TRIAL STATISTICAL ANALYSIS PLAN c17263334-04

BI Trial No.:	1379.1
Title:	An open-label Phase I dose finding trial with BI 891065 alone and in combination with BI 754091 to characterise safety, tolerability, pharmacokinetics, pharmacodynamics, and efficacy in patients with advanced and/or metastatic malignancies Including Protocol Amendments 1, 2, 3, 4, 5 and 6 (c11957282-07)
Investigational Product(s):	BI 891065 + BI 754091
Responsible trial statistician(s):	[redacted] Phone: [redacted]
Date of statistical analysis plan:	21 DEC 2020 REVISED
Version:	Revised

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2. LIST OF ABBREVIATIONS

Term	Definition / description
ADA	Anti-drug Antibody
AE	Adverse Event
AESI	Adverse Event of Special Interest
ATC	Anatomical Therapeutic Chemical
BI	Boehringer Ingelheim
BLRM	Bayesian Logistic Regression Model
BMI	Body Mass Index
cIAP	Cellular Inhibitor of Apoptosis
CR	Complete Response
CT	Concomitant Therapy
CTCAE	Common Terminology Criteria for Adverse Events
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
DILI	Drug-induced Liver Injury
DLT	Dose-limiting Toxicity
ECG	Electrocardiogram
ECGPCS	Electrocardiogram Pharmacokinetic Concentration Set
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
ES	Enrolled Set
HR	Heart Rate
ICH	International Conference on Harmonization
iCPD	Immune Confirmed Progressive Disease
iCR	Immune Complete Response
iPR	Immune Partial Response
IPD	Important Protocol Deviation
iRECIST	modified RECIST 1.1 for immune-based therapeutics
iSD	Immune Stable Disease
iUPD	Immune Unconfirmed Progressive Disease

MedDRA	Medical Dictionary for Regulatory Activities
ms	milliseconds
MTD	Maximum Tolerated Dose
NSCLC	Non-small Cell Lung Cancer
OR	Objective Response
ORR	Objective Response Rate
PBMCs	Peripheral Blood Mononuclear cells
PD	Progressive Disease
PFS	Progression-free Survival
PK	Pharmacokinetics
PKS	Pharmacokinetic Set
PR	Partial Response
PR interval	ECG interval from the onset of the P wave to the beginning of the QRS complex
PT	Preferred Term
QRS	Combination of the Q, R and S waves
QT	ECG interval from the beginning of the QRS complex to the end of the T wave
QTc	Generic term for QTcF and QTcB intervals
QTcB	QT interval, corrected by Bazett's formula
QTcF	QT interval, corrected by Fridericia's formula
RECIST	Response Evaluation Criteria In Solid Tumours
REP	Residual Effect Period
SCR	Screened Set
SD	Stable Disease
SOC	System Organ Class
SRC	Safety Review Committee
StD	Standard Deviation
TS	Treated Set
TSAP	Trial Statistical Analysis Plan
ULN	Upper Limit of Normal
WHO DD	World Health Organisation Drug Dictionary

3. INTRODUCTION

As per International Conference on Harmonisation E9 (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, and definition of measurements and variables.

The study is a multicentre study consisting of three study parts. Part A is an open-label, dose-escalation of BI 891065 alone. Part B is an open-label dose-escalation of BI 891065 in combination with a fixed dose of BI 754091. Part C consists of an expansion cohort in non-small cell lung cancer (NSCLC).

For the primary objective of the separate parts of the trial, refer to Section 2 of the CTP.

[redacted]

In the following, study medication always refers to BI 891065 in Part A, and to BI 891065 and/or BI 754091 in Parts B and C.

SAS® Version 9.4 or higher will be used for all analyses besides pharmacokinetic (PK) analyses if not specified otherwise. WinNonlin Version 8.1 will be used for PK analyses.

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

All analyses described in the CTP will be carried out.

[redacted]

Since t_{max} of BI 891065 appears to be earlier than expected, all ECG recordings collected at the scheduled time points listed in Tables 10:3:1, 10:3:2 and 10:3:3 of the CTP will be analysed.

Part C of this trial is cancelled and enrolled no patients. Hence, no planned analyses for this trial part will be conducted.

5. ENDPOINT(S)

5.1 PRIMARY ENDPOINT(S)

Part A:
The primary endpoints for Part A of the trial are the MTD of BI 891065 and the number of patients with dose-limiting toxicities (DLTs) during the MTD evaluation period (first treatment cycle). For definition of the MTD, refer to Section 2.1.2.1 of the CTP.

Part B:
The primary endpoints for Part B of the trial are the MTD of BI 891065 in combination with BI 754091 and the number of patients with DLTs during the MTD evaluation period (first treatment cycle). For definition of the MTD, refer to Section 2.1.2.2 of the CTP.

Part C:
The primary endpoint is OR by investigator's assessment based on RECIST version 1.1 (2). For definition of OR refer to CTP Sections 2.1.2.3.

5.2 SECONDARY ENDPOINT(S)

5.2.1 Key secondary endpoint(s)

Not applicable.

5.2.2 Secondary endpoint(s)

Part A:
- The number of patients with DLTs observed during the entire treatment period
- $C_{max,ss}$, $AUC_{0\text{-}tz}$ and $AUC_{\tau,ss}$ of BI 891065 in the first treatment cycle
- OR by investigator's assessment based on RECIST v1.1, defined in the same way as the primary endpoint for Part C.

Part B:
- The number of patients with DLTs observed during the entire treatment period
- $C_{max,ss}$, $AUC_{0\text{-}tz}$ and $AUC_{\tau,ss}$ of BI 891065 in the first treatment cycle and C_{max} and $AUC_{0\text{-}tz}$ of BI 754091 in the first treatment cycle
- OR by investigator's assessment based on RECIST v1.1, defined in the same way as the primary endpoint for Part C.

Part C:
Secondary endpoint for Part C is the duration of OR by investigator's assessment based on RECIST v1.1.

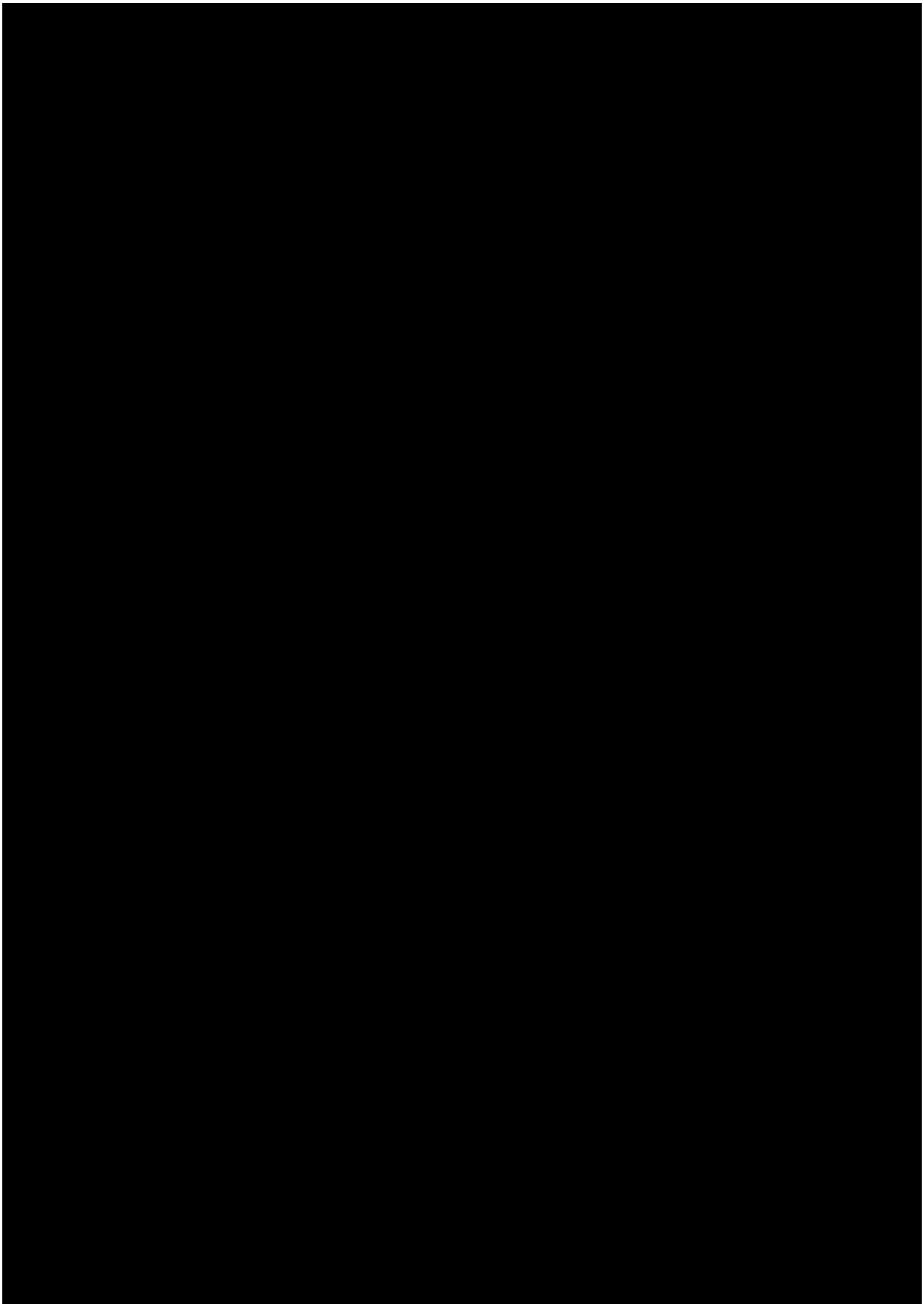
Duration of OR is defined as:

