# TRIAL STATISTICAL ANALYSIS PLAN

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|---|---|
| **Document No.:** | 228892_154372_1.0 |
| **BI Trial No.:** | 1467-0001 |
| **Title:** | An open-label, Phase I dose escalation and expansion trial to investigate safety and efficacy of BI182imput1736 in patients with advanced solid tumors. |
| **Investigational Product(s):** | BI 1821736 |
| **Responsible trial statistician(s):** | [redacted]<br>Phone: [redacted] |
| **Date of statistical analysis plan:** | 07 MARCH 2025 |
| **Version:** | 1.0 |
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# 1. TABLE OF CONTENTS

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# 2. LIST OF ABBREVIATIONS

| Term | Definition / description |
|---|---|
| ADA | Anti-Drug Antibodies |
| AE | Adverse Event |
| AESI | Adverse Event of Special Interest |
| ASTCT | American Society for Transplantation and Cellular Therapy |
| ATC | Anatomical Therapeutic Chemical |
| BLRM | Bayesian Logistic Regression Model |
| BMI | Body Mass Index |
| CDISC | Clinical Data Interchange Standards Consortium |
| CQMM | Clinical Quality Monitoring Meeting |
| CR | Complete Response |
| CRS | Cytokine Release Syndrome |
| CTCAE | Common Terminology Criteria for Adverse Events |
| CTP | Clinical Trial Protocol |
| CTR | Clinical Trial Report |
| DBL | Data Base Lock |
| [redacted] | [redacted] |
| DLT | Dose Limiting Toxicity |
| [redacted] | [redacted] |
| [redacted] | [redacted] |
| ECOG | Eastern Cooperative Oncology Group |
| eCRF | electronic Case Report Form |
| EDMS | Electronic Document Management System |
| ENR | Enrolled Set |
| EOT | End Of Treatment |
| EWOC | Escalation With Overdose Control |
| HR | Heart Rate |
| ICH | International Council for Harmonisation |
| iPD | important Protocol Deviation |
| IV | Intravenous |
| LLOQ | Lower Limit Of Quantification |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MTD | Maximum Tolerable Dose |
| MTDS | Maximum Tolerable Dose Set |
| nAB | Neutralizing Antibody |
| NE | Not Evaluable |
| [redacted] | [redacted] |
| PCR | Polymerase Chain Reaction |
| PK | Pharmacokinetics |
| PR | Partial Response |
| PR | Pulse Rate |
| PT | Preferred Term |

| Term | Definition / description |
|---|---|
| qPCR | quantitative Polymerase Chain Reaction |
| [redacted] | [redacted] |
| [redacted] | [redacted] |
| RECIST | Response Evaluation Criteria In Solid Tumors |
| REP | Residual Effect Period |
| RPM | Report Planning Meeting |
| RP2D | Recommended Phase 2 Dose |
| RR | Relative Rate |
| SD | Stable Disease |
| SD | Standard Deviation |
| SDTM | Study Data Tabulation Model |
| SOC | System Organ Class |
| TMF | Trial Master File |
| TS | Treated Set |
| TSAP | Trial Statistical Analysis Plan |
| ULN | Upper Limit of Normal |
| WHO DD | World Health Organisation Drug Dictionary |

# 3. INTRODUCTION

As per ICH E9 [9.1], 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 will be used for all analyses.*

# 4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

This is the initial version of the TSAP.

This study is currently on a temporary halt. A total of 10 patients have been treated with IV VSV-GP-[redacted] before the temporary halt. There is 1 patient in the study that was a screen failure. This initial TSAP is planned to analyze all these 10 patients.

The following analyses will not be performed by Boehringer Ingelheim:

- MTD/RP2D will not be estimated due to the statistical requirements not being met.
- Further endpoint 'Duration of Response' will not be reported.
- Supplementary analysis specified in Section 7.2.3.3 of the protocol will not be performed.
- [redacted]

The following are the changes in the analyses from what is described in the protocol:

- Further endpoints 'Objective Response' and 'Disease Control' will be reported via a summary table. Due to the lack of data, the rates along with their respective confidence intervals will not be reported.

# 5. ENDPOINTS(S)

## 5.1 PRIMARY ENDPOINT(S)

The primary endpoint of this trial is the occurrence of DLTs during the MTD evaluation period, defined as the first treatment cycle (Cycle 1; 21 days).

The definition of DLTs for patients treated in this study is provided in Section 5.2.7 of the CTP.

The MTD is defined as the highest dose of BI 1821736 with less than 25% risk of the true DLT rate being equal to or above 33% during the MTD evaluation period.

Patients who were replaced during the first treatment cycle will not be considered for MTD determination. Those patients who have completed the first treatment cycle without having been replaced will be referred to as patients evaluable for MTD.

