	Data base lock
DLT	Dose limiting toxicity
EOT	End of treatment
ICH	International Conference on Harmonisation
iCPD	Confirmed progressive disease according to iRECIST
iCR	Complete response according to iRECIST
iPD	Progressive disease according to iRECIST
iPR	Partial response according to iRECIST
iUPD	Unconfirmed progressive disease according to iRECIST
iSD	Stable disease according to iRECIST
MedDRA	Medical Dictionary for Regulatory Activities
MQRM	Medical Quality Review Meeting
MTD	Maximum tolerated dose
PD	Progression of disease
PD	Protocol deviation
PDc	Pharmacodynamics
PK	Pharmacokinetics
PR	Partial response
Q1	Lower quartile
Q3	Upper quartile
RPM	Report planning meeting

Term	Definition / description
SD	Stable disease
StD	Standard deviation
SOC	System organ class
SSAP	Safety statistical analysis plan
TS	Treated Set
TSAP	Trial statistical analysis plan
WHO	World Health Organization

3. INTRODUCTION

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

This TSAP assumes familiarity with the Clinical Trial Protocol (CTP), including Protocol Amendments. In particular, the TSAP is based on the planned analysis specification as written in CTP Section 7 “Statistical Methods and Determination of Sample Size”. Therefore, TSAP readers may consult the 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 or a newer version and Phoenix TM WinNonlin ® version 8.1will be used for PK analyses. SAS® Version 9.4 or a newer version will be used for all other analyses.

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

[redacted]

The analysis planned for Cohort E, Part III was deleted due to the cancellation of Cohort E.

Dose proportionality analysis will not be done [redacted]

[redacted]

5. ENDPOINTS(S)

5.1 PRIMARY ENDPOINT(S)

The primary endpoint of Part I (ezabenlimab dose escalation) and Part II (BI 754111 dose escalation in combination with ezabenlimab) of the trial is the:

- Maximum tolerated dose (MTD) of ezabenlimab (Part I) and ezabenlimab plus BI 754111 combination (Part II)
- Number of patients experiencing Dose Limiting Toxicities (DLTs) during the MTD evaluation period in patients with solid tumours

The primary endpoint of Part III (dose expansion cohorts) of the trial is:
Objective response (OR) - confirmed complete response (CR) and partial response (PR) according to RECIST Version 1.1 as assessed by the Investigator

5.2 SECONDARY ENDPOINT(S)

5.2.1 Key secondary endpoints

No key secondary endpoints specified in CTP

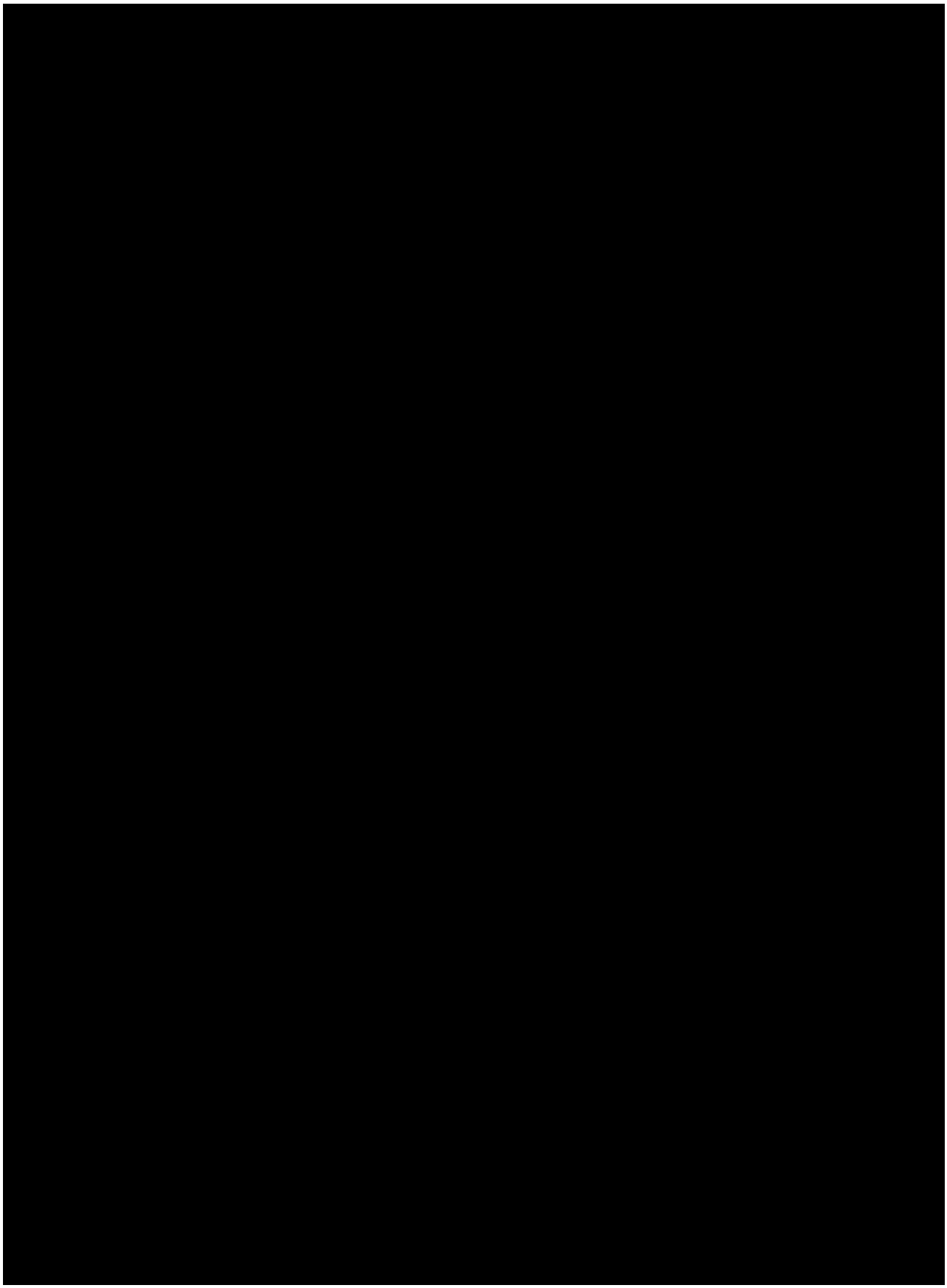
5.2.2 Secondary endpoints

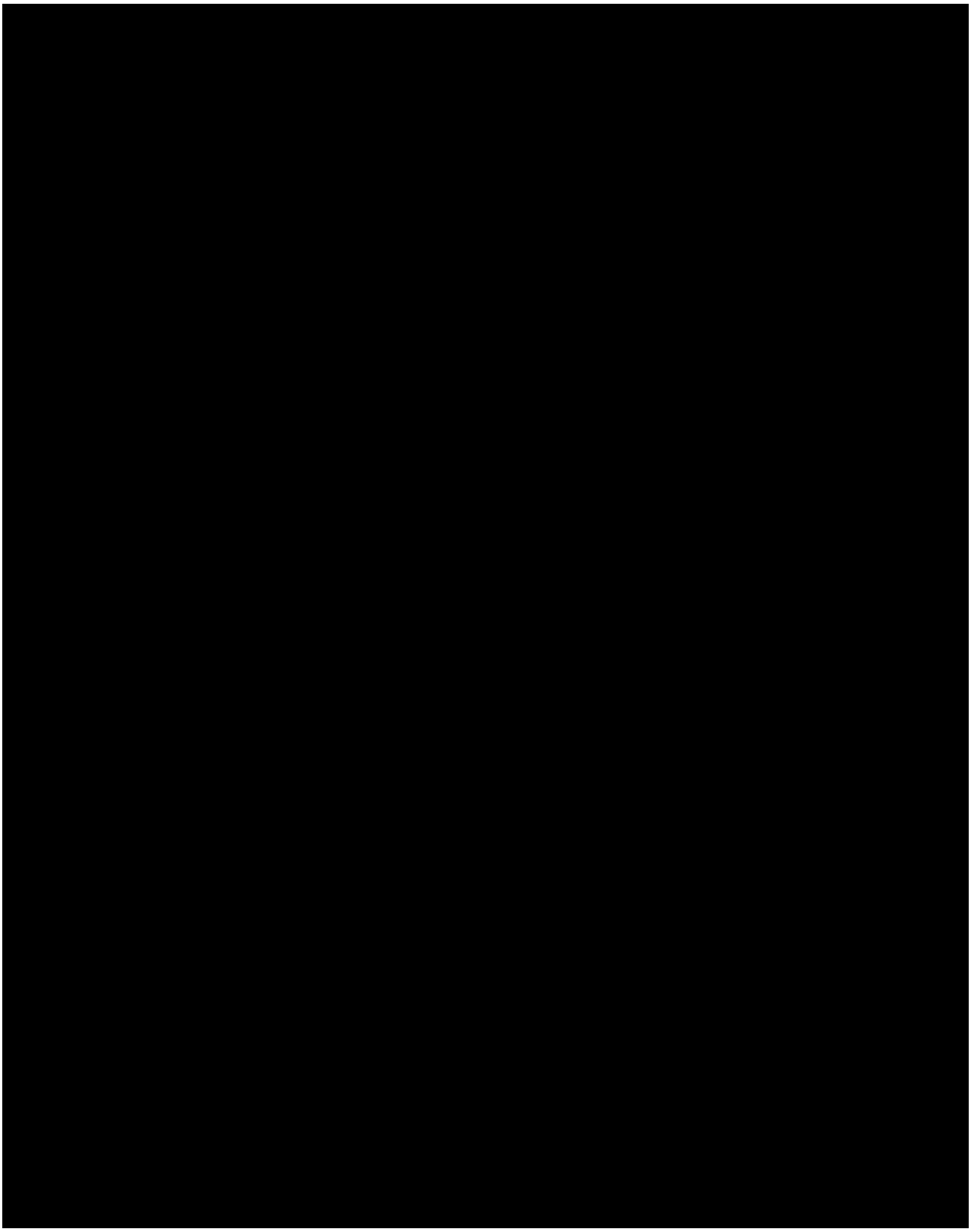
The secondary endpoints of Part I (ezabenlimab dose escalation) and Part II (BI 754111 dose escalation in combination with ezabenlimab) of the trial are the following:

- PK parameters to be calculated for ezabenlimab after single and multiple doses of therapy and also for BI 754111 after single and multiple doses of therapy in combination with ezabenlimab, include:
  - C_{max}: maximum measured concentration of ezabenlimab (part I) and BI 754111/ ezabenlimab (part II) in plasma
  - AUC_{0-504}: area under the concentration-time curve of ezabenlimab (part I) and BI 754111/ ezabenlimab (part II) in plasma over the time interval from 0 to 504 hours
- OR for patients with solid tumours: confirmed CR and PR according to RECIST Version 1.1 as assessed by the Investigator

The secondary endpoints of Part III (dose expansion) of the trial are the following:

- Duration of response is the duration from the date of first documented PR or CR according to RECIST Version 1.1 as assessed by the Investigator to the date of PD or death
- Disease control (CR, PR, or SD according to RECIST Version 1.1) as assessed by the Investigator





6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENT(S)

Treatments are not randomized. Different dose levels of ezabenlimab monotherapy and ezabenlimab / BI 754111 combination therapy will arise in two dose-finding parts (Part I and Part II) and there is only one dose level in expansion part (Part III). Data for Part I and II will be presented for all dose cohorts separately. Data of Part III will be displayed separately for different cohorts (cohort A to D).