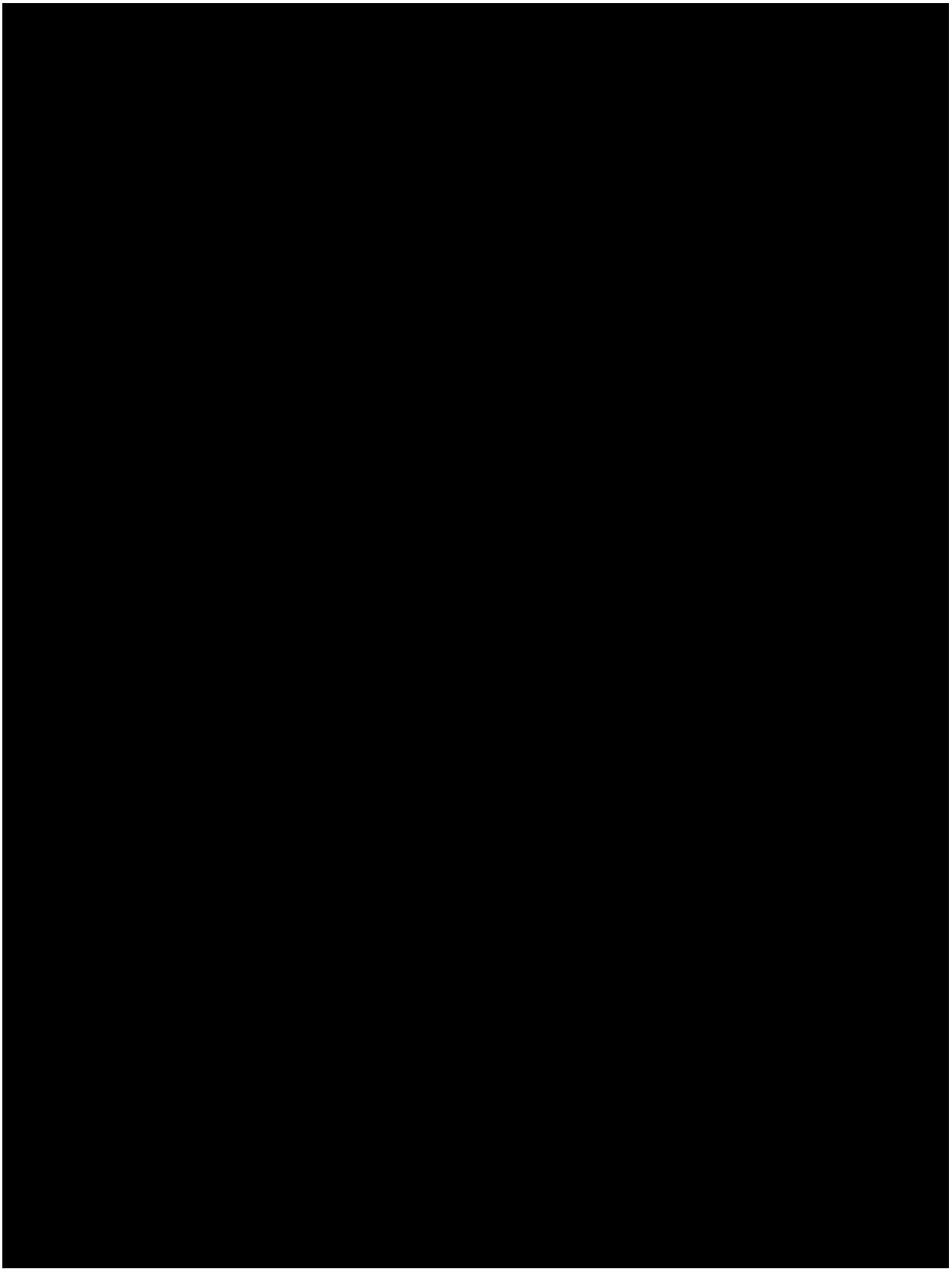
Duration of OR [days] = date of outcome – date of attaining complete response (CR) or partial response (PR) +1,

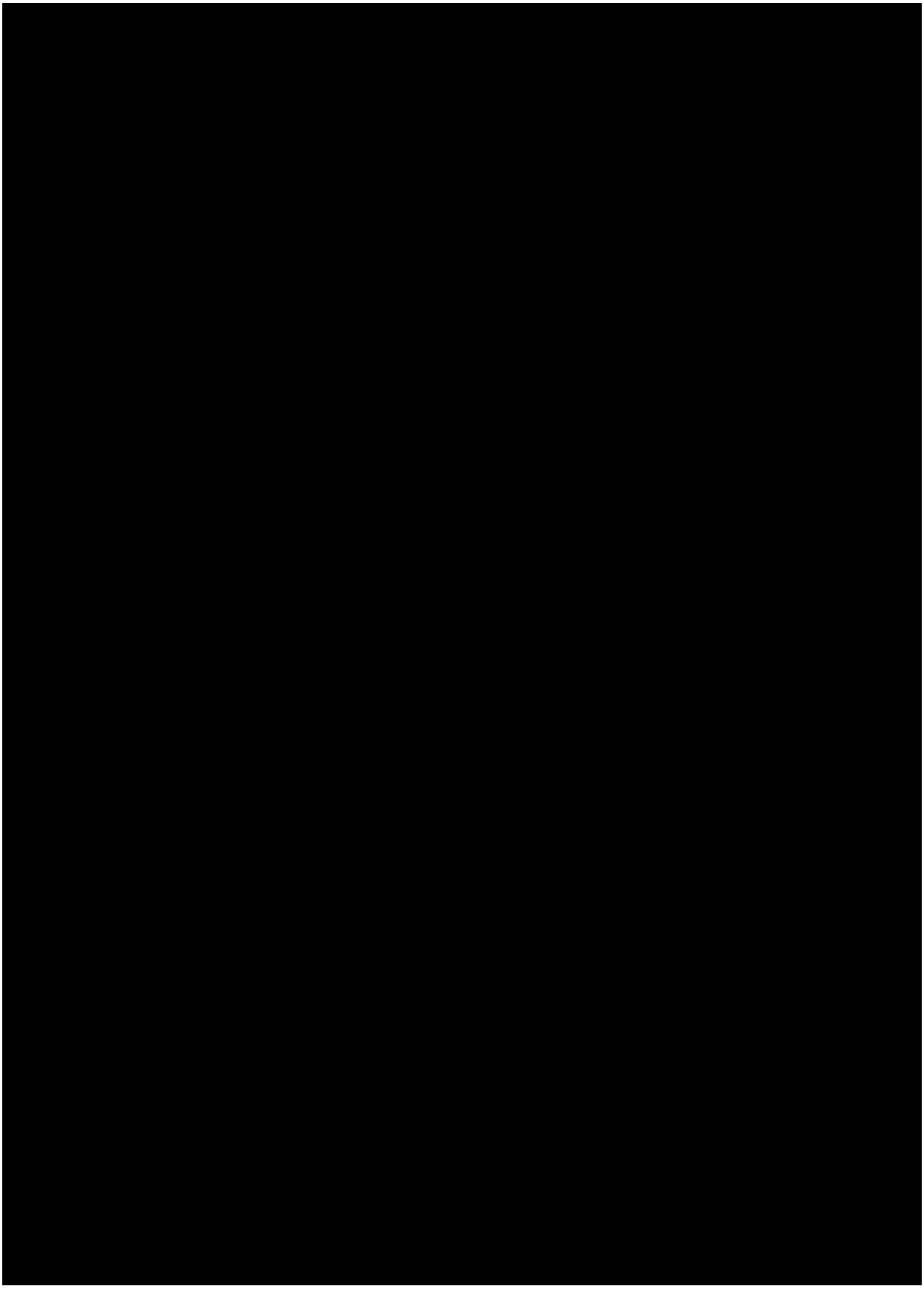
for patients who achieve a CR or PR according to RECIST v1.1. Censoring rules and applicable dates of outcome for duration of OR according to RECIST v1.1 are specified in Table 5.2.2: 1.

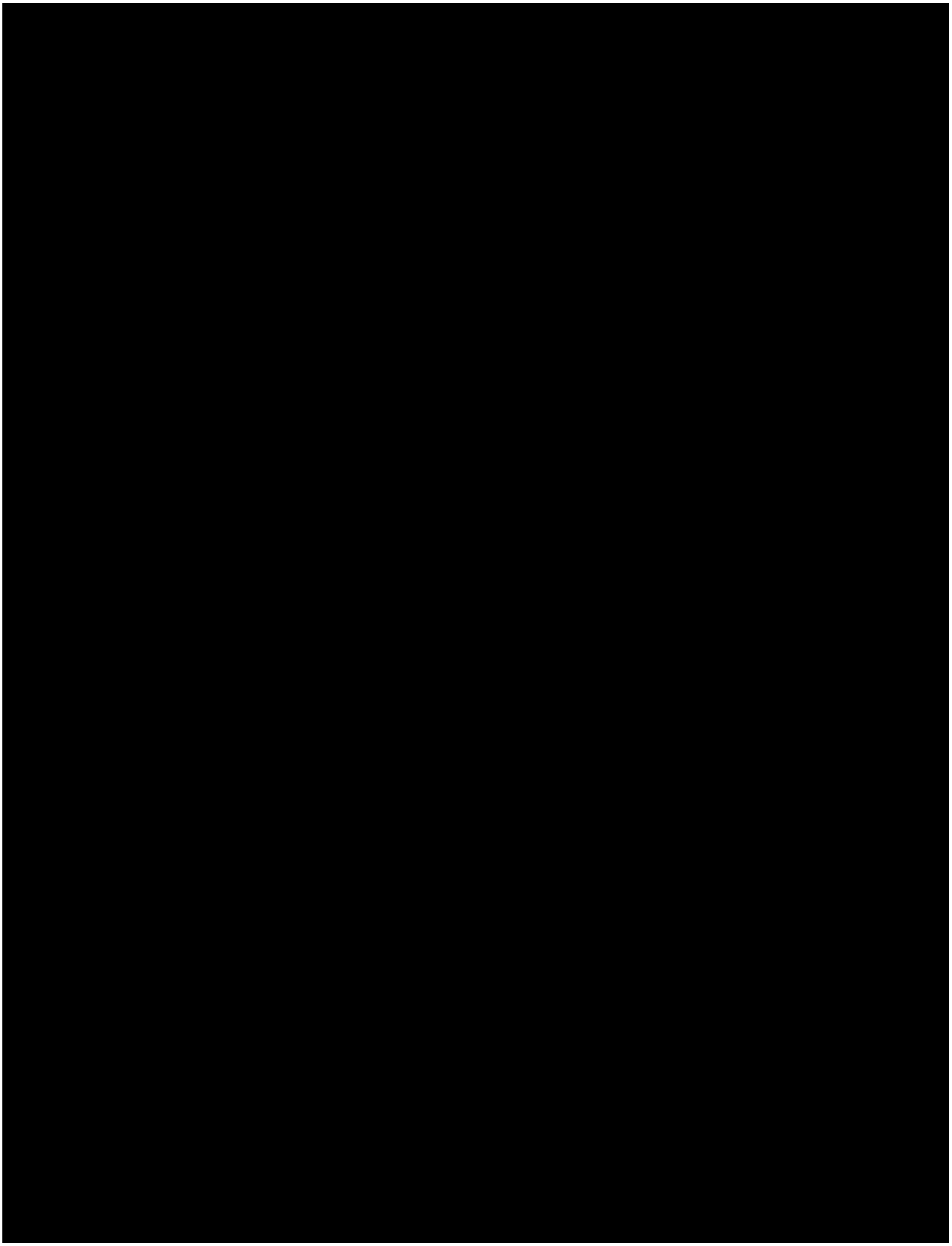
Table 5.2.2: 1 Censoring rules for duration of objective response according to RECIST v1.1