## 5.2 SECONDARY ENDPOINT(S)

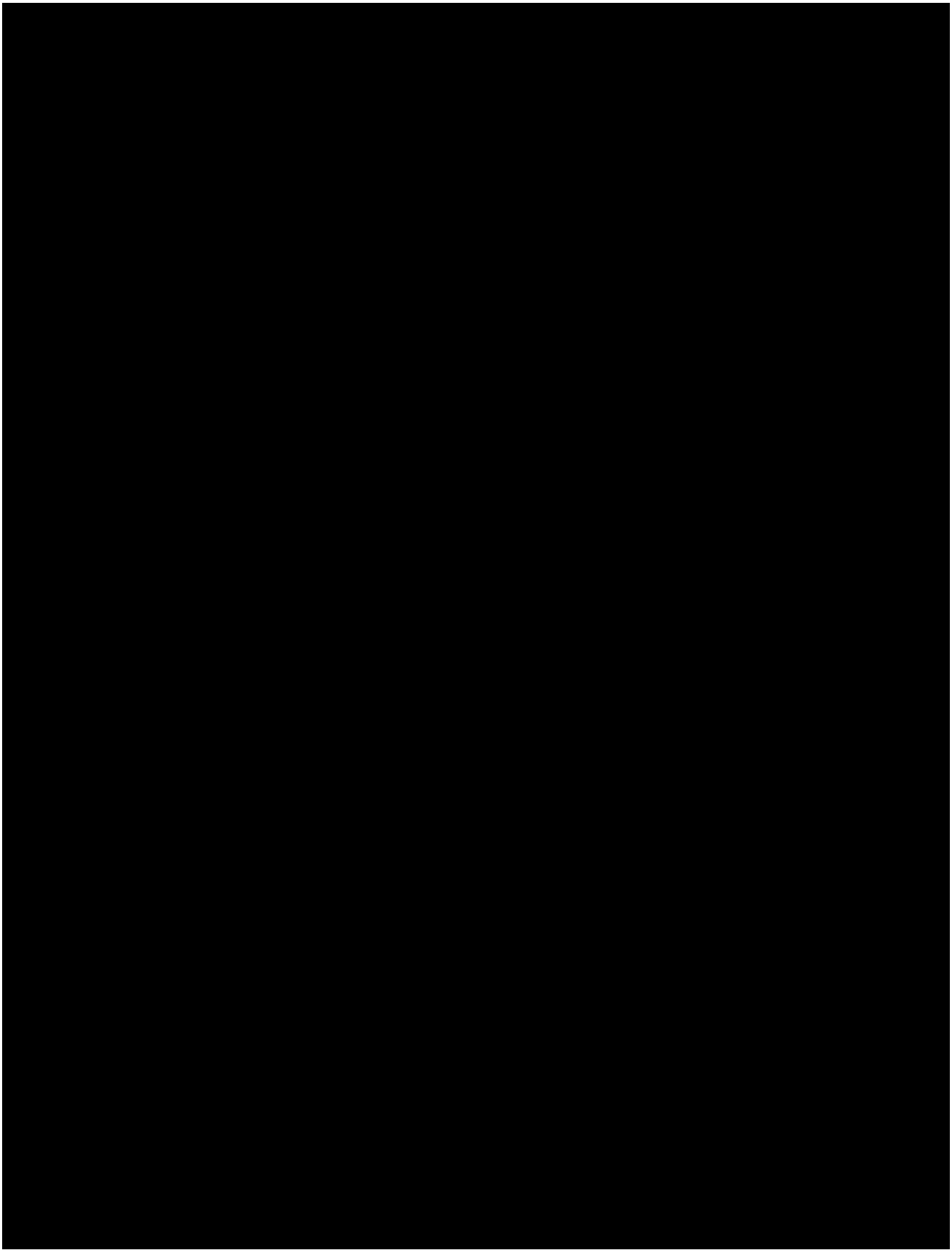
### 5.2.1 Key secondary endpoint(s)

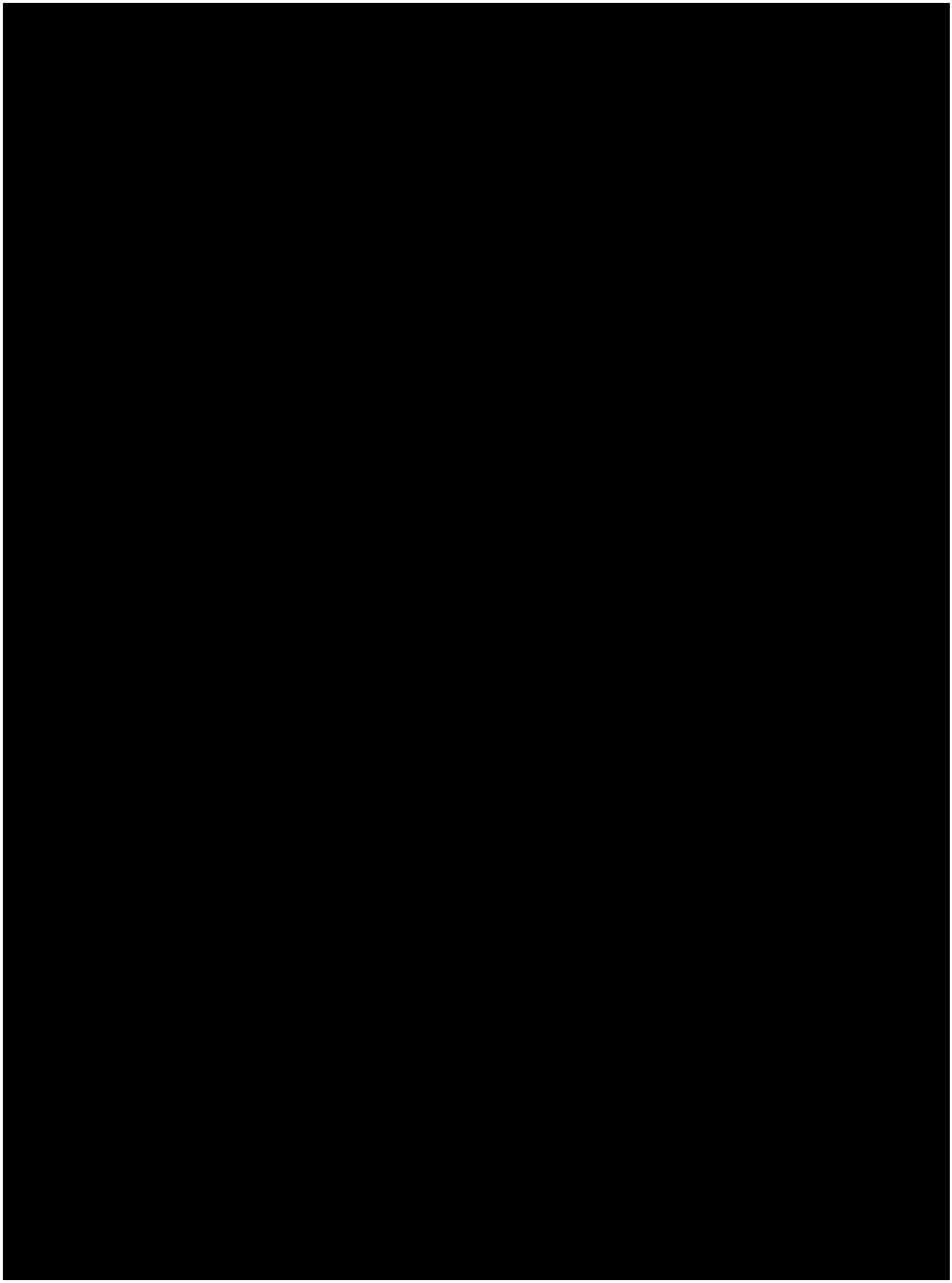
No key secondary endpoints are defined for this study.