For Part I and II, the initial trial medication (i.e. dose level) assigned at the beginning of the first treatment cycle will be used as label of the analysing treatment.

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/time of the first administration of trial treatment-1
On-treatment	Date/Time of the first administration of trial treatment	Date of the last administration of trial treatment + 30 days
Follow-up	Date of the last administration of trial treatment + 31 days	Date of the last contact or death, or DBL date, whichever comes first

Note: a 30-day residual effect period (REP) is defined for this trial.

For safety analyses, adverse events (AEs) will be classified to one of the following time periods: “Screening”, “On-treatment” or “Follow-up” This will be applied for all adverse events. It is indicated in the protocol Section 7.3.4 that the residual effect period of this trial is 30 days, and thus AE reported within 30 days of the last trial medication will be considered on treatment. Detailed rule for assigning AEs to these time periods are listed below:

- If the date of informed consent ≤AE onset date< date/time of first administration of ezabenlimab or BI 754111, then the AE is assigned to “Screening”;
- If date/time of first administration of ezabenlimab or BI 754111 ≤ AE onset date ≤ date of last administration of ezabenlimab or BI 754111 + 30 days, then the AE is assigned to “On-treatment”;
- If AE onset date > date of last administration of ezabenlimab or BI 754111 + 30 days, then the AE is assigned to “Follow-up”

6.2 IMPORTANT PROTOCOL DEVIATION

A protocol deviation (PD) is important if it affects the rights or safety of the study patients, or if it can potentially influence the primary outcome measurements in a non-negligible way. Patients with important PDs that could potentially impact the evaluation of the primary endpoints will be excluded.

A list of important PDs is given in Table 6.2: 1 below. Important PDs will be reviewed at Medical Quality Review Meetings (MQRMs) conducted periodically during the trial. A list of protocol deviations will also be discussed at the Report Planning Meeting (RPM).

If a detected important PD cannot be categorized in any of the following table, another important PD category will be defined in MQRMs or RPMs. The decision whether a patient will be excluded from the analysis will be made at the final RPM prior to DBL.

Table 6.2: 1 Important protocol deviations

Category / Code		Description	Requirements	Excluded from	Automatic/ Manual
A		**Entrance criteria not met**			
	A1	**Inclusion criteria not met**			
	A1.1	Deviation from Inclusion criterion (IN) 1. Of full age (according to local legislation) at the time of signing of the informed consent form (ICF)	IN 1 not met	None	Automatic
	A1.3	Deviation from IN 4. Patients with measurable lesions according to RECIST v1.1	IN 4 not met	None	Automatic
	A1.4	Deviation from IN 6. Eastern Cooperative Oncology Group (ECOG, R01-0787) performance status (PS): 0 to 1 at screening	IN 6 not met	None	Automatic
	A1.5	Deviation from IN 2. Women of childbearing potential (WOCBP) with negative serum pregnancy test at screening and men able to father a child, who agree to use highly effective methods of birth control per ICH M3 (R2) that result in a low failure rate of less than 1% per year when used consistently and correctly. A list of contraception methods meeting these criteria is provided in the patient information. The requirement of contraception does not apply to women of no childbearing potential but they must have an evidence of such at screening	IN 2 not met	None	Automatic
	A1.6	Deviation from IN 5. Conditions specific to respective part of the trial described in protocol	IN 5 not met	None	Automatic
	A2	**Exclusion criteria met**			
	A2.1	Deviation from Exclusion criterion (EX) 1. Major surgery (major according to the investigator's assessment) performed within 12 weeks prior to study entry or planned within 12 months after screening, e.g. hip replacement	EX 1 met	None	Automatic

Table 6.2: 1 Important protocol deviations (Continued)

Category / Code		Description	Requirements	Excluded from	Automatic/ Manual
	A2.2	Deviation from EX 2. Patients who must or wish to continue the intake of restricted medications (see Section 4.2.2.1) or any drug considered likely to interfere with the safe conduct of the trial	EX 2 met	None	Automatic
	A2.3	Deviation from EX 3. Previous treatment with study medications in this trial	EX 3 met	None	Automatic
	A2.4	Deviation from EX 4. Any investigational or anti-tumour treatment within 4 weeks or 5 half-life periods (whichever is shorter) prior to the initiation of trial treatment	EX 4 met	None	Automatic
	A2.5	Deviation from EX 6. (Part II and III only) Prior treatment with anti-LAG-3 agents	EX 6 met	None	Automatic
	A2.7	Deviation from EX 5. Any unresolved toxicities from prior therapy greater than Common Terminology Criteria for Adverse Events (CTCAE) Grade 1 at the time of starting study treatment with the exception of alopecia and Grade 2 neuropathy due to chemotherapy	EX 5 met	None	Automatic
	A2.8	Deviation from EX 7. Patients with lung cancer that have epidermal growth factor receptor (EGFR) mutations or anaplastic lymphoma kinase (ALK) rearrangements, unless disease has progressed following available EGFR or ALK targeted therapy	EX 7 met	None	Automatic
	A2.9	Deviation from EX 8. Presence of other active invasive cancers other than the one treated in this trial, with the exception of resected/ablated basal or squamous-cell carcinoma of the skin or carcinoma in situ of the cervix, or other local tumours considered cured by local treatment	EX 8 met	None	Automatic
	A2.10	Deviation from EX 9. Untreated brain metastasis(es) that may be considered active. Patients with previously treated brain metastases may participate provided they are stable (i.e., without evidence of PD by imaging for at least 4 weeks prior to the first dose of trial treatment, and any neurologic symptoms have returned to baseline), and there is no evidence of new or enlarging brain metastases	EX 9 met	None	Automatic
	A2.12	Deviation from EX 10. Inadequate organ function or bone marrow reserve as demonstrated by the following laboratory values:	EX 10 met	None	Automatic
	A2.13	Deviation from EX 11. Any of the following cardiac criteria:	EX 11 met	None	Automatic
	A2.14	Deviation from EX 12. History (including current) of interstitial lung disease or pneumonitis within the last 5 years	EX 12 met	None	Automatic
	A2.15	Deviation from EX 13. History of severe hypersensitivity reactions to other mAbs	EX 13 met	None	Automatic
	A2.16	Deviation from EX 15. Immunosuppressive corticosteroid doses (>10 mg prednisone daily or equivalent) within 4 weeks prior to the first dose of study treatment	EX 15 met	None	Automatic

Table 6.2: 1 Important protocol deviations (Continued)

Category / Code		Description	Requirements	Excluded from	Automatic/ Manual
	A2.17	Deviation from EX 16. Active autoimmune disease or a documented history of autoimmune disease, except vitiligo or resolved childhood asthma/atopy	EX 16 met	None	Automatic
	A2.18	Deviation from EX 17. Active infection requiring systemic treatment (antibacterial, antiviral, or antifungal therapy) at start of treatment in this trial	EX 17 met	None	Automatic
	A2.19	Deviation from EX 18. Known history of human immunodeficiency virus (HIV) infection. Test results obtained in routine diagnostics are acceptable if done within 14 days before the informed consent date	EX 18 met	None	Automatic
	A2.21	Deviation from EX 14. History of severe hypersensitivity reactions to the ingredients of study drug	EX 14 met	None	Automatic
	A2.22	Deviation from EX 19. Any of the following laboratory evidence of hepatitis virus infection. Test results obtained in routine diagnostics are acceptable if done within 14 days before the informed consent date	EX 19 met	None	Automatic
	A2.23	Deviation from EX 20. Chronic alcohol or drug abuse or any condition that, in the investigator's opinion, makes him/her an unreliable trial patient, unlikely to complete the trial, or unable to comply with the protocol procedures. However, in Part III Cohort C, patients with past chronic alcohol abuse are allowed	EX 20 met	None	Automatic
	A2.24	Deviation from EX 21. Women who are pregnant, nursing, or who plan to become pregnant during the trial. Women who are nursing can be enrolled if they stop nursing. In this case, the patient cannot resume nursing even after discontinuation of study treatment.	EX 21 met	None	Automatic
B		**Informed consent**			
	B1	Informed consent not available/not done	Informed consent date missing	TS	Automatic
	B2	Informed consent too late	Informed consent date was after the initiation of treatment	None	Automatic
C		**Trial medication**			

Table 6.2: 1 Important protocol deviations (Continued)

Category / Code		Description	Requirements	Excluded from	Automatic/ Manual
	C1.1	Non-compliance with ezabenlimab or BI 754111 administration per protocol	Incorrect trial medication dose taken or wrong dose schedule; (e.g. delay, infusion time, program) decision at MQRM	None	Automatic and manual
	C1.2	Continuation/Discontinuation of trial medication not following the protocol	Decision at MQRM	None	Automatic and manual
D		**Concomitant medication**			
	D1.1	Prohibited medication use	Review concomitant medications for prohibited medication use; also refer to Section 4.2.2.2 of the protocol	None	Manual
E		**Study Specific**			
	E1	Incorrect study procedures performed	Any deviation from protocol not defined above deemed important to document in study report by trial team.	Discussio n at MQRM/ RPM	Manual

Note: MQRM – Medical and Quality Review Meeting;

6.3 SUBJECT SETS ANALYSED

Screened Set:
This patient set includes all patients who have signed the informed consent. The screened set will be used for patient disposition tables.