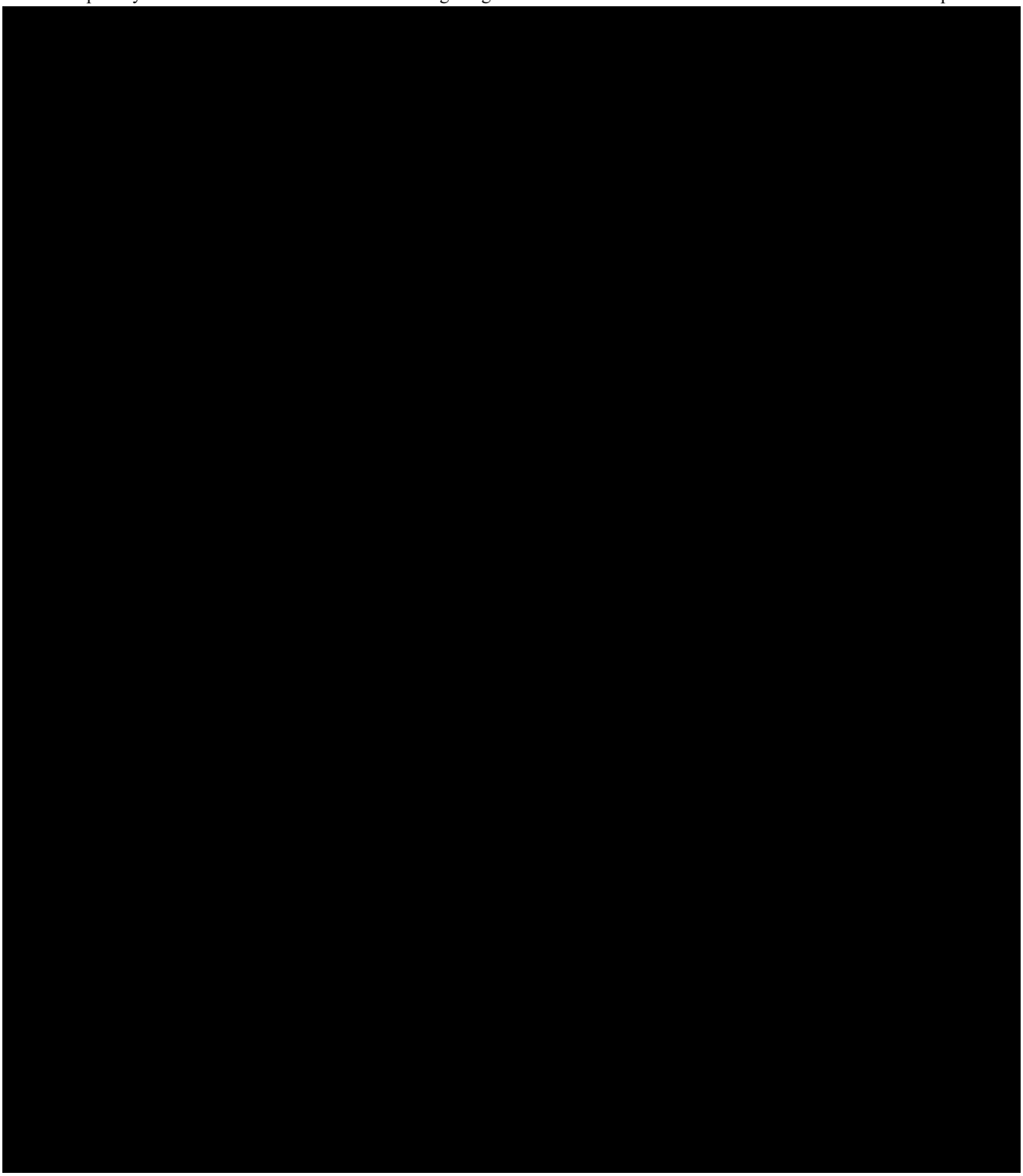
Situation	**Outcome (event or censored)**	**Date of outcome**
No other anti-cancer therapy		
Alive and not progressed according to RECIST v1.1, no more than one consecutively missed radiological assessment	Censored	Date of last radiological assessment
Alive and not progressed according to RECIST v1.1, two or more consecutively missed radiological assessments	Censored	Date of last radiological assessment prior to missed radiological assessments
Progressed according to RECIST v1.1, zero or one missed radiological assessment prior to progression	Event	Date of radiological assessment of progression
Progressed according to RECIST v1.1, two or more consecutively missed radiological assessments prior to progression	Censored	Date of last radiological assessment prior to missed assessments
Death but no progression according to RECIST v1.1, zero or one missed radiological assessment prior to death	Event	Date of death
Death without progression according to RECIST v1.1, but two or more consecutively missed radiological assessments prior to death	Censored	Date of last radiological assessment prior to missed assessments
Initiation of subsequent anti-cancer therapy		
Subsequent anti-cancer therapy started before progression according to RECIST v1.1 or death, no more than one consecutively missed radiological assessments prior to start of subsequent anti-cancer therapy	Censored	Date of last radiological assessment before initiation of subsequent anti-cancer therapy











5.4 OTHER VARIABLE(S)

5.4.1 Demographics and baseline history

Only derived variables are defined here. Standard demographic and baseline characteristics will be used as recorded in the electronic case report form (eCRF).

Body Mass Index (BMI):

$$\text{BMI}\left[\frac{\text{kg}}{\text{m}^2}\right] = \frac{\text{weight [kg]}}{(\text{height [m]})^2}$$

5.4.2 Extent of Exposure

Duration of BI 891065 intake is defined as the time from first administration of BI 891065 until the last administration of BI 891065 +1 day.

The duration of BI 754091 intake will be assessed in terms of number of BI 754091 courses administered for Part B and Part C.

The time to first dose reduction of BI 891065 is defined as the time from first administration of BI 891065 to the first administration of the first reduced dose of BI 891065 +1 day.

Dose intensity (%) will be calculated as the total dose received by the patient divided by the planned total dose, where the planned total dose will be calculated as the dose that the patient should have received between the day of first administration and the date of last administration of BI 891065 (for the dose intensity of BI 891065) and BI 754091 (for the dose intensity of BI 754091), respectively. That is, the actual dose will be divided by the amount of drug that would have been administered had the protocol-specified first dose been administered at each day according to the protocol schedule until the end of treatment.

5.4.3 ECG

Clinically relevant electrocardiogram (ECG) findings will be analysed in terms of adverse events (AEs). Additionally, statistical ECG analyses will be done with variables defined as in the following paragraphs for all 3 trial parts.

Refer to Section 7.8.4 for a detailed description of the derivation of ECG variables.

The generic term QTc for heart rate corrected QT intervals comprises the fixed corrections QTcF (Fridericia's correction) and QTcB (Bazett's correction). Results involving the QTcB interval will only be presented in listings in the appendix of the CTR. For ECG analyses, the on-treatment period refers to all scheduled time points with centrally evaluated ECG recordings following the first administration of trial medication in Cycle 1.

Quantitative variables

- Changes in QTcF interval between baseline and on-treatment
- Absolute QTcF intervals at baseline and on-treatment

These variables will also be computed for the uncorrected QT interval, QTcB, the heart rate, the PR interval, and the QRS complex. Furthermore, the percentage change will be calculated for PR interval and QRS complex.

Categorical variables

The following thresholds will be used for a categorization of the quantitative ECG variables for each patient per time point:

- QTc intervals ≤ 450 ms, > 450 to 480 ms, > 480 to 500 ms or > 500 ms, at baseline and for all on-treatment values
- QT intervals ≤ 500 ms, > 500 ms, at baseline and for all on-treatment values
- Change from baseline to on-treatment value in QTc interval ≤ 30 ms, 30 ms < QTcF interval ≤ 60 ms, > 60 ms
- Change from baseline to on-treatment value in QT interval ≤ 60 ms, > 60 ms

For the QTcF and uncorrected QT interval, the categorizations described above will be performed separately for the visit days where an ECG profile has been taken as well as for the overall on-treatment period using the maximum value per patient within the considered period.

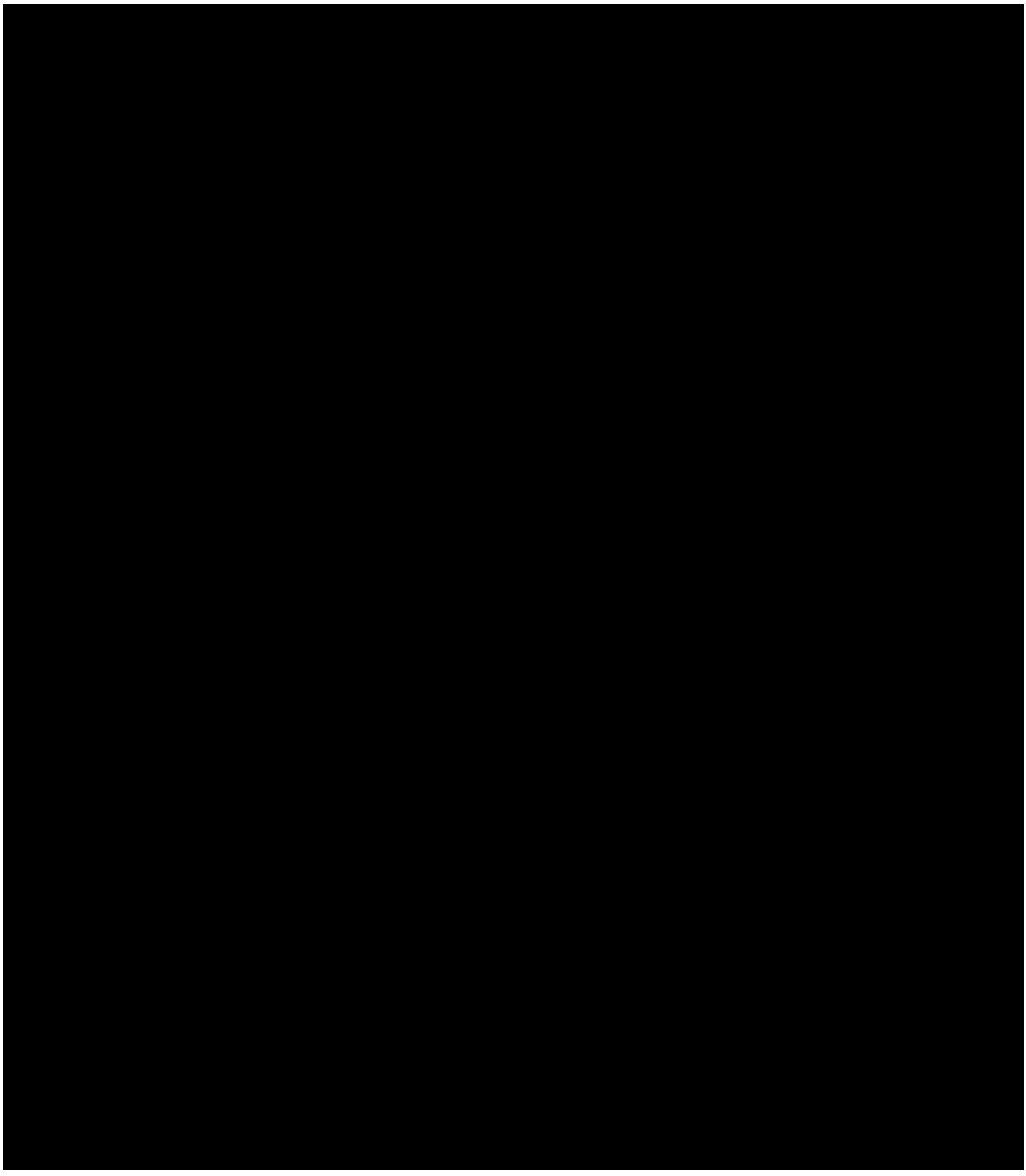
A notable finding in QT/QTcF interval in any on-treatment value for a given patient is defined as

- QTcF change from baseline to on-treatment value > 60 ms at any time on-treatment
- new onset of QT/QTcF > 500 ms, where "new onset" denotes the occurrence of a finding on-treatment which was not present at baseline
- Increase of the PR interval from baseline ≥ 25%, when the corresponding PR interval is > 200 ms
- Increase of QRS complex from baseline ≥ 25%, when the corresponding QRS complex is > 110 ms

Qualitative variables

- The overall interpretation of an ECG, which is classified as "normal", "abnormal", or "unable to evaluate",
- New onset of morphological findings, where "new onset" denotes the occurrence of an on-treatment finding, while at baseline this finding was not reported. Among these, new onset of the following findings are of special interest: atrial flutter, atrial fibrillation, any degree or type of heart block, ST-segment changes, T wave abnormalities, new U waves and myocardial infarction pattern.