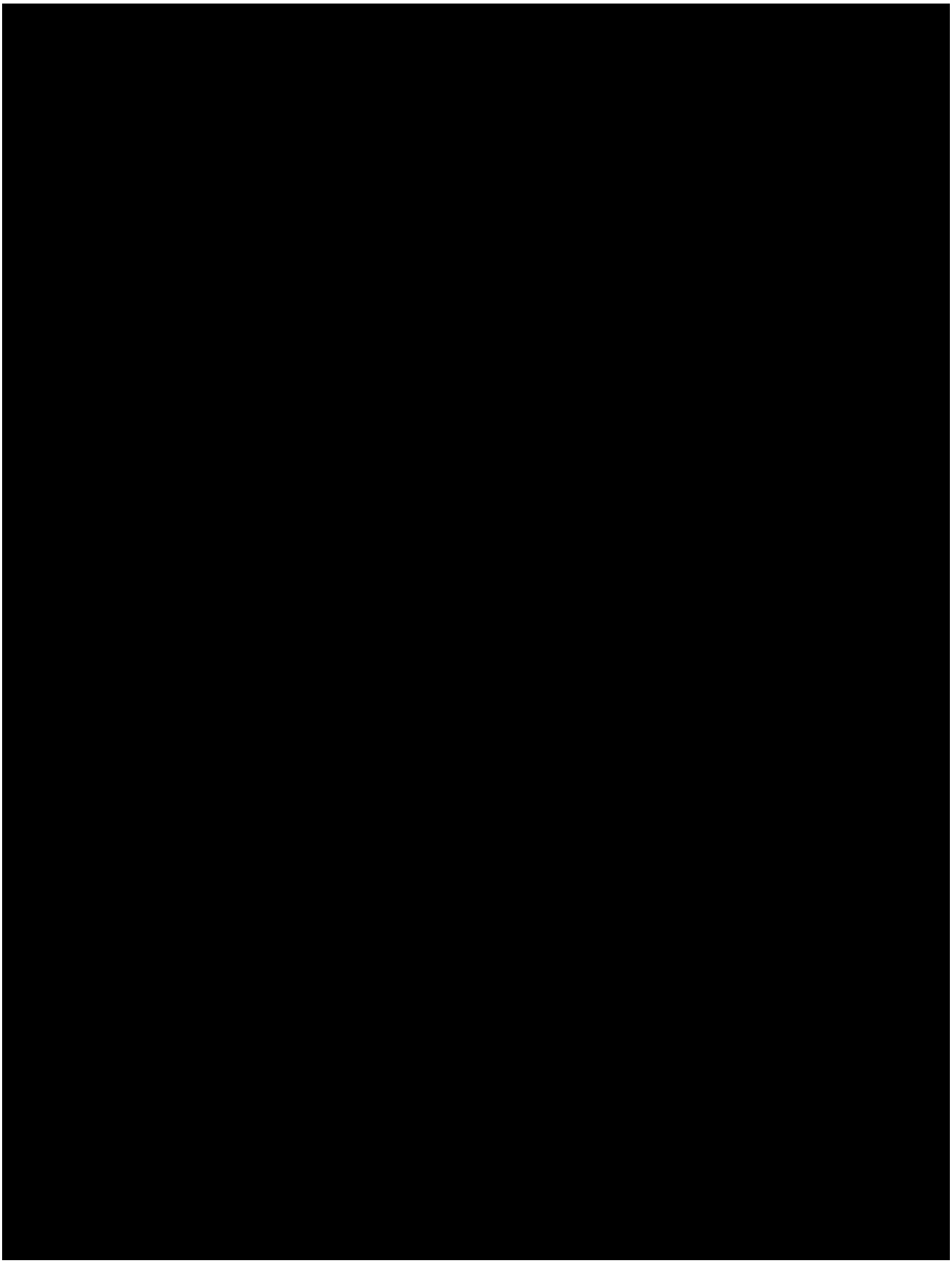
### 5.2.2 Secondary endpoint(s)

- Occurrence of DLTs during the study treatment period.
- Occurrence of AEs during the study treatment period.

Study treatment period is defined as the period between the start of treatment and end of Residual Effect Period (REP) defined as a period of 15 days after the last dose of trial medication.







[redacted]

# 6. GENERAL ANALYSIS DEFINITIONS

## 6.1 TREATMENT(S)

In this trial, treatments are not randomized (open-label, Phase 1 dose escalation). Different dose levels of BI 1821736 are being administered. The starting dose chosen is [redacted] Dose escalation decisions will be made by a Dose Escalation Committee guided by the BLRM with overdose control.

The treatment periods of the trial which will be used for the reporting of AEs and safety laboratory parameters are given in Table 6.1:1. Safety data recorded during the Residual Effect Period (REP) will be considered as on-treatment. In this trial, the REP is defined as 15 days.

Table 6.1: 1 Definition of Treatment Periods

| **Treatment Period** | **Start Date (including)** | **Stop Date (excluding)** |
|---|---|---|
| Screening period | Date of informed consent | Date of first trial medication administration |
| On-treatment period | Date of first trial medication administration | Date of last trial medication administration + REP[1] |
| Follow-up period | Date of last day of on-treatment period | Date of last contact, death or trial completion, or DBL date, whichever comes first + 1 day |
| MTD evaluation period | Date of first administration of BI 1821736 | Date of first administration of BI 1821736 + 21 days |

[1]Note: A 15-day residual effect period (REP) is defined.

## 6.2 IMPORTANT PROTOCOL DEVIATIONS

A protocol deviation is an important protocol deviation (iPD) 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. Handling of iPDs in analyses is included in the DV domain specifications and stored within the TMF in EDMS.

If the data show other iPDs, this table will be supplemented accordingly at Clinical Quality Monitoring Meetings (CQMMs) or Report Planning Meetings (RPMs) or through team review of the manual protocol deviation log. The final list of iPDs will be confirmed before Database Lock (DBL). No per protocol set is defined for this Phase I study, hence no patient will be excluded from the analyses. However, patients with an iPD will be identified and reported in the Clinical Trial Report (CTR).

## 6.3 INTERCURRENT EVENTS

For the endpoint "Occurrence of DLTs during the on-treatment period" the intercurrent events and their handling are the same as specified in Table 7 of Section 7.2.2 of the CTP, except that the MTD evaluation period will be replaced by the on-treatment period.