Treated Set (TS):
This patient set includes all patients who were documented to have received at least one dose of ezabenlimab or BI 754111. The TS is used for both efficacy analysis and safety analyses.

MTD set:
This patient set includes all patients who were documented to have received at least one dose of ezabenlimab or BI 754111 in part I and part II and were not replaced for the MTD determination. The MTD evaluation set will be used for the primary analyses of DLTs and

MTD determination. The list of replaced patients will be provided by the Clinical Trial Lead no later than the final RPM and should be attached to the decision log, if applicable.

PK Analysis Set (PKS):
This patient set includes all patients in the TS which provide at least one evaluable observation for at least one [redacted] and no PK relevant protocol deviation. PKS is used for statistical PK analysis, if applicable.

[redacted]

6.5 POOLING OF CENTRES

The section is not applicable.

6.6 HANDLING OF MISSING DATA AND OUTLIERS

No imputation will be performed on missing efficacy data. Missing or incomplete AE dates are imputed according to BI standards. Missing data and outliers of PK data are handled according to [2].
Incomplete date of histological diagnosis, start/end date of previous systemic chemotherapy and previous radiotherapy are imputed as first date of its month or January first if day part or both month and day part is missing respectively.

If the day of the start date of subsequent systemic therapy/subsequent radiotherapy is missing, then the first date of its month will be imputed unless this leads to a date before the stop date of study medication. In this case the stop date of study medication +1 day will be imputed.

If day and month, or day and month and year are missing, it will be distinguished whether the start date of subsequent systemic therapy/subsequent radiotherapy is required [redacted] or for other descriptive statistics:

- For [redacted] duration of response: If only the year is reported, January first of this year will be imputed unless this leads to a date before the stop date of study medication. In this case the stop date of study medication +1 day will be imputed. [redacted] Additionally, all imputed start dates of subsequent anti-cancer therapy/subsequent radiotherapy should be before death date, if available.

- For descriptive statistics: Dates will not be imputed if more than only the day of the date is missing.

No other handling of missing data is planned.

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

Baseline values will be the measurements taken most recently prior to first administration of study drug.

For the laboratories not only the examination date but also time is recorded, examination time has to be taken into account when defining baseline. That is, a laboratory value on the same date as the first study drug administration is considered as baseline value if and only if the time of laboratory value is before or the same as the time of study drug administration. If any of these times is missing and the date of laboratory assessment is equal to the date of first drug administration, then the laboratory assessment will be considered as according to protocol, i.e. as prior to first study medication.

Study day will be calculated relative to the date of the first administration of study drug. The day prior to first administration of study drug will be “Day -1” and the day of first administration of study drug will be “Day 1”; therefore “Day 0” will not exist.

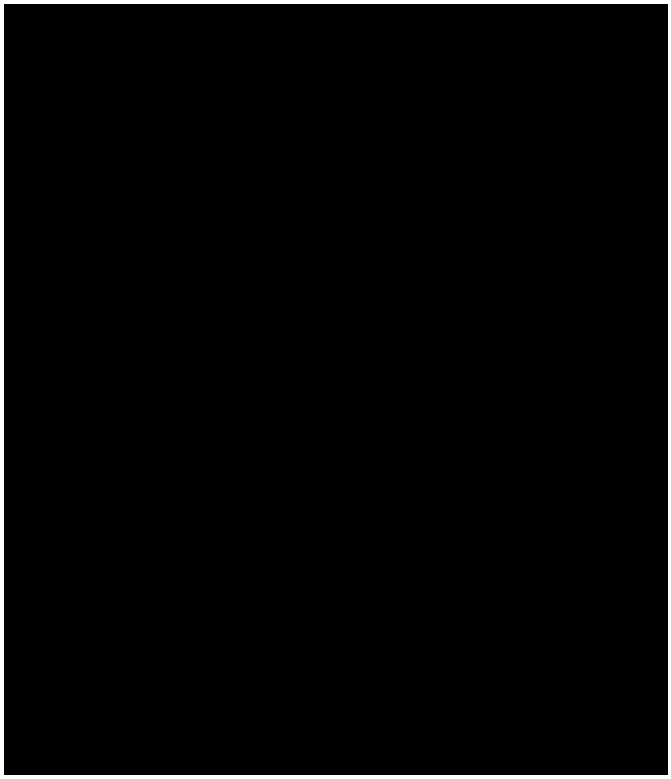
In order to identify whether consecutive imaging time points are missing for a given patient, a nominal time point (i.e. Week 6, 12, 18 … etc.) will be assigned to each and every image. This is achieved by creating windows for every radiological response assessment. These windows are defined in Table 6.7: 1.

Table 6.7: 1 Nominal time points and windows for imaging

Nominal time point (weeks from start of study medication)	**Due date of scans (days)***	**Window (days)**
6	43	1 to ≤ 64
12	85	65 to ≤ 106
18	127	107 to ≤ 148
24	169	149 to ≤ 200
33	232	201 to ≤ 263
42	295	264 to ≤ 326
51	358	327 to ≤ 389
9 week interval	…	…

* The date of the first dose of study medication is Day 1

If a patient does not have an image in one of the windows described above, the patient will be said to have missed an assessment for that time point.



7. PLANNED ANALYSIS

For End-Of-Text 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 should be preferred to Mean, StD, Min and Max.

For time-to-event analysis tables the set of statistics is: number of patients [N(%)], number of patients with event [N(%)], <time to event> [days] followed by P25 (25^{th} percentile), median, P75 (75^{th} percentile) and number of patients censored [N(%)]. If not specified otherwise the duration as well as the time to event will be displayed in days.

Tabulations of frequencies for categorical data will include all possible categories and will display the number of observations in a category as well as the percentage (%) relative to the respective treatment group (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.

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Descriptive statistics are planned for demographic characteristics, disease history, prior therapies, medical history, alcohol and tobacco use, baseline ECOG performance status, and baseline disease assessment.

7.2 CONCOMITANT DISEASES AND MEDICATION

Only descriptive statistics are planned for this section of the report. Concomitant diseases will be coded similarly as adverse events based on the most current Medical Dictionary for Regulatory Activities (MedDRA) version. Concomitant therapies (CTs) will be coded according to World Health Organization (WHO) Drug Dictionary. CTs will be classified according to the Anatomical Therapeutic Chemical (ATC) classification system. The third ATC level will be used to categorize 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 3 category will be counted more than once. Footnotes will clarify this possible double counting in tables.

7.3 TREATMENT COMPLIANCE

Not applicable in this study.

7.4 PRIMARY ENDPOINT(S)

Maximum tolerated dose (MTD) of ezabenlimab (Part I) and ezabenlimab plus BI 754111 combination (Part II);

Number of patients experiencing Dose Limiting Toxicities (DLTs) during the MTD evaluation period in patients with solid tumours
In order to identify the MTD and the recommended dose for ezabenlimab (Part I) and ezabenlimab in combination with BI 754111 (Part II), the number of patients with DLTs at each dose level during Part I and Part II (first three weeks) must be presented. Patients who discontinue during the first treatment course for reasons other than a DLT will be excluded from the determination of the MTD.

The analysis of the MTD is based on a BLRM guided by the escalation with overdose control principle. The MTD is defined as the highest dose for a given schedule that is expected to cause less than 25% risk of the true DLT rate being above or equal to 33% during the MTD evaluation period. Estimation of the MTD during the dose escalation phase of the study will be based upon the estimation of the posterior probability of the incidence of DLT in toxicity categories during the MTD evaluation period for all evaluable patients. The model to be used is specified in CTP Section 7.

In addition, the number of patients with DLTs that occurred during the trial will be summarised at each dose level (Part I and Part II) and each cohort (Part III). The BLRM will be rerun to re-evaluate the MTD and RD together with all relevant data collected during Part III.

Objective response (OR) - confirmed complete response (CR) and partial response (PR) according to RECIST Version 1.1 as assessed by the Investigator

For Part III, OR according to RECIST Version 1.1 will be summarised descriptively with exact 95% Clopper-Pearson CIs. Response data collected after the EOT or the start of subsequent anti-cancer therapy will not be used. This applies to other endpoints based on the response data. Confirmed best overall response (BOR) will be derived according to the following derivation rules:

- If CR or PR: look at subsequent visits, if there is another CR or PR >=28 days and no more than one missing visit (defined by time window Table 6.7: 1) in between, then the patient has a confirmed response. If there is not another CR or PR >=28 days and / or more than one missing visit between the two responses, then the patient can be a confirmed SD if the CR or PR is >=39 days from start of combination therapy.
- If SD: to be confirmed SD, the measurement must have been taken >=39 days from start of combination therapy (only one reading is necessary).
- Additional details are provided in Table 7.4: 1.

Table 7.4: 1 Details of confirmed BOR derivation rules

Overall response (time point 1)	Overall response (>=28 days from time point 1)	Confirmed BOR
CR	CR	CR
CR	PD	SD as long as >=39 days, otherwise, PD
CR	NE/Missing	SD as long as >=39 days, otherwise, NE
PR	CR	PR
PR	PR	PR

Table 7.4:1 Details of confirmed BOR derivation rules (Continued)

Overall response (time point 1)	Overall response (>=28 days from time point 1)	Confirmed BOR
PR	SD	SD as long as >=39 days, otherwise, PD
PR	PD	SD as long as >=39 days, otherwise, PD
PR/SD	NE/Missing	SD as long as >=39 days, otherwise, NE
NE	NE/Missing	NE

7.5 SECONDARY ENDPOINT(S)

7.5.1 Key secondary endpoint

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

7.5.2 Other secondary endpoints

7.5.2.1 Other secondary endpoints in Part I and Part II

PK parameters evaluated after the single and after multiple administrations of ezabenlimab in combination with BI 754111, and also for ezabenlimab after single and multiple doses of therapy

The PK parameters will be evaluated using noncompartmental analysis methods according to 001-MCS-36-472_RD1 [2].

Descriptive statistics will be calculated for all concentration time points and PK parameters. The following descriptive statistics will be calculated for ezabenlimab and BI 754111concentrations: N (number of patients with non-missing values), arithmetic mean, standard deviation, minimum, median, maximum, arithmetic coefficient of variation, geometric mean, and geometric coefficient of variation and for PK parameters: N, arithmetic mean, standard deviation, minimum, median, maximum, tenth percentile (P10), Q1, Q3, ninetieth percentile (P90), arithmetic coefficient of variation, geometric mean, and geometric coefficient of variation.