The occurrence of notable or qualitative ECG findings will also be derived for the aggregated on-treatment time points of the visit days where an ECG profile has been taken as well as for the overall on-treatment period.



6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENT(S)

In this Phase I trial, treatments are not randomized. In Parts A and B, different dose levels of BI 891065 alone (Part A) or of BI 891065 in combination with BI 754091 (Part B) are being administered. In the expansion part (Part C), patients will be treated with the dose combination that has been determined in Part B.

The data will be presented separately for each part, if not specified otherwise. All planned analyses will be presented by initial treatment group, i.e. in Parts A and B for all dose cohorts separately and in total over all dose cohorts of that trial part. Patients where treatment group assignment in terms of dose cohorts within a trial part has not been followed will be handled on a case-by-case basis and will be agreed upon latest at the report planning meeting before database lock of the specific trial part.

For safety summaries events that start from the first administration of any trial medication until 30 days (REP) after the last administration of any trial medication will be considered as having occurred “on-treatment”. If not specified otherwise, all safety tables will be based on the on-treatment period. Adverse events that have onset during the screening or the follow-up period will be displayed in separate listings from those that occurred during the on-treatment period. The MTD evaluation period will be defined as start of cycle 1 + 21 days for all patients. Labels of each analysing treatment period, analysis numbers, the labels used for displays in the tables and listings in the CTR, as well codes, decodes, sort order and labels for each trial medication are provided in the TSAP technical documents.

6.2 IMPORTANT PROTOCOL DEVIATIONS

No per protocol set analysis will be performed for this study, hence no patient will be excluded from this analysis. However, patients with important protocol deviations (IPDs) will be documented. The following table defines the different categories of IPDs. The final list of IPDs will be confirmed at the last report planning meeting before database lock for the analysis.

Table 6.2: 1 Important protocol deviations

Category / Code		Description	Comment / Example	Excluded from	Automatic / Manual
A		**Entrance criteria not met**			
	A1	Patient has condition that may cause additional risk from study medication	IN3; EX7, EX8, EX9, EX10, EX12, EX13, EX16, EX17	None	Automatic

Table 6.2: 1 Important protocol deviations (cont.)

Category / Code		Description	Comment / Example	Excluded from	Automatic / Manual
	A2	Patient has laboratory assessment that may cause additional risk	EX11, EX21	None	Automatic
	A3	Patient is unable to comply with the protocol	EX3, EX15	None	Automatic
	A4	Patient does not have trial diagnosis or is not part of the target population	IN2, IN4, IN5, IN6, IN7, IN8, IN9 EX20, EX22, EX23, EX24	None	Automatic
	A5	Patient has condition that may interfere with evaluation of safety and/or efficacy	EX1, EX2, EX4, EX5, EX6, EX14, EX18, EX19	None	Automatic
B		**Informed consent**			
	B1	Trial Informed consent not available, not done	IN1	All	Automatic
	B2	Informed consent too late	Date of informed consent later than the first study related procedure (This does not include the informed consent for biobanking and the informed consent for treatment beyond progression)	None	Automatic

Table 6.2: 1 Important protocol deviations (cont.)

Category / Code		Description	Comment / Example	Excluded from	Automatic / Manual
	B3	Informed consent for treatment beyond progression not available or too late	Date of informed consent for treatment beyond progression not available although patient treated after progression or date of informed consent for treatment beyond progression later than first administration of trial medication after progression	None (as long as patient has not withdrawn from the general study informed consent)	Automatic
C		**Trial medication**			
	C1	Incorrect treatment taken	• Study medication dispensing error leading to change in actual treatment	None	Manual
	C2	Incorrect dose administered	E.g. reduction criteria as specified in CTP Section 4.1.7 met but no dose reduction	None	Manual
	C3	Discontinuation of study medication not according to protocol	Discontinuation criteria as specified in CTP Section 4.1.7 met but study medication not discontinued	None	Manual
D		**Concomitant medication**			
	D1	Prohibited medication	• Immunosuppressive medications • Live attenuated vaccines • Herbal preparations / medications	None	Automatic & Manual

Table 6.2: 1 Important protocol deviations (cont.)

Category / Code		Description	Comment / Example	Excluded from	Automatic / Manual
E		**Trial specific violations**			
	E1	Pregnancy test not done	Pregnancy test not done in women of childbearing potential although indicated by the protocol	None	Automatic & Manual

6.3 SUBJECT SETS ANALYSED

The Screened Set (SCR) includes all patients who signed the informed consent form and will be used to summarise patient disposition.

The Enrolled Set (ES) includes all patients who have been enrolled into the study and will be used for demographics analyses.

The Treated Set (TS) consists of all patients who have received at least one administration of any trial medication and will be used for all planned safety, efficacy and biomarker analyses in the CTRs besides the MTD determination.

The MTD Evaluation Set includes all patients from the TS who have not been replaced for the MTD evaluation; patients who has no actual replacement but satisfies the replacement criteria per protocol thus ineligible for MTD evaluation will also be excluded form the MTD Evaluation set. This set will be used for the primary analyses of DLTs and MTD determination.

Rules for replacement of patients are defined in CTP Section 3.3.4.4. The list of patients replaced for MTD evaluation or ineligible for MTD evaluation will be stored in the trial master file.

The Pharmacokinetic Parameter Set (PKS) consists of all patients in the TS who have at least one valid secondary PK endpoint available and will be used for all pharmacokinetic analyses.

The ECG Set includes all patients in the treated set who do not have an artificial pacemaker and have at least one on-treatment value for at least one ECG variable.

The ECG Pharmacokinetic Concentration Set (ECGPCS) includes all patients from the ECG Set who provide at least one time-matched pair of valid BI 891065 plasma concentration and corresponding ECG variable to be used in the exposure-response analysis.

The decision about concentration value validity needs to be made within the Clinical Pharmacology group. Refer to the Section 7.8.4 for the definition of the maximum acceptable

time deviation between PK blood sampling and ECG recording at different time points during the trial.

The analysis of ECG data will be based on the ECG Set, except those analyses concerning the relationship between plasma concentrations and ECG variables which will be based on the ECGPCS. Listings for patients with artificial pacemakers will be based on the TS.

[redacted]

6.5 POOLING OF CENTRES

This section is not applicable since there will be no inferential analyses. Thus, no statistical model in which centre or country is included as factor will be applied.

6.6 HANDLING OF MISSING DATA AND OUTLIERS

Missing or incomplete AE dates are imputed according to BI standards (4). Missing data and outliers of PK data are also handled according to BI standards (5). Potential outliers will be reported and analysed as observed. In general, missing data not discussed in (4) and (5) will not be imputed unless required for the following analyses and definitions. Then the rules as described below apply.

1) **Change of laboratory values from baseline**

   Laboratory values at baseline: For missing laboratory data at cycle 1 day 1 (before the first administration of any study medication) the data of preceding visits will be used if available.

2) **Definition of on-treatment period and actual treatment**

   Date of permanent discontinuation of study medication: All reasonable efforts should be undertaken during the study to obtain the dates of permanent discontinuation of study medication. However, if the date of the very last administration is missing this will be imputed with:

   - If only month and year are given, the last day of the month will be used for imputation
   - If only the year is given, the 31st of December of this year will be used for imputation

   If the imputed date leads to a date that is later than the date of the EOT visit, then the imputed date is the date of the EOT visit. If the imputed date leads to a date that is later than the death date, then the imputed date is the date of death.

3) **Partial death dates**

If a partial (year and month) death date is reported, the date will be imputed with the end of the month for the analysis of PFS. This is in line with the imputation of partial dates for the analysis of AEs.

4) Partial or missing start date of subsequent anti-cancer therapy/subsequent radiotherapy

If the day of the start date of subsequent systemic therapy/subsequent radiotherapy is missing, then the 1st of the 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 for censoring of PFS or for other descriptive statistics:

- For censoring of PFS: If only the year is reported, the 1st of January 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. In case of a completely missing start date of subsequent anti-cancer therapy/subsequent radiotherapy and the patient did not have any post-baseline tumour assessment or did not progress or die, the PFS of this patient will be censored at the day of first administration of BI 836826. 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.

5) ECG analysis

Quantitative and derived categorical ECG endpoints

- If single cardiac cycles are missing, the arithmetic means per single ECG will be computed with the reduced (1, 2 or 3) number of cardiac cycles.

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

- If the actual times of all triplicate pre-dose ECG recordings on Day 1 or the time of the first drug administration are missing, or the planned pre-dose ECGs are recorded after the first drug administration, they will not be used as baseline values and will be excluded from the analyses.

- If baseline is missing, a QTcF/QT interval > 500 msec at any time on treatment will be a notable finding.

Qualitative ECG findings

- In case a certain qualitative ECG finding is not reported at baseline but occurring on-treatment, this will be categorized as a 'new onset' of this finding.
- For the analysis of overall ECG interpretation values (comparison of on-treatment with baseline results), missing values will be handled as indicated in the following table.

Table 6.6: 1 Interpretation of qualitative ECG findings

Condition: Overall ECG interpretation		**Aggregated result presented in Table**
At baseline	**On treatment (specific time interval under consideration)**	**Overall ECG interpretation**
Normal, abnormal or unable to evaluate	Normal (all time points)	Normal
Abnormal	Abnormal (at least one time point)	Abnormal, and abnormal at baseline
Normal or unable to evaluate	Abnormal (at least one time point)	Abnormal (new onset)
Normal, abnormal or unable to evaluate/missing	Unable to evaluate (at least one time point), normal or unable to evaluate/missing at the other time points	Unable to evaluate/missing

Exposure-response analysis

- Missing BI 891065 plasma concentration data which are identified by BLQ (below lower limit of quantification) will be replaced by zero if measured at baseline and by ½ LLOQ (lower limit of quantification) if measured on-treatment.
- If the actual sampling time of the blood sample or of the ECG recording is not available, the pair of plasma concentration and time-matched ECG endpoint will be excluded from the analyses at the corresponding planned time point. Furthermore, plasma concentration data will be excluded from the ECG exposure-response analyses, if it is excluded from all calculations in PK analysis.

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

Study days and visits will be labelled according to the flowchart in the CTP.