The expected intercurrent events of interest for this trial are:

- Permanent treatment discontinuation
- Disease progression
- Death
- Breaks from treatment
- Missed visits

## 6.4 SUBJECT SETS ANALYSED

- **Enrolled Set (ENR):**
  This subject set includes all patients who have signed the informed consent form and will be used for patient disposition.
- **Treated Set (TS):**
  This subject set includes all subjects who were dispensed study medication and were documented to have taken at least one dose of investigational treatment. The TS will be used for all safety and efficacy analyses.
- **MTD Evaluation Set (MTDS):**
  This subject set includes all patients in the TS who received both doses of the trial medication in the first treatment cycle and were not replaced for the MTD determination. The MTD evaluation set will be used for the primary analysis of DLTs and MTD determination.
  Rules for replacement of patients are defined in Section 3.3.4.1.1 of the CTP
- [redacted]

[redacted]

## 6.6 BASELINE, TIME WINDOWS AND CALCULATED VISITS

Every effort should be made to collect complete data at each visit for each patient. Missing baseline laboratory values will be imputed by the respective values from the screening visit. If not specified otherwise, missing data will not be imputed and remain missing. Potential outliers will be reported and analysed as observed. No other imputations will be performed on missing data although every effort will be made to obtain complete information on AEs, with particular emphasis on potential DLTs.

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

In general, missing data not discussed in the BI standards will not be imputed unless required for the following analyses and definitions, where the rules 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 treatment) 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 treatment: All reasonable efforts should be undertaken during the study to obtain the dates of permanent discontinuation of study treatment. 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 31$^{st}$ 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 thar is later than the death date, then the imputed date is the date of death.

3) **Partial death dates**

   If a partial death date is reported, then the following imputations will be performed. If the month is missing, then the month will be imputed with the month of January. If the day is missing, then the day will be imputed with day 1 (i.e., the first day of the month).

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 efficacy endpoints or other descriptive statistics:

- For censoring of efficacy endpoints: 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 patients did not have any post-baseline tumor assessment or did not progress or die, the response of this patient will be censored at the day of first administration of the study medication. 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.

## 6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

Study days and visits will be labelled according to the flow charts in the CTP. For nominal time points and windows of tumor imaging, see Table 6.7:1.

Unless specified otherwise, baseline is defined as the time point closest to and prior to the first administration of study treatment. If this criterion is not fulfilled, then no baseline will be derived. Note that for some study procedures (e.g. Eastern Co-operative Oncology Group (ECOG) performance score, body weight, vital signs, laboratory tests) baseline may be the measurement made on the same day the study treatment was started. In such cases, these measurements will be assumed to have been taken according to the protocol, i.e. prior to the first administration of study treatment.

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.

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, a laboratory value on the same date as first study drug administration is considered as baseline value if and only if the time of laboratory value is before or at the same time as the time of first study drug administration. If any of those times are missing and the date of laboratory value is equal to the date of first study drug administration, then the laboratory assessment will be considered as according to protocol, i.e. as prior to first study medication.

Imaging time windows:

Time windows for imaging will not be calculated. All available post-baseline tumor measurements and response assessments will be anlaysed as described in Section 7.6.1.

# 7. PLANNED ANALYSIS

For End-Of-Text (EoT) tables, the set of summary statistics is: N / Mean /Standard Deviation [SD] / Min / Median / Max. Quartiles may be included additionally if considered necessary.

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

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 subjects in the respective subject set whether they have non-missing values or not).

The precision for percentages should be one decimal point, unless the denominator is smaller than 100 (in all treatment columns), in which case percentages are given in integer numbers. The category "missing" will be displayed only if there are actually missing values.

If needed, 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

Only standard descriptive statistics and summary tables are planned for this section of the report.

## 7.2 CONCOMITANT DISEASES AND MEDICATION

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

Concomitant disease and non-drug therapies will be coded using the most current version of Medical Dictionary for Regulatory Activities (MedDRA) at the time of database lock.

Concomitant medications will be coded according to World Health Organization Drug Dictionary (WHO DD). Concomitant medications will be classified according to the Anatomical Therapeutic Chemical (ATC) classification system. The third ATC level will be used to categorize concomitant medications 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 concomitant medications with more than one possible ATC level grade 3 category will be counted more than once. Footnotes will clarify possible double counting in tables.

Summaries will be presented for previous and concomitant medications started before baseline and for concomitant medications started after first administration of the trial medication.

## 7.3 TREATMENT COMPLIANCE

Not applicable in this study.

## 7.4 PRIMARY OBJECTIVE ANALYSIS

### 7.4.1 Main analysis

Due to the temporary hold of this trial, the statistical requirements to estimate the MTD and/or RP2D are not met and hence the primary analysis cannot be conducted.
The number of patients at each dose level with a DLT during the MTD evaluation period will be summarized descriptively using the MTD set.
The BLRM will be run on the available MTD set and the resulting posterior distributions of the DLT rates of doses tested during the trial will be summarized using their mean, SD, 2.5% quantile, median, and 97.5% quantile. Additionally, the posterior probabilities of the DLT rate lying in the intervals [0, 0.16) (underdosing), [0.16, 0.33) (target dosing) and [0.33, 1] (overdosing) will be computed and listed for each dose. The posterior probabilities of underdosing, target dosing and overdosing of the tested dose levels will additionally be visualized in a bar graph that further displays which of the dose levels satisfy the EWOC criterion.

## 7.5 SECONDARY OBJECTIVE ANALYSIS

### 7.5.1 Key secondary objective analysis

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

### 7.5.2 Secondary objective analysis

The analysis of the secondary endpoints occurrence of DLTs and AEs during the on-treatment period is described in Section 7.8.

## 7.7 EXTENT OF EXPOSURE

Standard descriptive statistics over all treatment cycles will be calculated. This will include a summary of the variables defined in Section 5.4.2 and will comprise a mixture of frequency and percentages, as well as summary statistics.

## 7.8 SAFETY ANALYSIS

All safety analyses will be performed on the TS as well as the MTD set.

Patients who were replaced within the MTD evaluation period will be excluded from the safety analysis on the MTD set but will be included in all other safety assessments. Replaced patients will be listed.

### 7.8.1 Adverse Events

Adverse events will be coded using the Medical Dictionary for Drug Regulatory Activities (MedDRA). Standard BI summary tables and listings will be produced. All adverse events with an onset between start of treatment and end of the residual effect period (REP), a period of 15 days after the last dose of trial medication, will be assigned to the on-treatment period for evaluation.
All treated patients will be included in the safety analysis. In general, safety analyses will be descriptive in nature and will be based on BI standards. No hypothesis testing is planned.
Statistical analysis and reporting of adverse events will concentrate on treatment-emergent adverse events. Adverse events that start before first drug intake and deteriorate under treatment will also be considered as ‘treatment-emergent’.