Treated and evaluable patients will be included in the PK analysis. A patient is considered not evaluable if the patient had an important protocol violation relevant to the evaluation of PK or had insufficient PK data. Non evaluable patients will be listed with their individual PK parameters, but such data will not be included when calculating descriptive statistics. If the data suggest a PK / PD relationship of special parameters (e.g. PK vs. RO), a detailed analysis may be performed and documented in a separate report.

OR for patients with solid tumors according to RECIST Version 1.1 as assessed by the investigator

OR will be summarized descriptively with exact 95% Clopper-Pearson CIs. Derivation rule of confirmed BOR is defined in Table 7.4:1.

7.5.2.2 Other secondary endpoints in Part III

Duration of response according to RECIST Version 1.1 as assessed by the Investigator

Duration of response is defined as the duration from the date of first documented PR or CR according to RECIST Version 1.1 as assessed by the Investigator to the date of PD or death. Duration of response will be summarized descriptively by quartiles with 95% confidence interval (based on the Greenwood's method) calculated from Kaplan-Meier estimate. Kaplan-Meier plots will also be produced. Duration of objective response will use the censoring rule defined in below Table 7.5.2.2:1

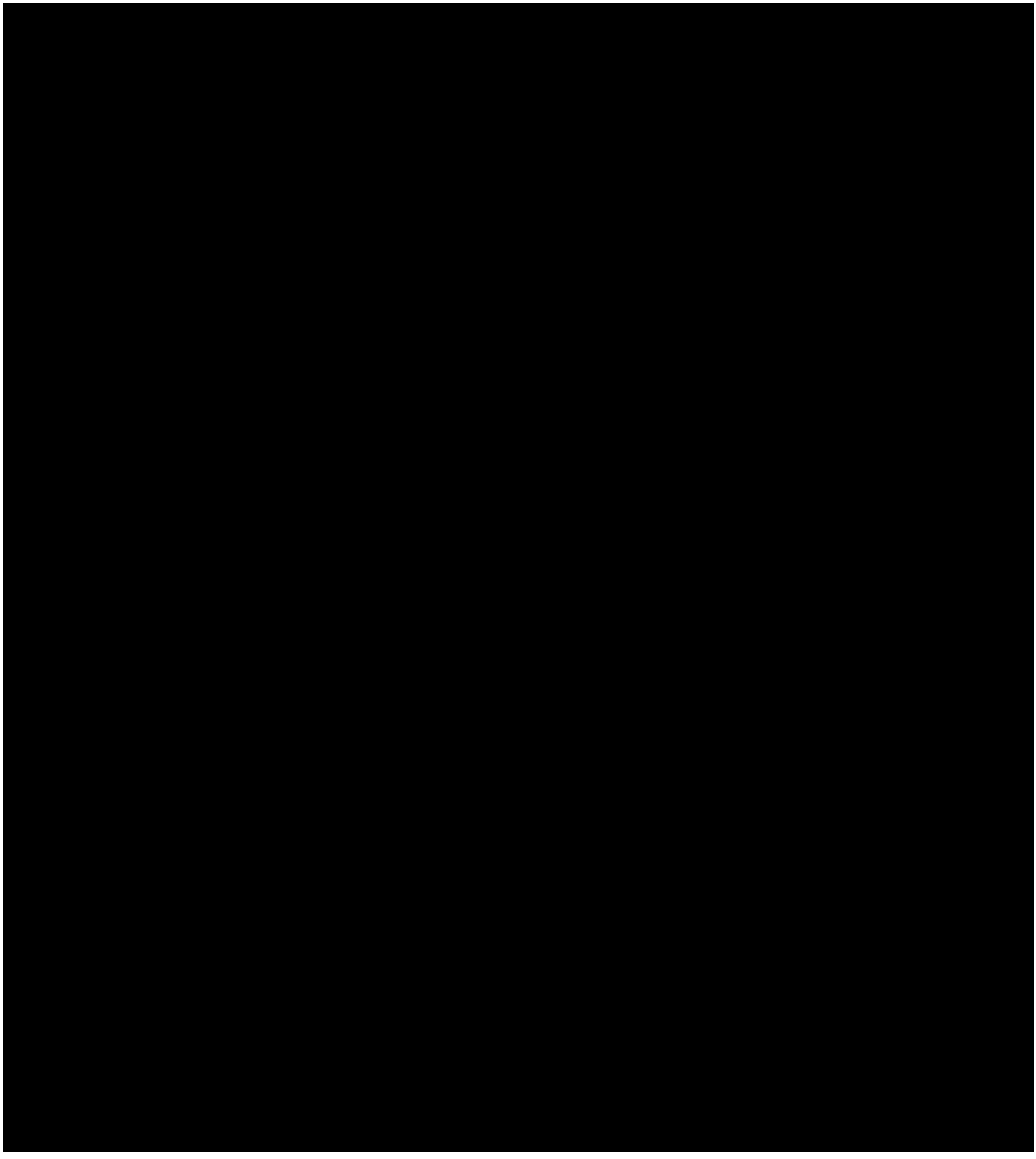
Table 7.5.2.2:1 Censoring rules and determination of date of event or censoring for duration of response

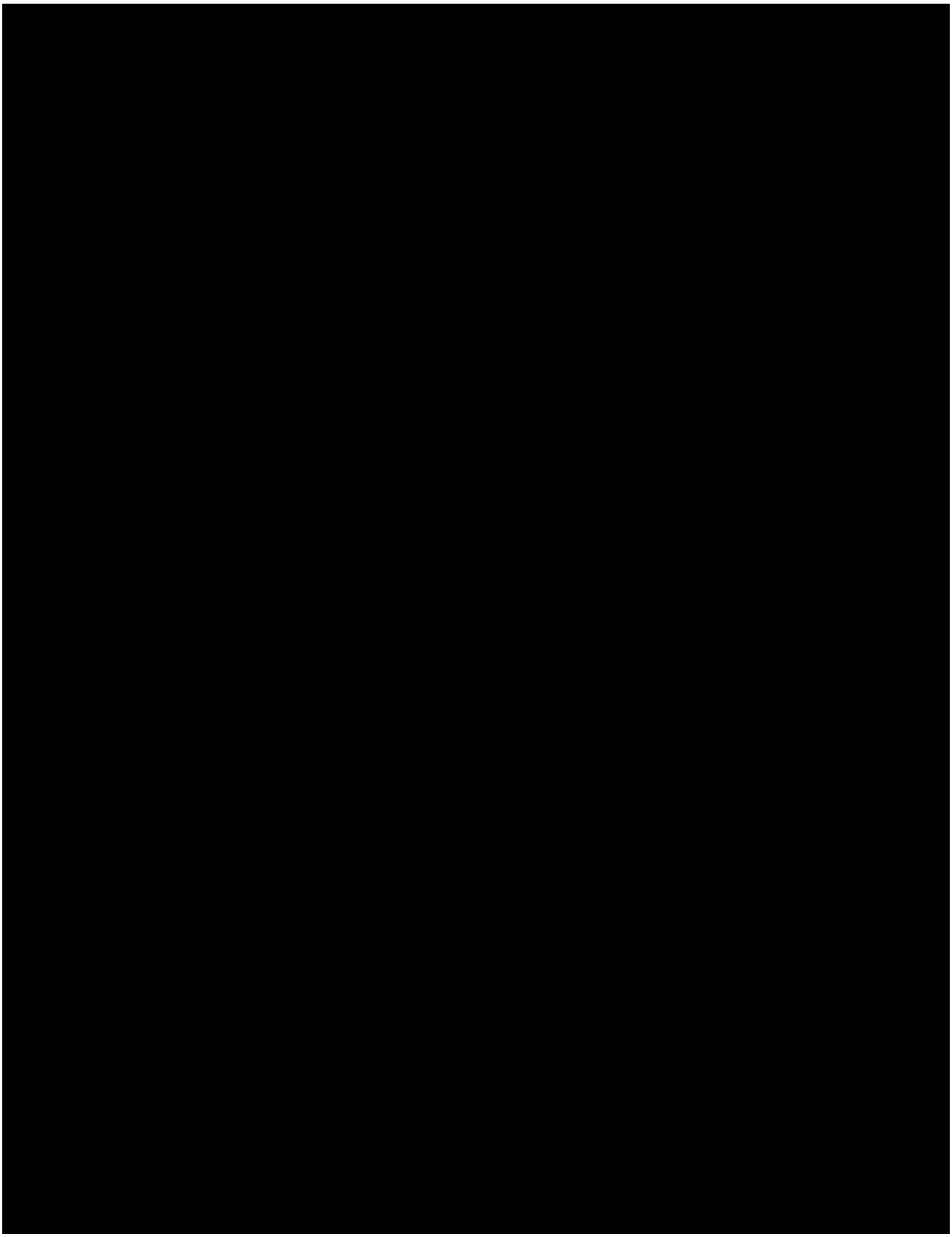
Situation	**Outcome (event or censored)**	**Date of outcome**
No other anti-cancer therapy		
Alive and not progressed, no missed radiological assessments window*	Censored	Date of last radiological assessment
Alive and not progressed, one or more consecutively missed radiological assessments window*	Censored	Date of last radiological assessment prior to missed radiological assessments
Progressed, no radiological assessment window* prior to progression	Event	Date of radiological assessment of progression
Progressed, but one or more consecutively missed radiological assessments window* prior to progression	Censored	Date of last radiological assessment prior to missed radiological assessments
Death but no progression, no missed radiological assessment window* prior to death	Event	Date of death
Death without progression, but one or more consecutively missed radiological assessments window* prior to death	Censored	Date of last radiological assessment prior to missed radiological assessments
Initiation of subsequent anti-cancer therapy		
Subsequent anti-cancer therapy started before progression or death, no missed radiological assessments window* prior to start of subsequent anti-cancer therapy	Censored	Date of last radiological assessment before initiation of subsequent anti-cancer therapy