Unless otherwise specified baseline is defined as the time point closest to but prior to the first administration of any study medication. If no time is specified and the date is the same as the first administration date, then it will still be considered baseline if not specified otherwise. If there is no measurement earlier than the first administration of study medication, then no baseline will be derived.

Laboratory values:
Baseline is defined as the latest time point before the very first administration of any study medication. For laboratories where not only the examination date but also time are recorded, examination time has to be taken into account when defining baseline. That is, a laboratory value on the same date as the first administration of study medication is considered as baseline value if and only if the time of laboratory assessment is before or the same as the time of first study drug administration.

If any of these times is missing and the date of laboratory assessment is equal to the date of first administration of study medication, then the laboratory assessment will be considered as according to protocol, i.e. as prior to first study medication.

Imaging time windows:
In order to identify whether consecutive imaging time points are missing for a given patient, a nominal time point (6, 12, … weeks 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
Etc., 9 week interval	Etc.	Etc.

* 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, he/she will be said to have missed an assessment for that time point.

ECG analysis:
Baseline values will be derived from the 1-3 triplicate ECG recordings prior to the first drug administration on Day 1 (refer to Section 7.8.4).

7. PLANNED ANALYSIS

The labelling and display format of statistical parameters will follow the BI guideline (8).

All analyses are presented separately for the 3 trial parts, if not specified otherwise. Efficacy data are presented by dose cohort for Parts A and B and in total for Part C. Displays of safety data will be presented by dose cohort and in total for Parts A and B and in total for Part C, if not specified otherwise.

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> [months] 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 months.

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. The denominator of the main categories is defined by the number of patients in the used patient set. The main categories define the denominators of the subcategories. Subcategories should be intended and "[N(%)]" will be displayed only for the main category. If a table includes only categorical data, "[N(%)]" is to be displayed in the column header.

Sort order for general categorical variables: If categories correspond to the collected categories on the eCRF and the table shells do not explicitly specify the ordering, the "default ordering" defined by the eCRF is to be used in such cases. If categories are derived, the ordering as specified in the table shell document should be used; in general ordinal data (e.g. categorised continuous data) are to be displayed in ascending order.

Abbreviations (e.g. Wors.) should not be displayed without any explanations. They will be either spelled out in the table or explained in footnotes (whatever is more reasonable from the programming point of view).

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

- Weeks = Days / 7
- Months = (Days * 12) / 365.25
- Years = Days / 365.25

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 eastern cooperative oncology group (ECOG) performance status, and baseline disease assessment.

7.2 CONCOMITANT DISEASES AND MEDICATION

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 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 3 category will be counted more than once. Footnotes will clarify this possible double counting in tables.

7.3 TREATMENT COMPLIANCE

Treatment compliance will be listed in the appendix of the CTR. In general, the amount of and time for which BI 891065 and BI 754091 are taken will be interpreted in light of treatment exposure, efficacy and safety. Refer to Section 5.4.2 and Section 7.7 for further details on exposure analysis.

7.4 PRIMARY ENDPOINT(S)

Part A:
The primary endpoints of Part A are the MTD of BI 891065 and the number of patients with DLTs in the first treatment cycle. The number of patients with DLTs at each dose level will be presented for the first cycle for the MTD evaluation set and for the whole on-treatment period for the treated set separately.

The MTD will be determined by the SRC using recommendations from a Bayesian logistic regression model (BLRM, see CTP Section 7 for details on the model and on the prior). BLRM evaluations for the CTR will be performed once using the number of patients with DLTs during the first cycle from the MTD evaluation set and once using the number of patients with DLTs during the whole on-treatment period from the treated set.

Tables and bar charts displaying the posterior probabilities of the true DLT rates being in either the underdosing interval, the targeted toxicity interval or the over toxicity interval will be produced.

Part B:
The primary endpoints of Part B are the MTD of BI 891065 in combination with BI 754091 and the number of patients with DLTs in the first treatment cycle. The number of patients

with DLTs at each dose level will be presented for the first cycle for the MTD evaluation set and for the whole on-treatment period for the treated set separately.

The MTD will be determined by the SRC using recommendations from a BLRM (see CTP Section 7 for details on the model, the prior for Part B is described in Section 9.1 of this TSAP). BLRM evaluations for the CTR will be performed once using the number of patients with DLTs during the first cycle from the MTD evaluation set and once using the number of patients with DLTs during the whole on-treatment period from the treated set.

Tables and bar charts (per dose level of BI 754091) displaying the posterior probabilities of the true DLT rates being in either the underdosing interval, the targeted toxicity interval or the over toxicity interval will be produced.

Part C:
The primary endpoint of Part C is OR by investigator's assessment based on RECIST v1.1. OR will be analysed descriptively for the treated set in terms of objective response rate (ORR), defined as the proportion of patients with best overall response of CR or PR.

An interim futility analysis will be performed by the SRC after 20 patients have been treated for at least 18 weeks. Enrolment into Part C will be stopped if less than 2 patients with OR have been observed in these 20 patients. Results of this interim analysis will be documented in the SRC minutes.

7.5 SECONDARY ENDPOINT(S)

7.5.1 Key secondary endpoint(s)

Not applicable as no key secondary endpoints have been defined in the CTP.

7.5.2 (Other) Secondary endpoint(s)

Part A:
The number of patients with DLTs observed during the on-treatment period will be analysed descriptively and will be displayed by dose level.

PK endpoints will be analysed descriptively as well. Plasma (and urine) concentrations of BI 891065 will be plotted against time. The calculation of the PK parameters, as well as the descriptive and comparative analysis of the PK parameters, will be based on the methods outlined in Section 7.3.5 of the CTP, as well as in (9).

OR by investigator's assessment based on RECIST v1.1 will be analysed descriptively for the treated set in terms of the ORR, defined as the proportion of patients with best overall response of CR or PR.

Part B:
The number of patients with DLTs observed during the on-treatment period will be analysed descriptively and displayed by dose level.

PK endpoints will be analysed descriptively as well. Plasma concentrations of BI 891065 and of BI 754091 will be plotted against time. The calculation of the PK parameters, as well as the descriptive and comparative analysis of the PK parameters, will be based on the methods outlined in Section 7.3.5 of the CTP as well as in (9).

OR by investigator's assessment based on RECIST v1.1 will be analysed descriptively for the treated set in terms of the ORR, defined as the proportion of patients with best overall response of CR or PR.

Part C:
Duration of OR by investigator's assessment based on RECIST v1.1 will be summarised by its median and quartiles derived using the Kaplan-Meier estimation procedure. Duration of OR can only be calculated for patients in the treated set that have an OR.

7.7 EXTENT OF EXPOSURE

For all 3 trial parts, duration of BI 891065 intake will be summarised descriptively.

The number of BI 754091 courses will be assessed for Part B and Part C.

For all 3 trial parts, the number of patients with at least one dose reduction of BI 891065 will be displayed and the time to first dose reduction of BI 891065 will be analysed descriptively as well as using Kaplan-Meier methods based on the treated set. Patients who discontinue BI 891065 without a dose reduction will be censored at the date of the last BI 891065 intake for this analysis. Furthermore, dose intensity of BI 891065 will be calculated for all 3 trial parts and dose intensity of BI 754091 will be calculated for Part B and Part C.

7.8 SAFETY ANALYSIS

All safety analyses will be performed on the TS, besides the analyses of MTD determination. These will be performed on the MTD evaluation set.

7.8.1 Adverse events

The analyses of AEs will be descriptive in nature. All analyses will be based on the number of patients with AEs (not on the number of AEs). The analysis will be based on BI standards (6). AEs will be coded using the most recent version of MedDRA. According to the BI standards multiple overlapping or adjacent recordings (AE occurrences) of the same AE are collapsed into one AE event if all AE attributes are identical (lower level term, severity, action taken, therapy required, seriousness, reason for seriousness, relationship, outcome, AE of special interest (AESI) flag).

The analyses of AEs will be based on the concept of treatment-emergent AEs, where a treatment-emergent AE has an onset in the analysing treatment period. The AE analysis will be based on the on-treatment period which starts with the date of the first administration of study medication and ends 30 days after the last administration of study medication. AEs with an onset date in the screening period (time between informed consent date and date of the first administration of study medication) or follow-up period (time after the on-treatment period) will be tabulated and listed separately.

Sorting order: In AE tables, system organ classes (SOCs) will be sorted alphabetically and preferred terms (PTs, within SOCs) will be sorted by descending frequency.

Listings of AEs will be displayed by patient. The actual planned dose of BI 891065/dose combination of BI 891065 and BI 754091 will be derived and included in the listings. AEs will be reported with start day and end day as calculated from the first day of treatment with study medication. For listings displaying AEs during the screening or follow-up period, the start and stop day are calculated from the start of the respective analysis period.

The incidence of AEs overall, related AEs, serious AEs (SAEs), and immune-related AEs will be reported by severity according to common terminology criteria for adverse events (CTCAE) grades (CTCAE version 4.03 for Part A, CTCAE version 5.0 for Part B and Part C). Drug-related serious AEs will also be tabulated. Protocol-specified AESI will be analysed based on data reported in the eCRF.

AEs leading to death during the on-treatment period will be tabulated by SOC and PT. Reported fatal AEs during the follow-up period will be listed.

Other significant AEs are defined as serious and non-serious AEs that lead to dose reduction of BI 891065 (for all trial parts) or permanent discontinuation of study medication (BI 891065 in Part A, BI 891065 and BI 754091 in Parts B and C). Their incidence will be reported by severity according to CTCAE grades. A listing of patients who developed other significant AEs will be provided and a flag for serious and non-serious will be included. In addition, AEs leading to treatment interruption will be reported by severity according to CTCAE grades.

7.8.2 Laboratory data

The analysis of laboratory data will be descriptive in nature and will be based on BI standards (7). The same on-treatment period as considered for the analysis of adverse events will be applied for laboratory values. Patients having at least one post-baseline laboratory value will be displayed in the descriptive analyses. Patients with missing CTCAE grade at baseline or no baseline value but with post-baseline values will be displayed in a new category “missing CTCAE grade at baseline” for those laboratory parameters where CTCAE grading is applicable. CTCAE grades for applicable laboratory parameters will be calculated according to CTCAE v5.0.

For Primary laboratory tests listed in Table 7.8.2: 1, the following outputs will be presented:

- Descriptive statistics, including changes from baseline
- Shift tables in terms of:
    - CTCAE grade, for laboratory tests with CTCAE grade defined;
    - Upper and lower reference limits, for laboratory tests without CTCAE grades;
    - Multiples of upper reference limit for customized shift tables of ALP, ALT, AST, bilirubin and creatinine.
- Frequency of patients with potential clinically significant abnormalities.

For secondary laboratory tests listed in Table 7.8.2: 2, analyses will be limited to frequency of patients with potential clinically significant abnormalities.

For other laboratory tests, only listing of observed values will be presented.

Analyse of descriptive statistics should use normalized lab values. Analyses of frequencies of patients with potential clinical significance, analyses of shift, and liver function categories tables should use converted values.