The analyses of AEs will be based on the number of patients with AEs and not on the number of AEs. Frequency of patients with AEs will be tabulated by highest CTCAE grade, primary system organ class (SOC) and preferred term (PT).

Adverse events will be reported with start day and end day calculated relative to the first day of treatment with study medication. The system organ classes (SOCs) will be sorted alphabetically. Preferred terms (PTs) will be sorted by descending frequency of adverse events (within SOC) in the “total” group.
Reporting of CTCAE grades: in general, the categorization “All grades”, “Grade 1”, “Grade 2”, “Grade 3”, “Grade 4” and “Grade 5” will be used.
Cytokine Release Syndrome (CRS) events will be reported based on American Society for Transplantation and Cellular Therapy (ASTCT) consensus grading.

AEs with missing CTCAE grade will be displayed under the category of “All Grades”. No “Missing Grade” category will be displayed. If applicable, a footnote will be added to explain that the “Grade 1”, “Grade 2”, “Grade 3”, “Grade 4” and “Grade 5” categories might not add up to the “all Grades” category.

An overall summary of AEs will be presented.

Frequency tables will be provided for patients with:

- AEs
- DLTs
- Drug-related AEs
- Serious AEs
- Drug-related serious AEs
- AEs leading to death
- AEs leading to permanent discontinuation of the trial medication
- Immune-related AEs
- Infusions-related AEs
- AESIs
- Procedural complications (biopsy/injection) AEs
- Cytokine Release Syndrome (CRS)

All deaths during the entire trial period will be listed by primary cause of death (death due to disease or AE of underlying cancer disease, death due to unknown cause, death due to other reason). Duration in days from last administration of study drug till death will also be included in the listings.

### 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 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 the CTCAE grading is applicable. CTCAE grades for applicable laboratory parameters will be calculated according to CTCAE Version 5.0.

The laboratory tests will be classified into the following categories:

- Primary
- Secondary
- Not analysed

The classification, direction of interest and potential clinical significance rule for a laboratory test are detailed in Section 10.1 of the TSAP.

The following outputs will be presented for primary laboratory tests:

- Descriptive statistics of normalized value for baseline, minimum value on treatment, maximum value on treatment and last value on treatment, and their changes from baseline.
- Transitions of CTCAE grade from baseline to last value on treatment, from baseline to worst value on treatment, and from worst value to last value on treatment for

laboratory parameters with CTCAE grading. In addition, the worst CTCAE grade per laboratory parameter will be displayed.

- Transitions relative to reference ranges from baseline to last value on treatment, from baseline to worst value on treatment, and from worst value to last value on treatment for laboratory parameters with no CTCAE grading defined.
- Transitions relative to following multiples of upper limit of normal (ULN) from baseline to last value on treatment, from baseline to worst value on treatment, and from worst value to last value on treatment for ALT, AST, bilirubin, and creatine:
  - ALT and AST: ≤ULN, >1 – 3×ULN, >3 – 5×ULN, >5 – 20×ULN, >20×ULN
  - Bilirubin: ≤ULN, >1 – 1.5×ULN, >1.5 – 3×ULN, >3 – 10×ULN, >10×ULN
  - Alkaline phosphatase: ≤ULN, >1 – 2.5×ULN, >2.5 – 5×ULN, >5 – 20×ULN, >20×ULN
  - Creatinine: ≤ULN, >1 – 1.5×ULN, >1.5 – 3×ULN, >3 – 6×ULN, >6×ULN

  Transition tables for these lab parameters will not be based on CTCAE version 5.0 because the grading rules depend on baseline value.
- Frequency of patients with possible clinically significant abnormalities.

The analyses of secondary laboratory tests will be limited to tabulation of the frequency of patients with possible clinically significant abnormalities.

Liver function tests, potential sever drug-induced liver injury (DILI) and potential Hy's Law

The frequencies of patients falling into the following categories will be explored:

- Maximum ALT / AST:
  - > ULN - 3×ULN
  - > 3 - 5×ULN
  - > 5 - 10×ULN
  - > 10 - 20×ULN
  - > 20×ULN
- Maximum total bilirubin:
  - > ULN - 1.5×ULN
  - > 1.5 - 3×ULN
  - > 3×ULN - 10×ULN
  - > 10×ULN
- Maximum ALKP:
  - > ULN - 2.5×ULN
  - > 2.5 - 5×ULN
  - > 5 - 20×ULN
- ALT and/or AST ≥3×ULN and total bilirubin ≥2×ULN measured at the same time.

Where applicable for defining the above, events can occur in any order but must occur within 30 days of each other with an increase of either ALT or AST being the trigger for evaluations.

Along with the summaries of the above, eDISH plots of maximum ALT versus total bilirubin and maximum AST versus total bilirubin (maximum within 30 days after maximum ALT / AST elevation) will be produced.

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 in the case for laboratory parameters without CTCAE grade definitions will be done.

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:

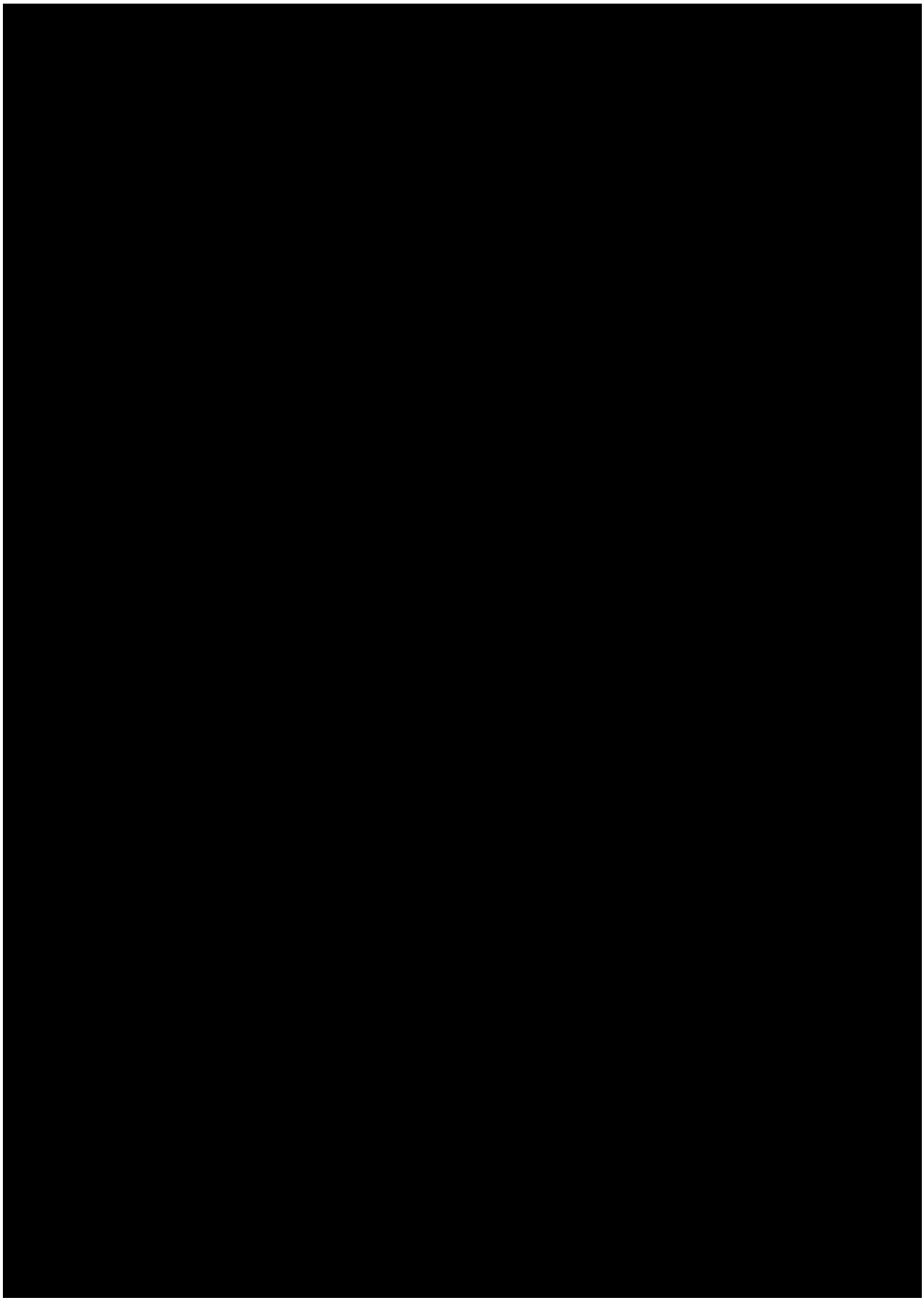
Corrected calcium [mmol/L] = Total calcium [mmol/L] + 0.02 × (40g/L - Albumin [g/L])

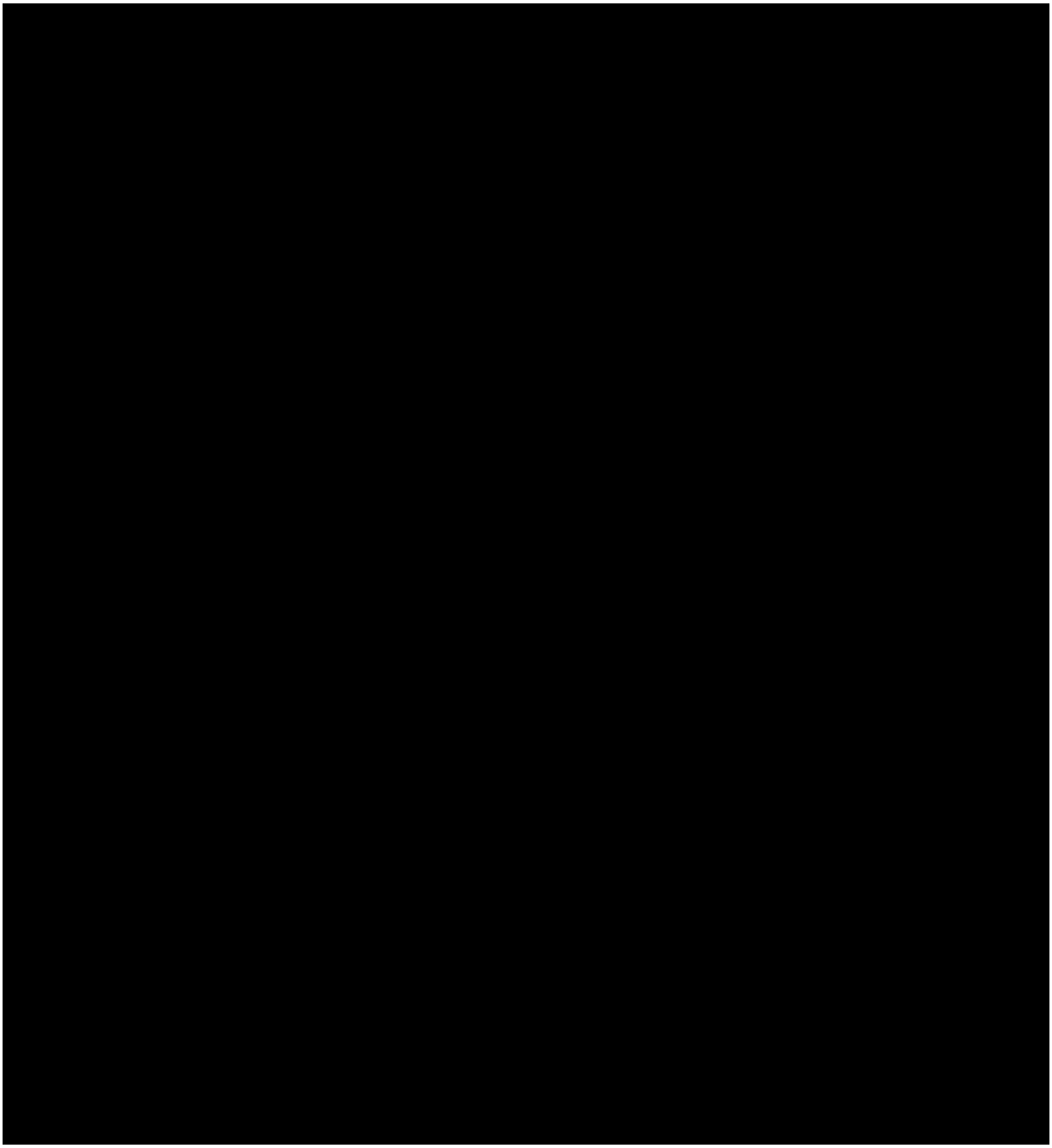
No correction of the reference range has to be made. The reported reference range of total calcium will be used for analyses.