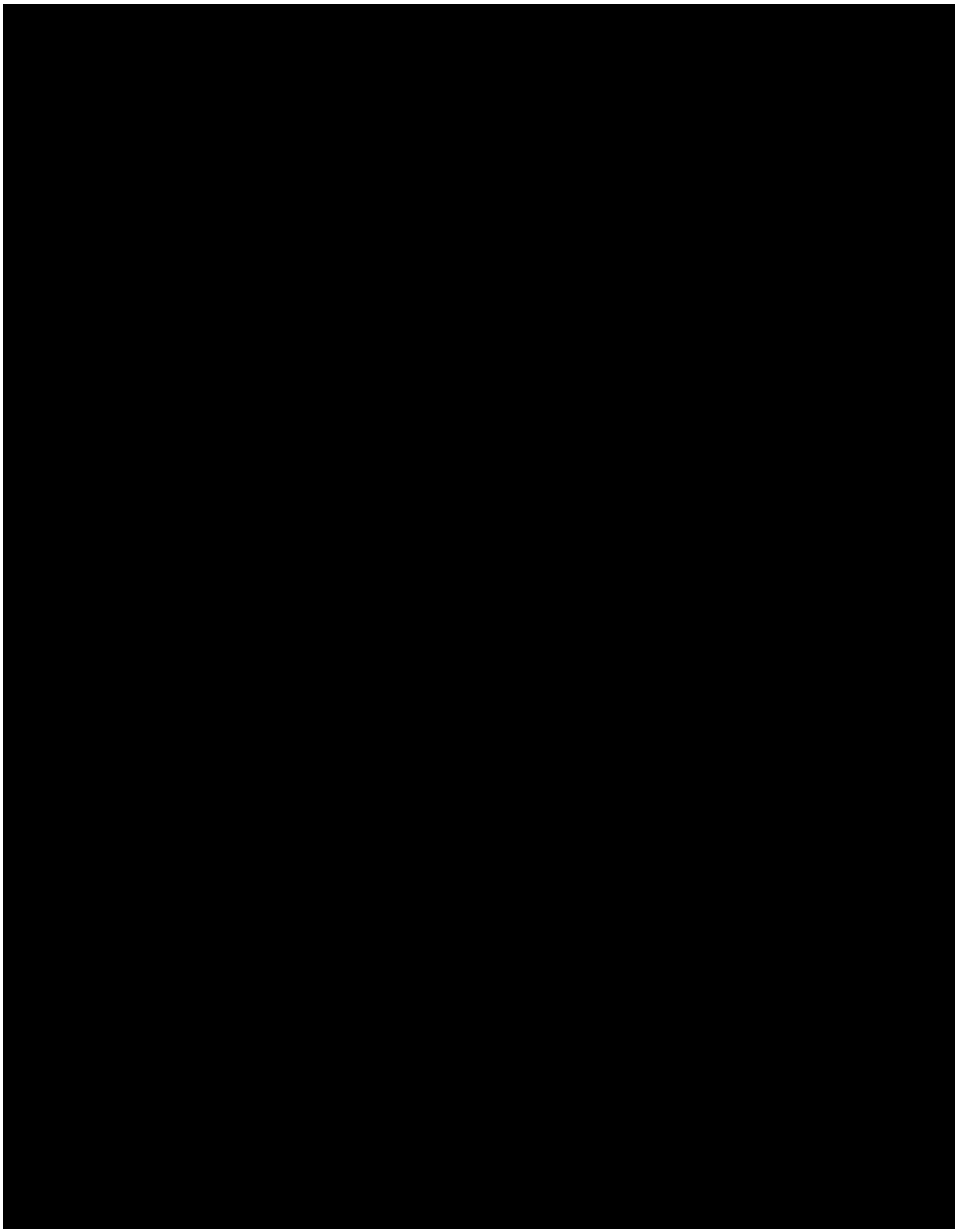
* Windows for radiological assessments are defined in Table 6.7: 1

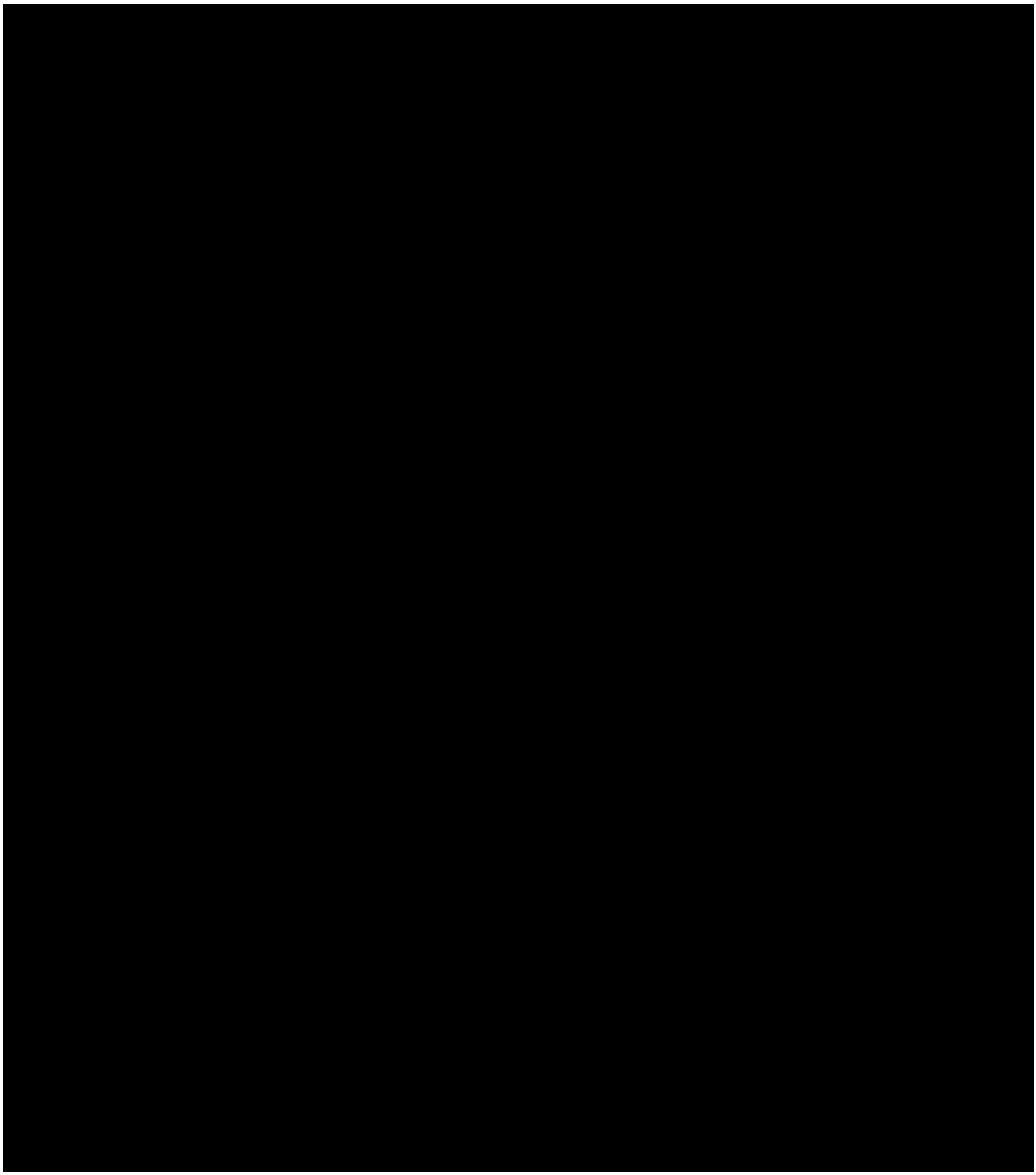
Disease control according to RECIST Version 1.1 as assessed by the Investigator

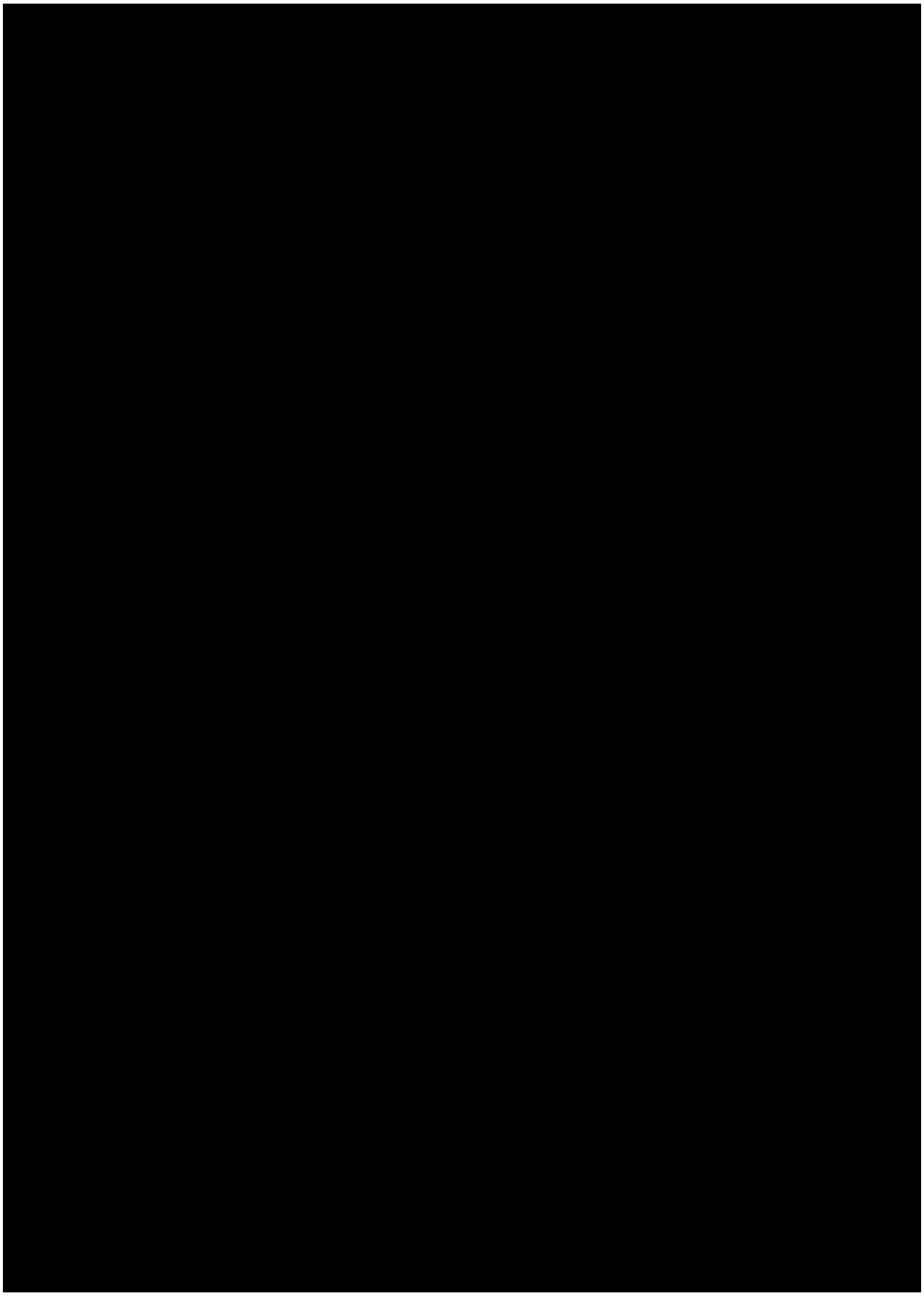
Disease control is defined as a BOR of CR, PR or SD. Disease control rates will be presented with exact 95% Clopper-Pearson CIs.