Table 7.8.2: 1 Primary laboratory tests

Label	Lab test name	Direction of interest	Potential Clinical significance rule
A1AGLP	Alpha-1 Glycoprotein	High[4]	>ULN and >baseline No CTCAE defined
ALP	Alkaline Phosphatase	High	CTCAE Grade 2 or higher[3]
ALT	Alanine Aminotransferase	High	CTCAE Grade 2 or higher[3]
AST	Aspartate Aminotransferase	High	CTCAE Grade 2 or higher[3]
BILI	Total Bilirubin	High	CTCAE Grade 2 or higher[3]
BILIND	Indirect Bilirubin	High	CTCAE Grade 2 or higher[3] using grades defined for Total Bilirubin
BILDIR	Direct Bilirubin	High	CTCAE Grade 2 or higher[3] using grades defined for Total Bilirubin
CK	Creatine Kinase	High	A[1,2]
CREAT	Creatinine	High	>1.5xULN and >baseline Ambiguous CTCAE not used[3]
GLUC	Glucose	Low, High[4]	Low: A[1,2] High: >10 mmol/L and > baseline No CTCAE defined
HAPTOG	Haptoglobin	Low[4]	<LLN and <baseline No CTCAE defined
HGB	Hemoglobin	Low	A[1,2] (listed in CTCAEv5 as "Anemia")
K	Potassium	Low[4], High	Low: <3 mmol/L and <baseline High: A[1,2]
LDH	Lactate Dehydrogenase	High[4]	≥3xULN and >baseline No CTCAE defined
LYM	Lymphocytes	Low	A[1,2]
NEUT	Neutrophils	Low	A[1,2]
PLAT	Platelets	Low	A[1,2]
RETI	Reticulocytes	Low[4]	<LLN and <baseline No CTCAE defined
SODIUM	Sodium	Low[4], High	Low: <130 mmol/L and <baseline High: A[1,2]
T3FR	Triiodothyronine, Free	Low[4], High[4]	Low: <LLN and <baseline High: >ULN and >baseline No CTCAE defined
T4FR	Thyroxine, Free	Low[4], High[4]	Low: <LLN and <baseline High: >ULN and >baseline No CTCAE defined
TSH	Thyrotropin	Low[4], High[4]	Low: <LLN and <baseline High: >ULN and >baseline No CTCAE defined

Table 7.8.2: 1 Primary laboratory tests (cont')

Label	Lab test name	Direction of interest	Potential Clinical significance rule
UREAN	Blood Urea Nitrogen	High[4]	>10 mmol/L and >baseline No CTCAE defined
WBC	Leukocytes	Low	A[1,2]

[1]A= CTCAE grade 2 or greater with an increase of at least one CTCAE grade from baseline
[2]Separate shift tables for the low and high directions, when both directions are specified. Shift tables compare baseline vs. on-treatment CTCAE grades. CTCAE grading will not consider symptoms.
[3]CTCAE grades will not be defined for baseline values for ALP, ALT, AST, BILI (total, direct, and indirect) and CREAT. Special categories are defined for shift tables.
[4]Separate shift tables for the low and high directions, when both directions are specified. Shift tables compare baseline vs on-treatment using the three categories (1) below reference range, (2) within reference range, and (3) above reference range.

Table 7.8.2: 2 Secondary laboratory tests

Label	Lab test name	Direction of interest	Potential Clinical significance rule
ALB	Albumin	Low	A[1]
APTT	Activated Prothrombin Time	High	A[1,2]
CA	Calcium	Low, High	A[1]
CHOL	Cholesterol	High	A[1]
CL	Chloride	Low, High	Low: <80 mmol/L and <baseline High: >120 mmol/L and >baseline No CTCAE defined
EOS	Eosinophils	High	>1.0 10**9/L and > baseline No CTCAE defined
INR	Prothrombin Normalized ratio	High	>1.5 and >baseline
PHOS	Phosphate	Low, High	High: >1.7 mmol/L and >baseline Low: <0.7 mmol/L and <baseline
PROT	Serum Protein	High	>ULN and >baseline No CTCAE defined
PT	Prothrombin Time	High	>ULN and > baseline No CTCAE defined
TRIGL	Triglycerides	High	A[1]
UREA	Urea	High	>1.5 x ULN and >baseline No CTCAE defined
URATE	Uric Acid	High	Females: >600 umol/L and >baseline Males: >650 umol/L and >baseline CTCAE based upon AE

[1]A= CTCAE grade 2 or greater with an increase of at least one CTCAE grade from baseline
[2]CTCAE grading will not consider symptoms presence of bleeding or use of anticoagulation.

Handling of CTCAE grade -1 and -9 laboratory parameters:
Generally, in case only one direction of worsening (high or low laboratory value) is specified in the CTCAE document, there is no need to examine the other direction. Therefore, for

calculating the change in CTCAE grade, patients with a CTCAE grade of -9 (no CTCAE grade defined) will be automatically treated as CTCAE grade 0 for all analyses. In laboratory listings, the CTCAE grade will be displayed as -9.

There are certain parameters for which CTCAE grades can only be differentiated by taking physiological consequences into account. These laboratory values will be coded as -1. As these definitions aggregate laboratory data and adverse events or concomitant therapies no analyses based on CTCAE grades will be done. Instead standard laboratory analyses as for laboratory parameters without CTCAE grade definitions will be done. Nevertheless, a laboratory listing including -1 values will be added to the CTR.

Corrected calcium:
The grading of hypocalcemia is based on corrected calcium as calcium can be falsely low if hypoalbuminemia is present. The following corrective calculation will be performed:

$$\text{Corrected calcium (mg/dL)} = \text{Total Calcium (mg/dL)} - 0.8[\text{Albumin (g/dL)}-4]$$

No correction of the reference range has to be done. The reported reference range of total calcium will be used for analyses. Corrected calcium can be only derived at a certain time point in case both laboratory values total calcium and albumin have been reported for the patient in the same laboratory sample.

Hepatic enzyme elevations (potential Hy's law cases):
These are defined as those cases where a combination of all of the following events occurred: any on-treatment value of ALT and/or AST > 3ULN (upper limit of normal) with total bilirubin ≥ 2ULN and ALP < 2ULN. 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. Patients with missing laboratory values for liver enzymes will be excluded from these analyses, but presented separately.

Tabulations of hepatic enzyme elevations and liver laboratory values will be done according to the FDA Drug Induced Liver Injury (DILI) guidance (10).

Hepatic enzyme elevations will be displayed for the treated set for the whole on-treatment period.

7.8.3 Vital signs

Descriptive statistics are planned for the analysis of vital signs.

7.8.4 ECG

For all 3 trial parts, analyses of ECG will be descriptive in nature. Newly emergent abnormalities will be recorded and analysed as adverse events.

In addition, statistical ECG analyses will be performed for the centrally evaluated digital ECG recordings as follows.

Derivation of ECG variables

Three replicate digital ECG recordings will be collected as specified in the flowchart of the CTP. Each of the three recorded single ECGs will then be evaluated semi-automatically for cardiac intervals, which comprise the RR, PR and QT interval and the QRS complex. Measurements of these intervals will be made on four (possibly consecutive) cardiac cycles from the lead chosen (usually lead II). The measurements of the cardiac cycles will be stored in the database, i.e. usually 12 values per time point. The four cardiac cycles will be averaged prior to the calculation of the heart rate and heart rate corrected QT intervals (QTc).

The heart rate will be derived from the RR interval as

HR [beats/min] = 60000/RR [ms]

Heart rate corrected QT intervals (generally denoted by QTc) will be calculated using Fridericia's (QTcF) formula and Bazett's formula (QTcB):

- QTcF [ms] = (1000/RR)^(1/3) * QT [ms]
- QTcB [ms] = (1000/RR)^(1/2) * QT [ms]

Further aggregation of the three replicate ECG intervals and HR at each scheduled time point will then be performed using arithmetic means. Additional averaging over 1-3 time points will be performed to derive the baseline values: they will be calculated as the mean values of the 1-3 triplicate ECG recordings collected pre-dose on Day 1.These mean values will be used for the derivation of the ECG variables as they are specified in Section 5.4.3.

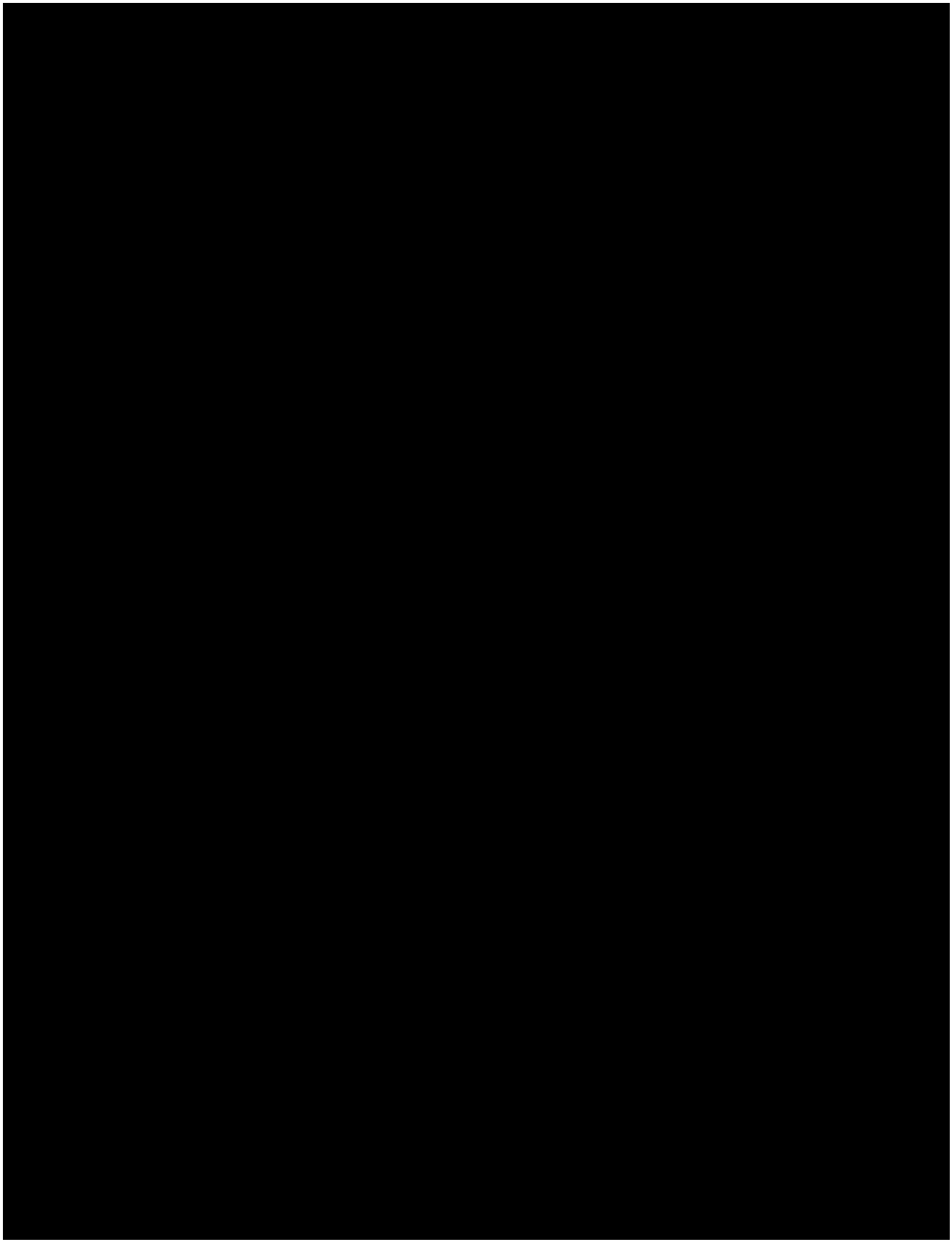
ECG analyses

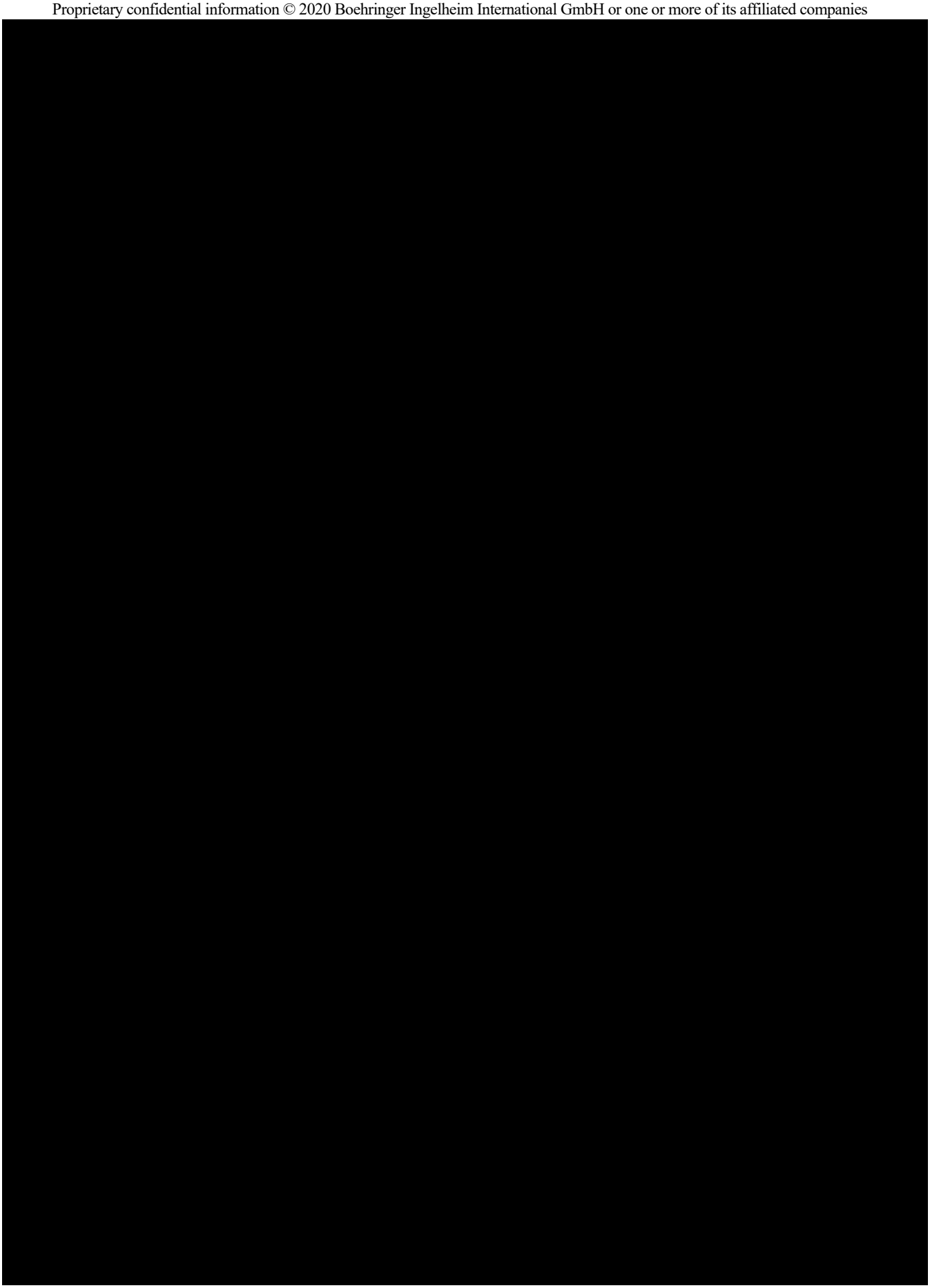
For all ECG variables, listings of individual data will be shown in the appendix of the CTR. Absolute values and changes from baseline in QTcB interval as well as the percentage changes for PR interval and QRS complex will only be displayed in listings.

Absolute values and changes from baseline in QTcF interval, QT interval, HR, PR interval, and QRS complex will be summarised descriptively by treatment, cycle, day, and time point using the ECG set. The time profiles of mean and standard deviation for the absolute values and changes from baseline on treatment will be displayed graphically by treatment.

Frequency tables will be provided for all categorical variables including notable findings and qualitative ECG findings. The tables will be presented separately for the visit days where an ECG profile has been taken as well as for the overall on-treatment period using the maximum value per patient. Frequencies of the increases in QTcF and QT intervals above thresholds as defined in Section 5.4.3 between baseline and on-treatment will be displayed in two-way shift tables by treatment. Frequency tables with regard to the new onset of qualitative (morphological) ECG findings will display categories of grouped findings based on the CDISC (EGTEST) terminology as well as the frequencies per each observed type of finding. These descriptive analyses will be performed for patients in the ECG Set separately for Part A, B and C.

For all patients with any notable finding (see Section 5.4.3), a separate listing in Section 15 of the CTR will be created and the corresponding time profiles will be shown. Notable findings of patients in the TS who are excluded from the ECG Set will be listed in separate listings.