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.

### 7.8.3 Vital signs

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



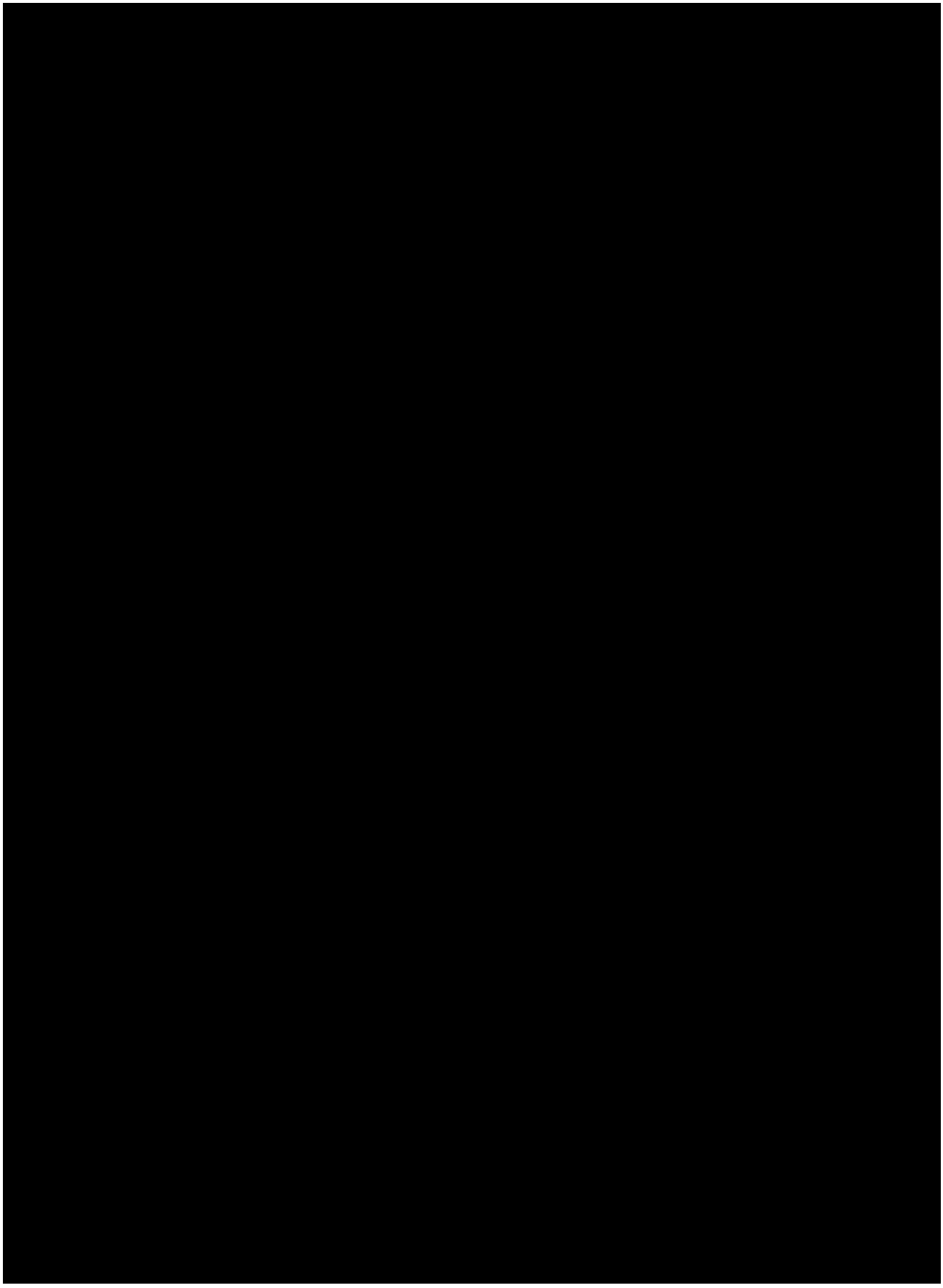


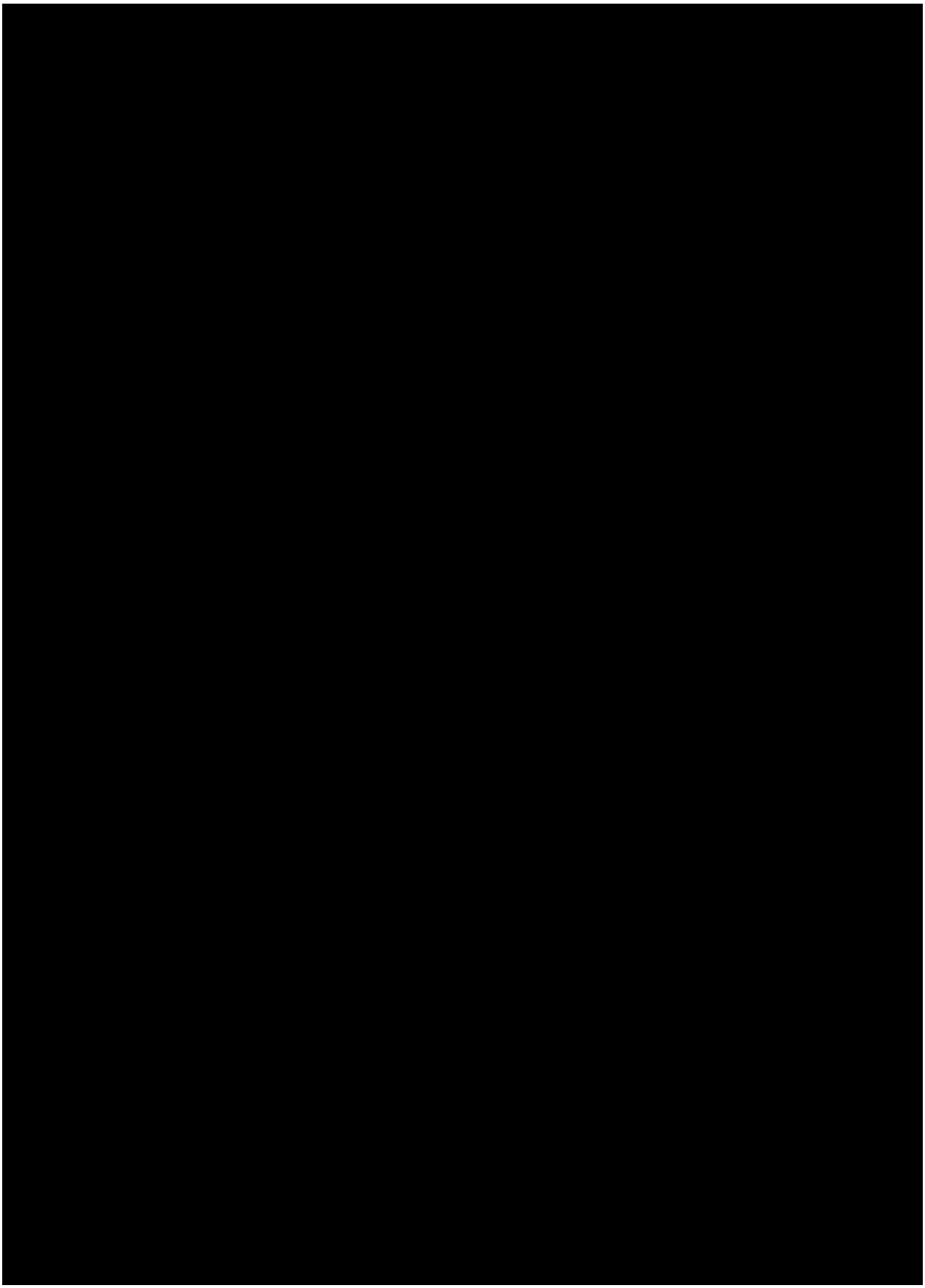
# 8. TIMEPOINT OF RELEASE OF TREATMENT INFORMATION

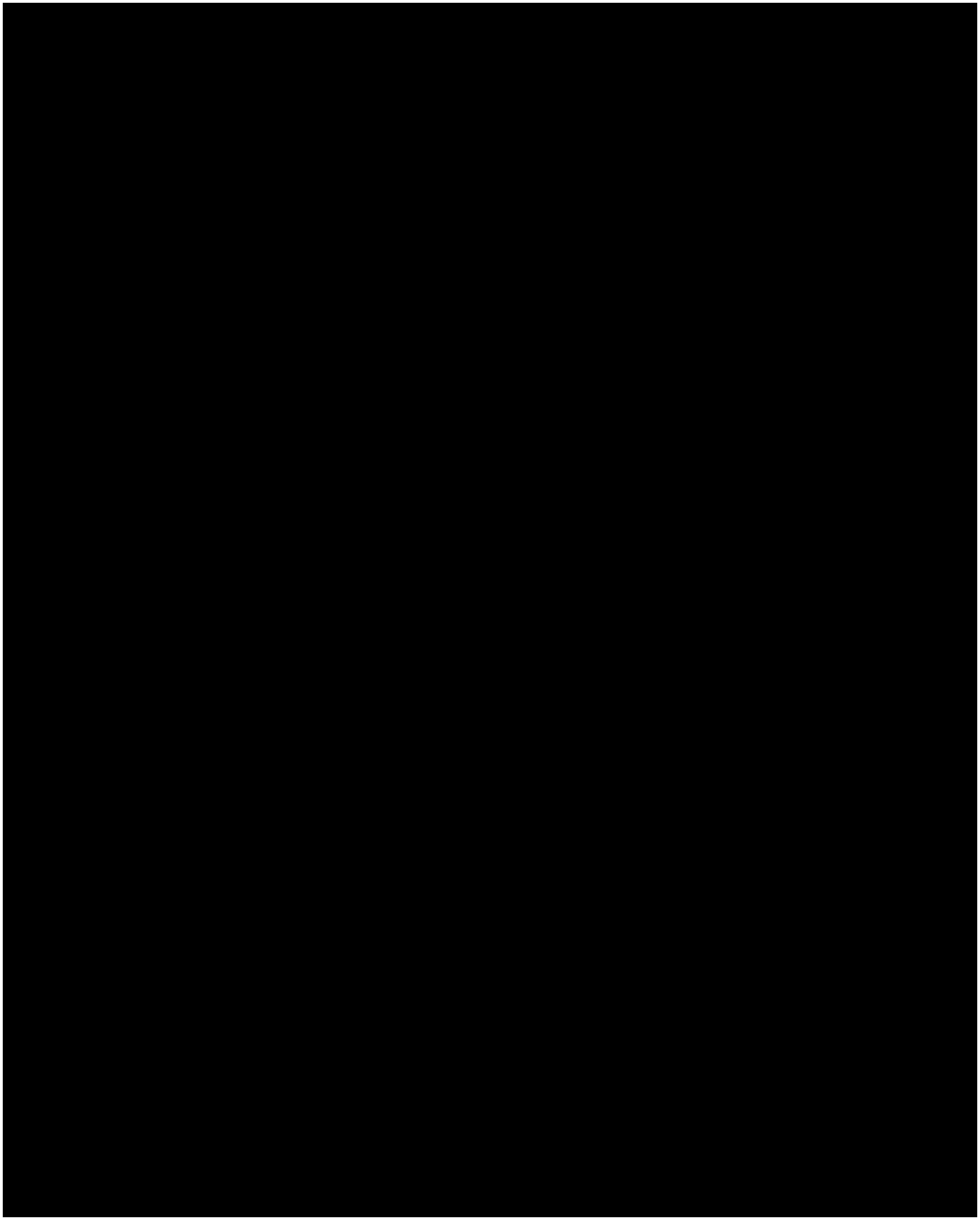
This is an open-label non-randomized Phase 1 trial. Treatment information is readily available in the eCRF and SDTM database.

# 9. REFERENCES


| | |
|---|---|
| 9.1 | *CPMP/ICH/363/96:* "Statistical Principles for Clinical Trials", ICH Guideline Topic E9, Note For Guidance on Statistical Principles for Clinical Trials, current version |







# 11. HISTORY TABLE

Table 11: 1 History table

| Version | Date (DD-MMM-YY) | Author | Sections changed | Brief description of change |
|---|---|---|---|---|
| 1.0 | **24-Feb-2025** | [redacted] | None | This is the final SAP. |