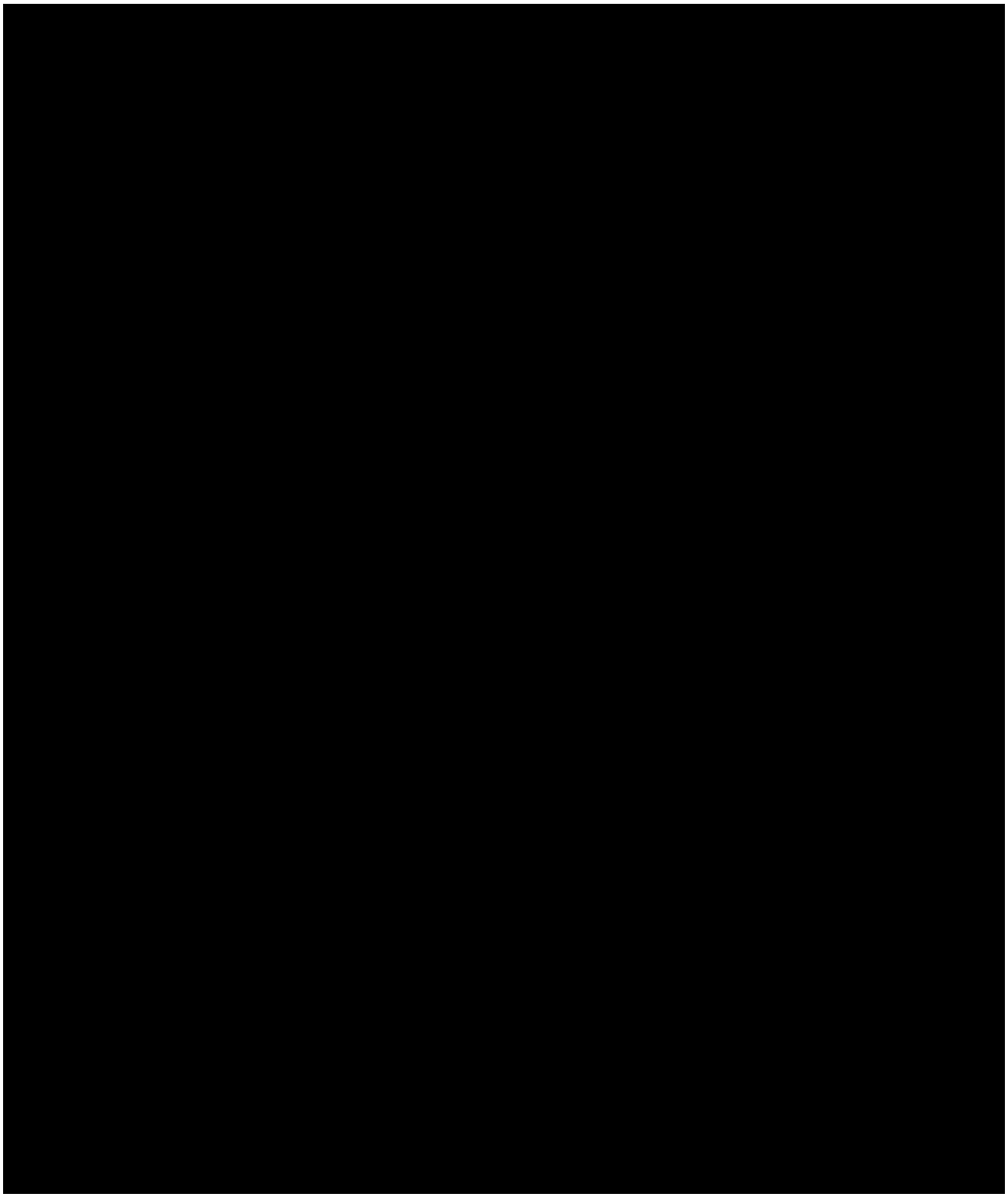


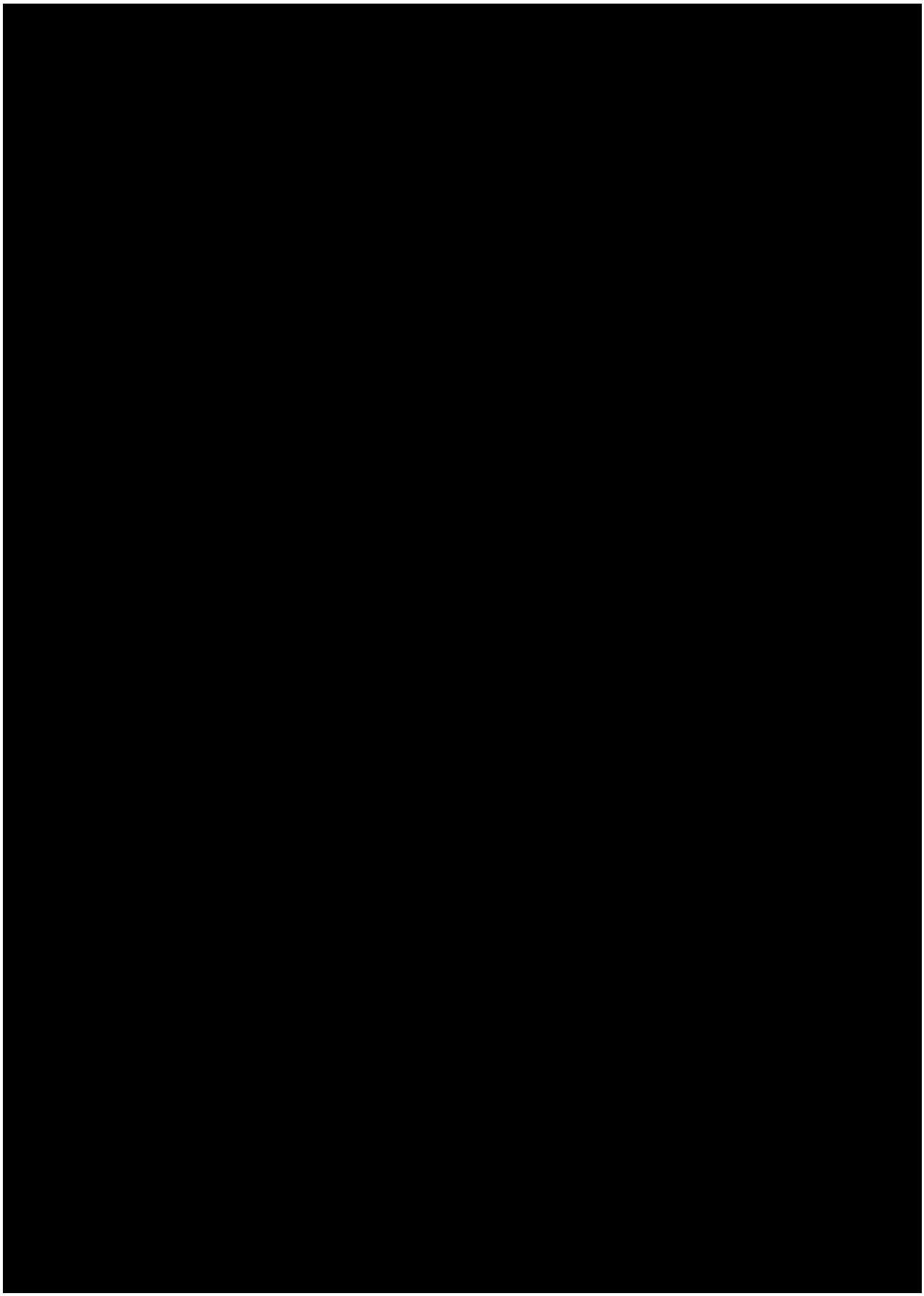












7.7 EXTENT OF EXPOSURE

The total number of cycles initiated, the numbers of cycle initiated and treatment duration will be summarized descriptively for each dose cohort.

Treatment duration [days] = Date of last treatment administration – date of first treatment administration + 1.

Results from each part will be presented separately.

7.8 SAFETY ANALYSIS

All safety analyses will be performed on the TS.

Patients who were replaced within the MTD evaluation period will be excluded from the determination of the MTD but will be considered for all other safety evaluations.

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 subjects with AEs and not on the number of AEs. The reporting and analyses of AEs will follow the BI standards. 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 Part I and Part II, and version 5.0 for Part III.

Unless otherwise specified, the analysis of adverse events will be based on the concept of treatment emergent adverse events. 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.

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

- DLTs
- All adverse events by highest CTCAE grade
- Serious adverse events (SAEs) by highest CTCAE grade
- Investigator assessed drug-related AEs by highest CTCAE grade
- Investigator assessed drug-related serious AEs by highest CTCAE grade
- AEs leading to treatment discontinuation by highest CTCAE grade
- AEs leading to death
- Investigator assessed treatment emergent immune-related AEs (irAEs) by highest CTCAE grade
- irAEs through the whole trial (i.e. including irAEs occurred after residual effect period) by highest CTCAE grade
- AEs of special interest by highest CTCAE grade.

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

7.8.2 Laboratory data

The analyses of laboratory data will be descriptive in nature and will be based on BI standards. 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 5.0. The following outputs will be presented:

- Worst CTCAE grade experienced during the on-treatment phase
- Transitions of CTCAE grade from baseline to worst 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".

For lab tests for which CTCAE grades are not sued for at least one direction of interest, frequency of patients with shifts from baseline defined in SSAP [3] will be followed.

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, definition in SSAP 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 has 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.