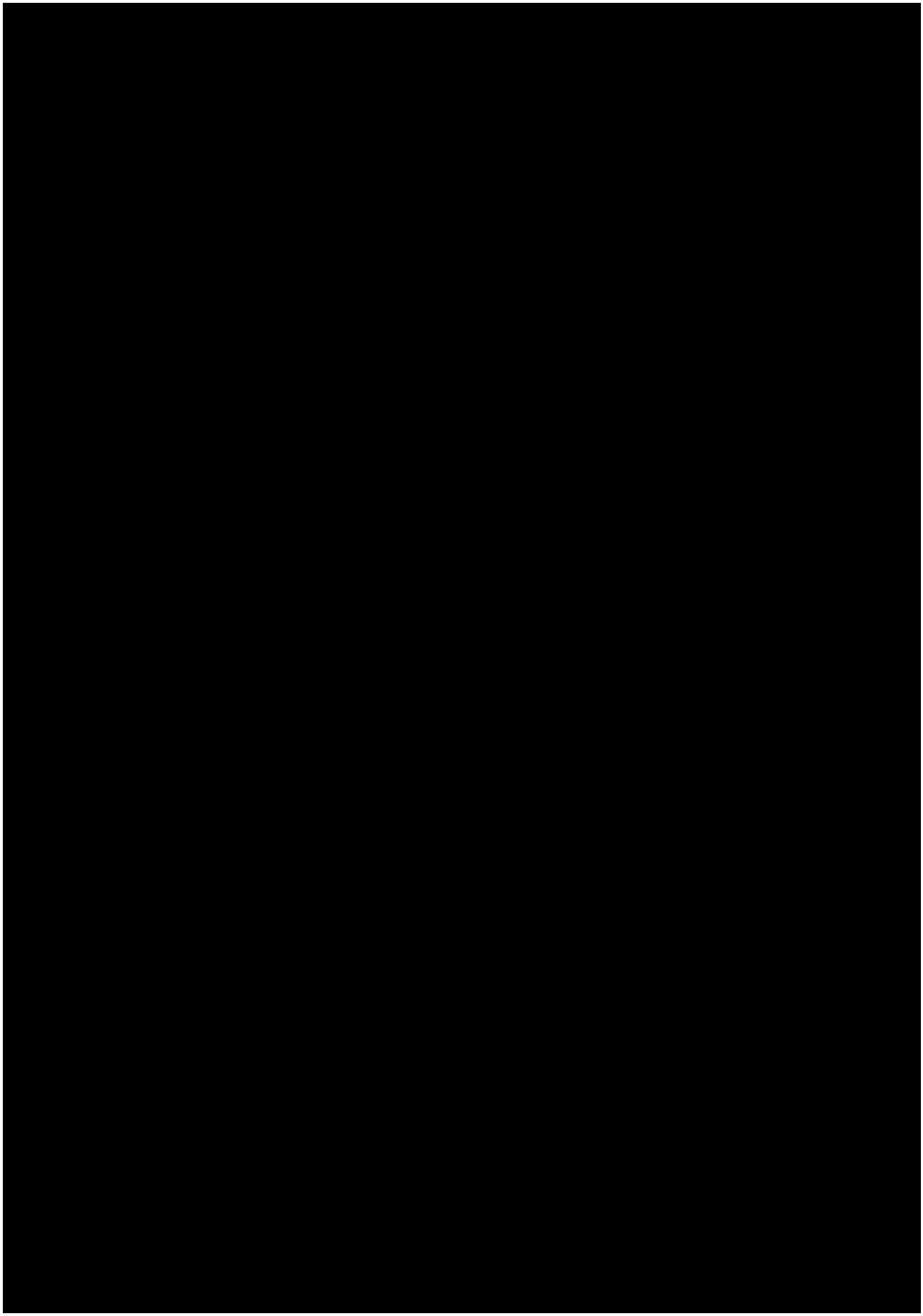


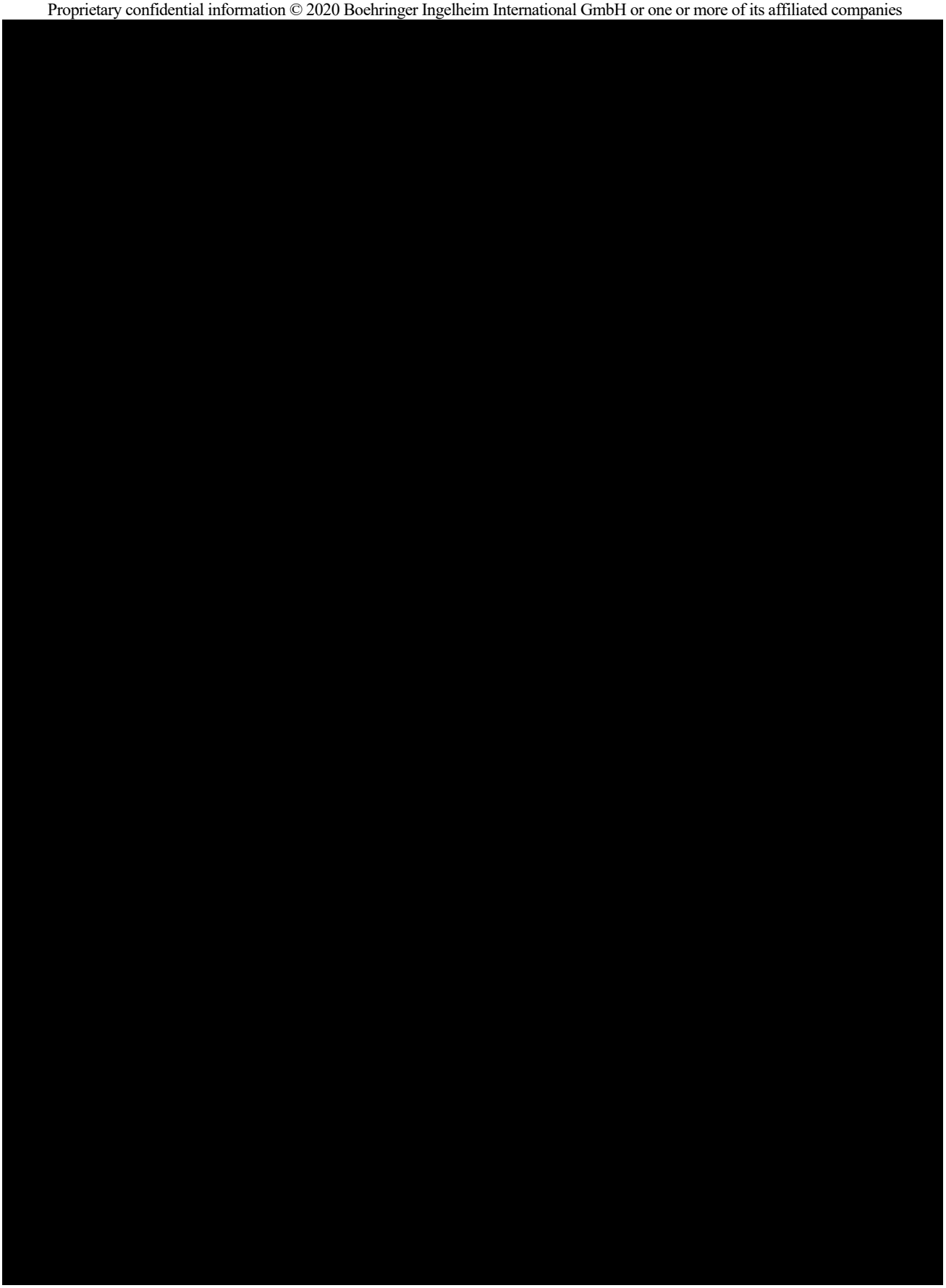
[redacted]

7.8.5 Others

Pregnancy tests:
A listing showing the results of pregnancy tests will be provided.

[redacted]





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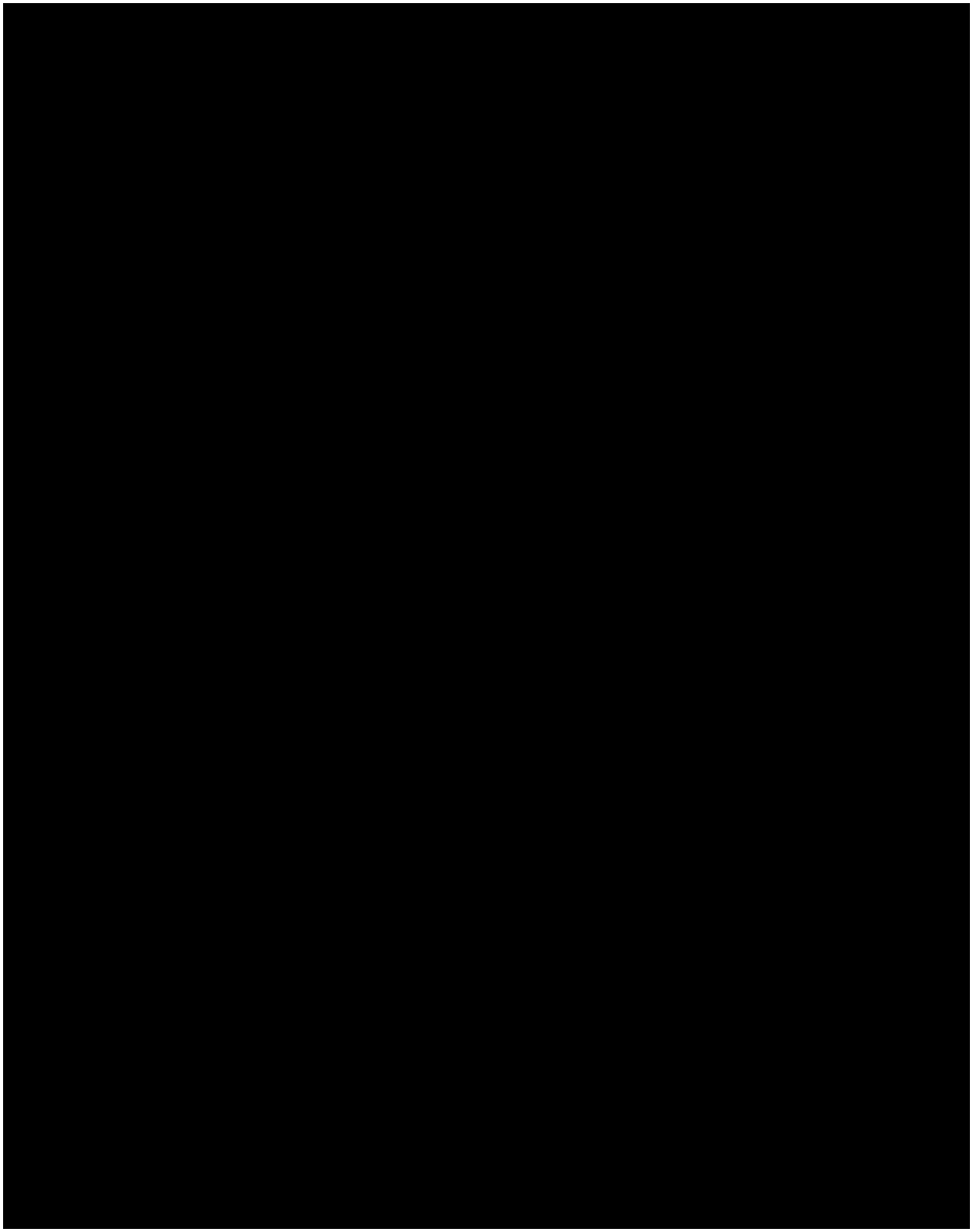

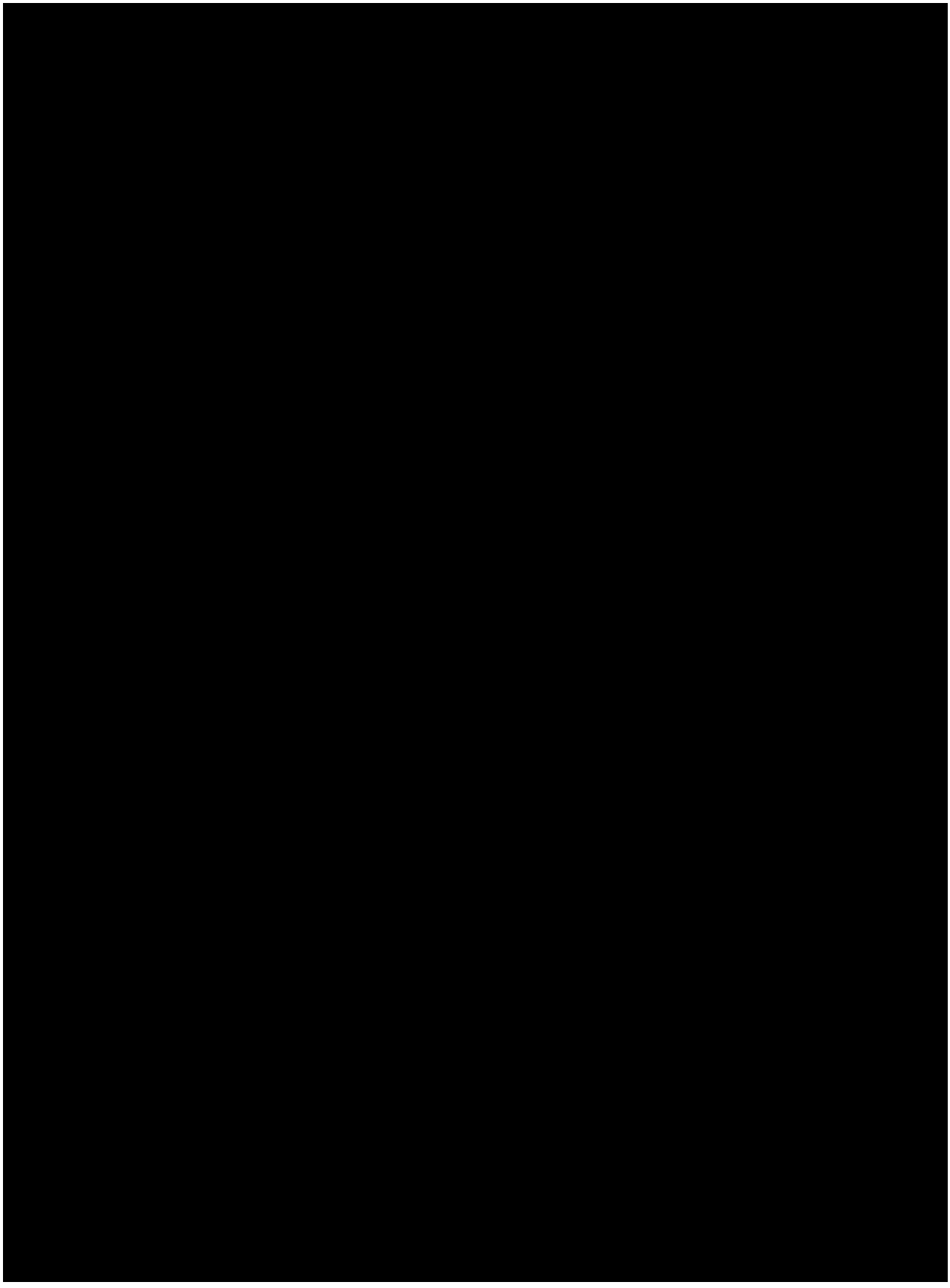

10. HISTORY TABLE

Table 10: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
Initial	**18-AUG-2017**	[redacted]	None	This is the initial TSAP with necessary information for trial conduct
Final	**01-OCT-2018**	[redacted]	All	This is the final TSAP
Revised	**22-AUG-2019**	[redacted]	Sections 4.[redacted]	Updates to Section 4. [redacted]. Description of the interim futility analysis for Part C added in Section 7.4. [redacted]
Revised	**21-DEC-2020**	[redacted]	Sections 4, [redacted] 6.3, [redacted] 7.8.2, [redacted]	Section 4 updated to explain cancellation of Part C planned analyses. [redacted] Section 6.3 updated to clarify the definition of MTD set. [redacted] Section 7.8.2 updated to clarify classification of lab parameters, clinical significance rules and outputs. [redacted]