Potential Hy's law cases:

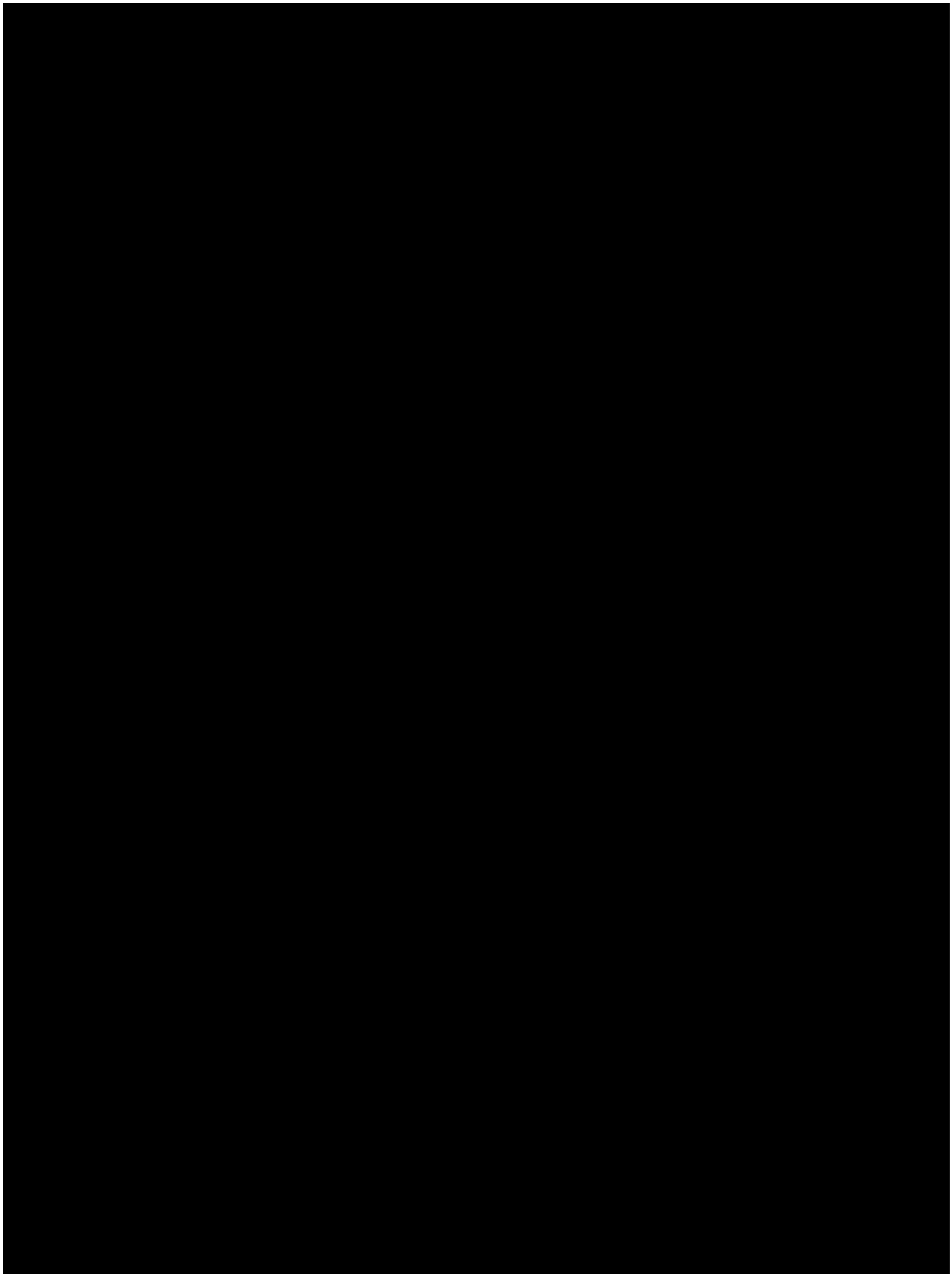
Analysis for potential Hy's law cases would be performed, if necessary.
A listing of all liver function tests will be provided for all patients who meet the following criteria at any time:

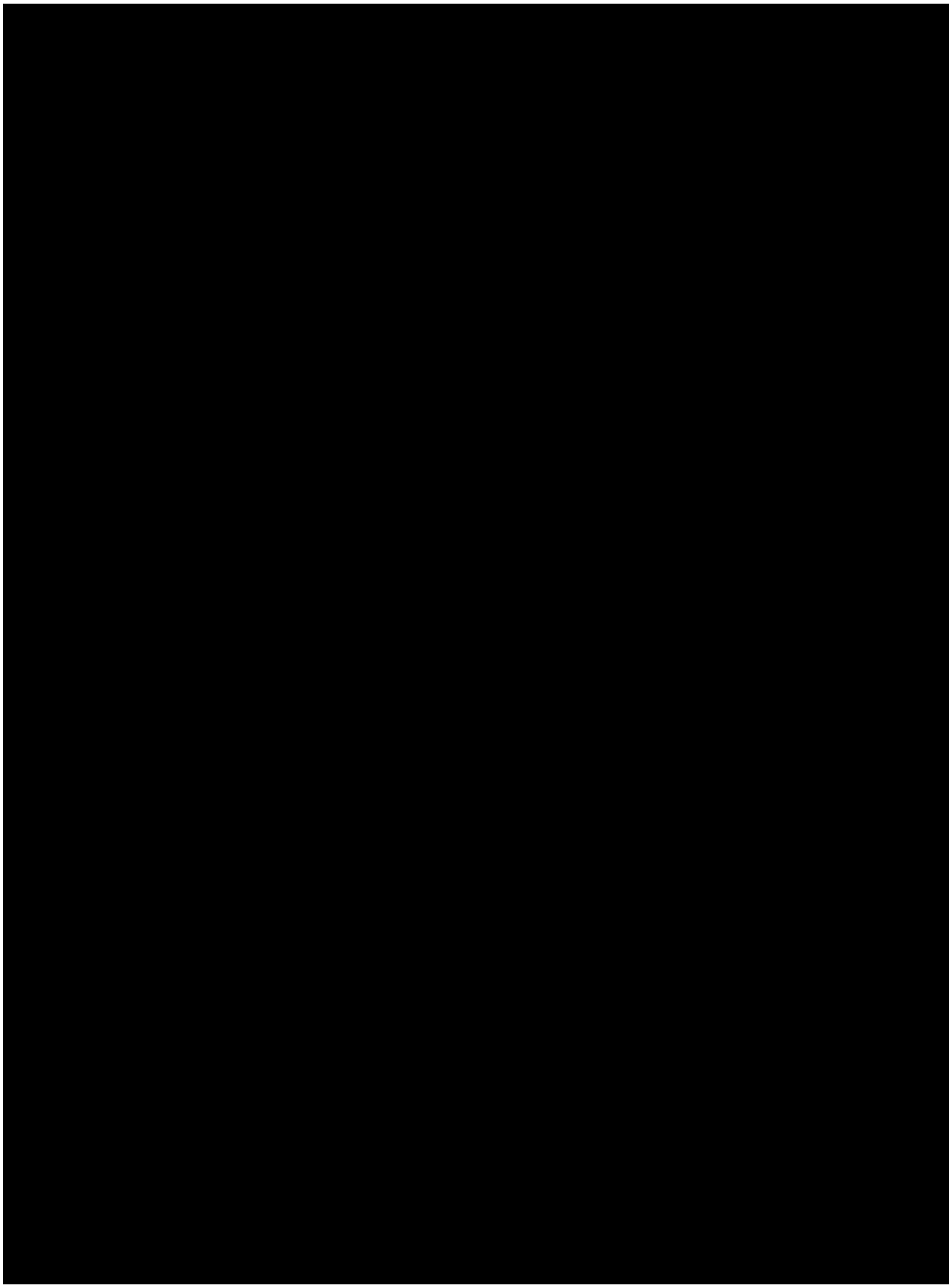
- ALT or AST ≥ 3*ULN and elevation of total bilirubin ≥2*ULN within +/- 30 days

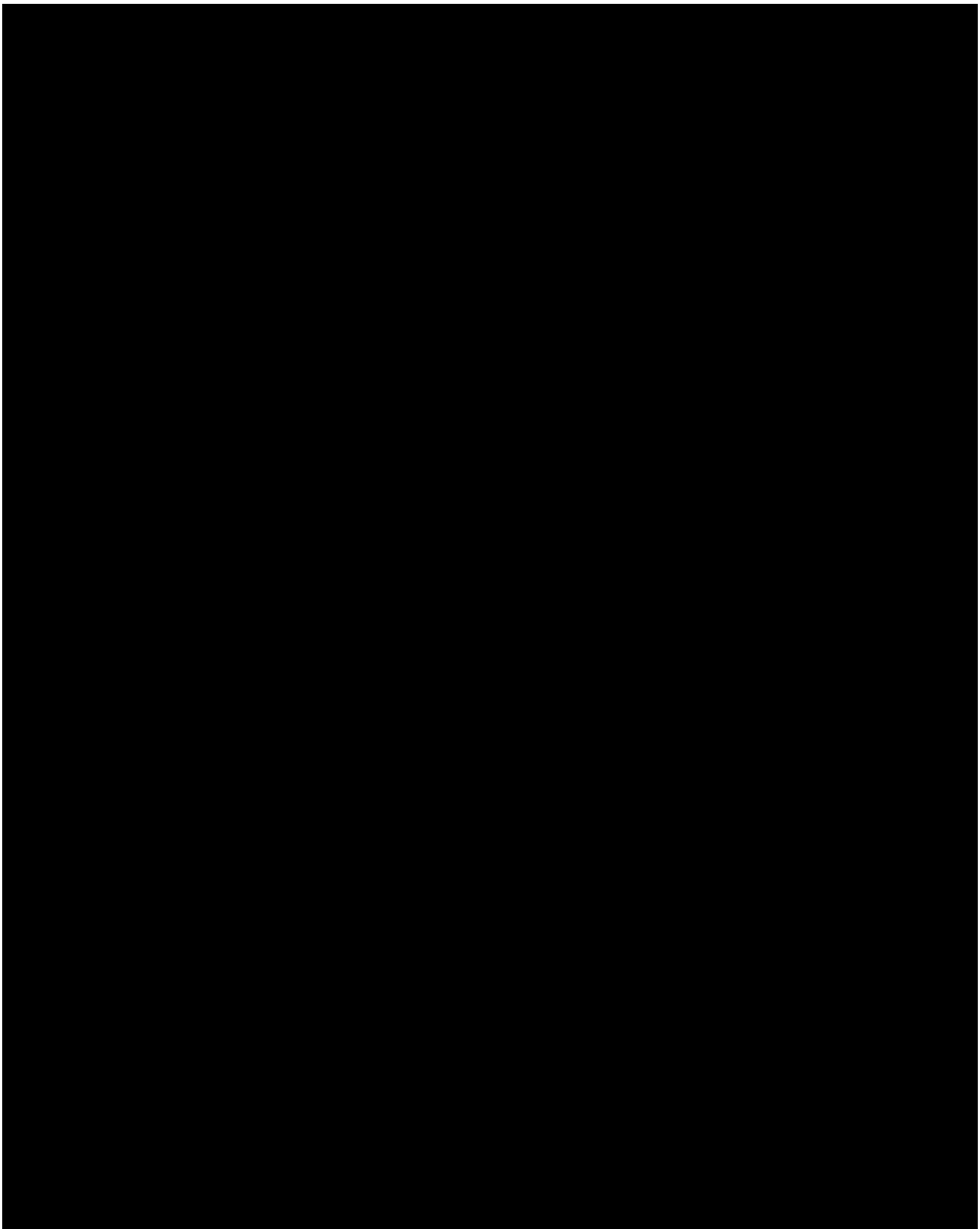
Tables of liver function test abnormalities will be produced.

7.8.3 Vital signs

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

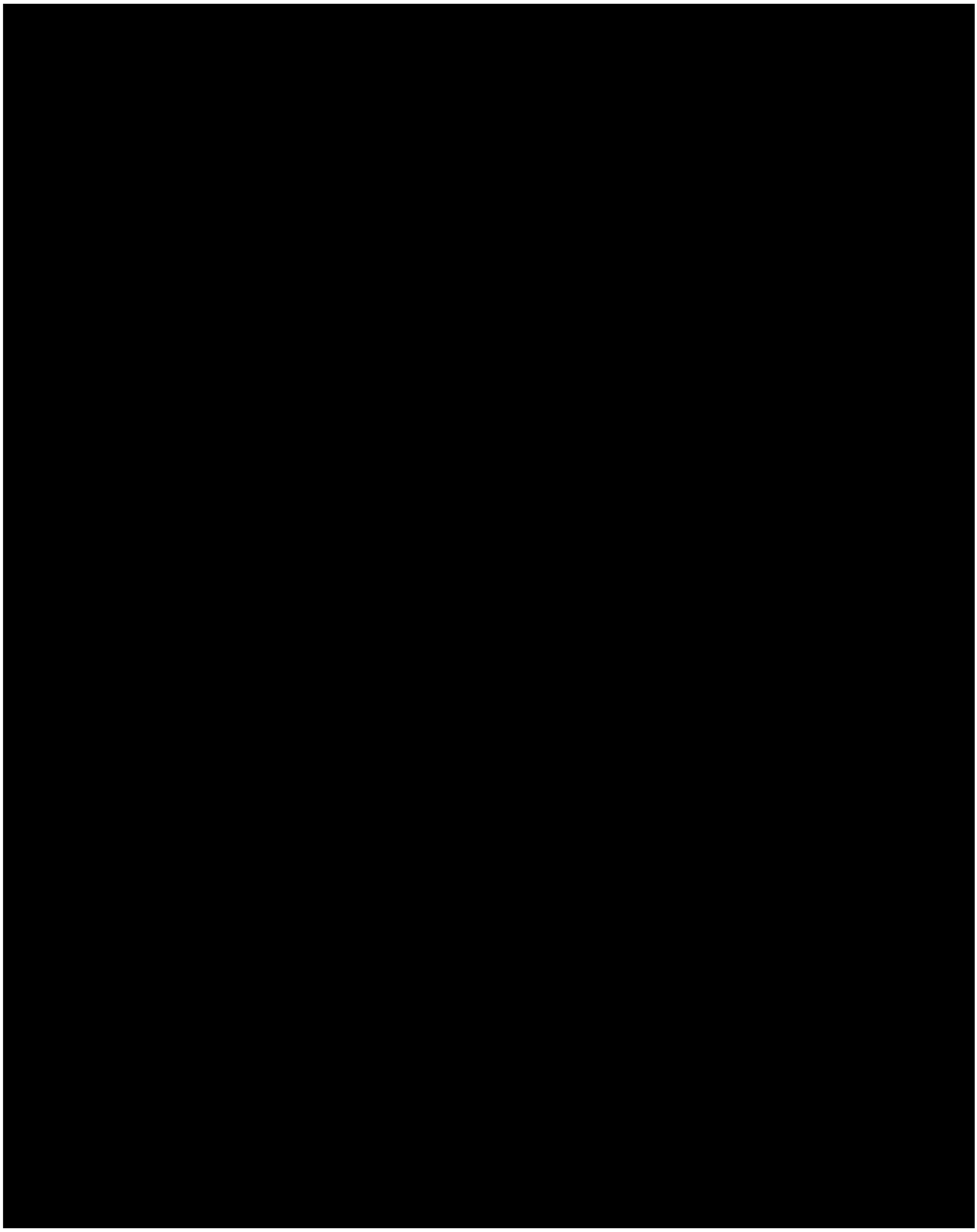


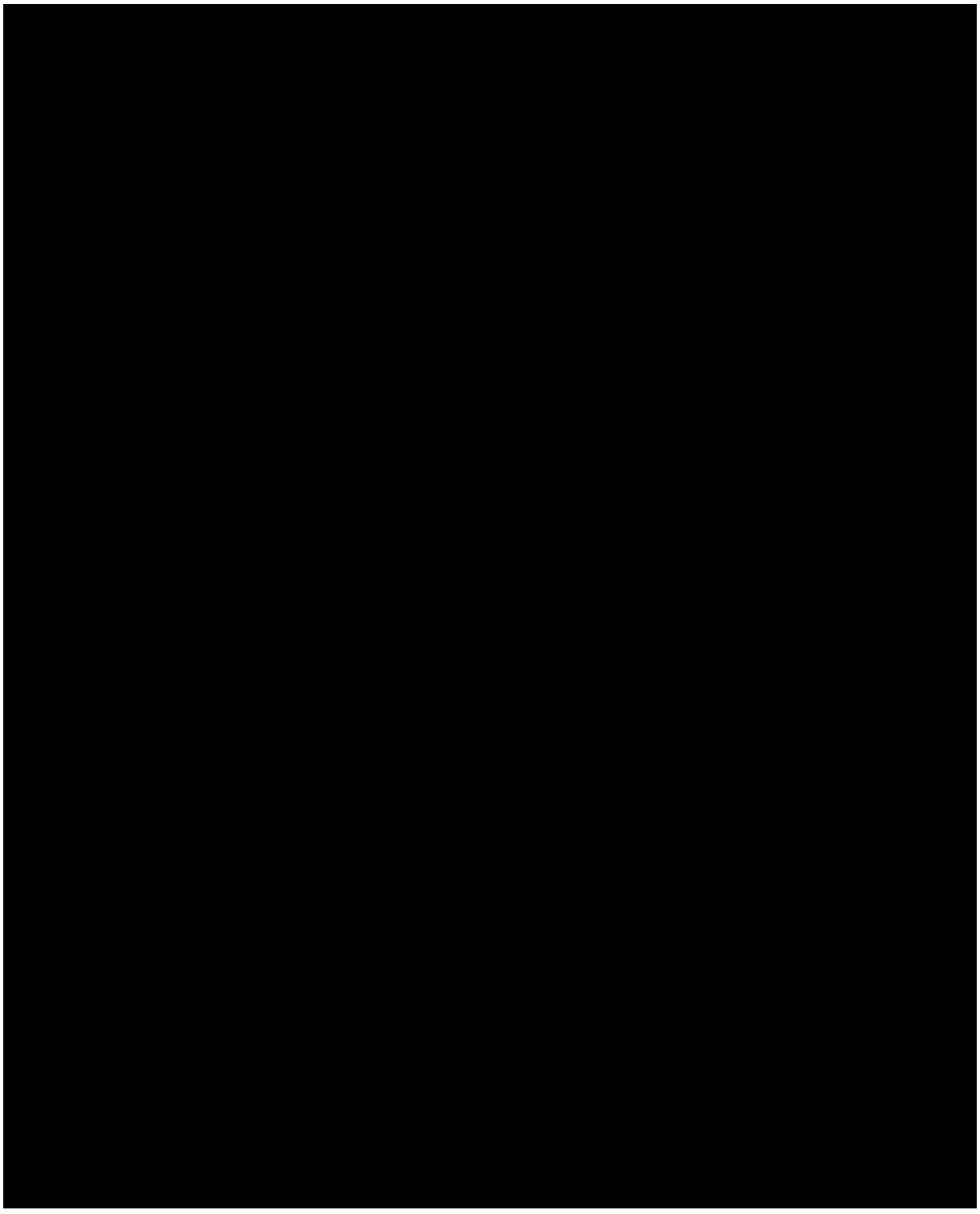




8. REFERENCES

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.	*BI-KMED-TMCP-MAN-0014: "Noncompartmental PK/PD Analyses of Clinical Studies", current version; IDEA for CON.*
3.	*1381.P1 Safety SAP, current version; BIRDS.*





10. HISTORY TABLE

Table 10: 1 History table

Version	**Date (DD-MMM-YY)**	**Author**	**Sections changed**	**Brief description of change**
Initial	**01-MAR-18**	[redacted]	None	This is the initial TSAP with necessary information for trial conduct
Final	**15-JUN-21**		Section 1 to 9	This is the final TSAP with updated from initial version.

APPROVAL / SIGNATURE PAGE

Document Number: c22546283 **Technical Version Number:2.0**

Document Name: 8-01-tsap-core

Title: An open label, Phase I study of BI 754091 monotherapy and combination therapy of BI 754091 and BI 754111 in Asian patients with advanced solid tumours

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Author-Trial Statistician	[redacted]	15 Jun 2021 14:38 CEST
Approval-Team Member Medicine		15 Jun 2021 16:10 CEST
Author-Trial Clinical Pharmacokineticist		16 Jun 2021 02:09 CEST
Approval-Clinical Trial Leader		16 Jun 2021 03:04 CEST
Approval-Project Statistician		16 Jun 2021 03:44 CEST
Approval-Medical Writer		18 Jun 2021 04:08 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed