TRIAL STATISTICAL ANALYSIS PLAN

c40575634-01

BI Trial No.:	1412-0003
Title:	A phase Ia/b, open label, multicentre, dose escalation study of BI 905711 in combination with chemo-therapy followed by expansion cohorts in patients with advanced gastrointestinal cancers
Investigational Product(s):	BI 905711
Responsible trial statistician(s):	[redacted] Phone: [redacted]
Date of statistical analysis plan:	05 JAN 2024 the date (DD MMM YYYY) for SIGNED/REVISED must be the date when the TSAP is sent for approval in the EDMS
Version:	"Final"

1. TABLE OF CONTENTS

LIST OF TABLES

2. LIST OF ABBREVIATIONS

Term	Definition / description
AE	Adverse Event
ADA	Anti-Drug Antibodies
RPM	Report Planning Meeting
BLRM	Bayesian Logistic Regression Model
CRC	Colon Rectal Cancer
CTC	Common Terminology Criteria
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
DM&SM	Boehringer Ingelheim Data Management And Statistics Manual
DRA	Drug Regulatory Affairs
DLT	Dose Limiting Toxicities
DMG	Dictionary Maintenance Group
EDC	Electronic Data Capture
EMEA	European Agency For The Evaluation Of Medicinal Products
FAS	Full Analysis Set
ICH	International Conference On Harmonization
LOCF	Last Observation Carried Forward
MedDRA	Medical Dictionary For Regulatory Activities
MQRM	Medical Quality Review Meeting
PD	Protocol Deviation
PDAC	Pancreatic ductal adenocarcinoma
PK	Pharmacokinetics
PPS	Per Protocol Set
PSTAT	Project Statistician
PT	Preferred Term
Q1	Lower Quartile
Q3	Upper Quartile
SA	Statistical Analysis
SD	Standard Deviation
SMQ	Standardised MedDRA Query

Term	Definition / description
SOC	System Organ Class
TCM	Trial Clinical Monitor
TESS	Treatment Emergent Signs And Symptoms
ToC	Table of Contents
TMW	Trial Medical Writer
TSAP	Trial Statistical Analysis Plan

3. INTRODUCTION

As per ICH E9, 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 later version) will be used for all analyses including immunogenicity assessment.

For PK the following applies: Pharmacokinetic (PK) parameters will be calculated using Phoenix WinNonlin™ software (version 8.1 or higher, [redacted]) or SAS Version 9.4 (or later version).

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

This section is not applicable as this is the first version of the TSAP. This TSAP reflects all amendments in CTP up to and including Amendment 4.

As of March 2023 the study was terminated due to lack of efficacy signal and it was decided to produce an abbreviated report for CTR. The abbreviated CTR will include primary and secondary endpoint analyses. There will be limited analyses provided for PK and biomarkers as detailed in section 7.5.1.2 and section 7.6.

5. ENDPOINTS

5.1 PRIMARY ENDPOINT(S)

The primary endpoints in Phase Ia are:

- Maximum tolerated dose (MTD) defined as the highest dose with less than 25% risk of the true DLT rate being equal or above 33% during the MTD evaluation period as determined by the BLRM defined in section 7 of the CTP. For the definition of DLTs, refer to Section 5.2.7 of the CTP.
- Number of patients with DLTs in the MTD evaluation period.

The MTD evaluation period is defined as a two 14-day treatment cycle from cycle 1 Day 1 until the day before cycle 3 Day 1, or end of the REP (30 days + 5 days) in case of discontinuation before start of cycle 3.

The primary endpoints in Phase Ib are:

- Confirmed objective response (OR) as assessed by the investigator based on Response Evaluation Criteria in Solid Tumors (RECIST 1.1) in patients with measurable disease, defined as the best overall response of complete response (CR) or partial response (PR), from the first administration of trial treatment until the earliest of progressive disease (PD), death or last evaluable tumor assessment before start of subsequent anti-cancer therapy.
- In safety run-in part of PDAC cohort: number of patients with DLTs during the MTD evaluation period assessed in the first 6 patients.

5.2 SECONDARY ENDPOINT(S)

5.2.1 Key secondary endpoint(s)

No key secondary endpoint is defined for this study.

5.2.2 Secondary endpoint(s)

The secondary endpoints in Phase Ia:

The following PK parameters will be calculated after study treatment administration, as measured during the first cycle and after multiple cycles:

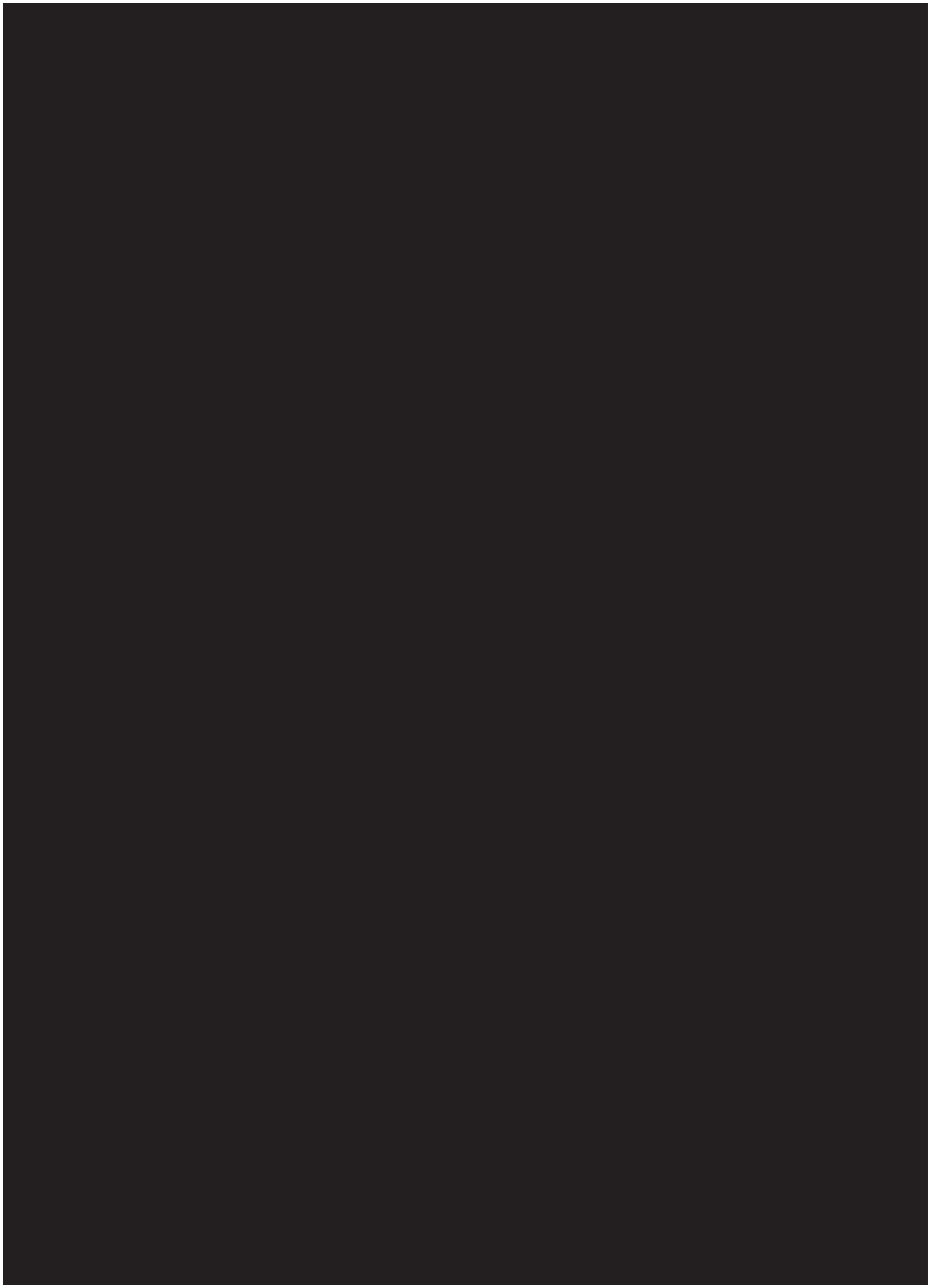
- C_{max}: Maximum measured plasma concentration of BI 905711.
- AUC_{0-t2}: Area under the concentration-time curve in plasma of BI 905711

The secondary endpoints in Phase Ib:

- Progression-Free Survival (PFS) defined from date of start of treatment to the date of disease progression or death, whichever is earlier as assessed by the investigator according to RECIST 1.1.
- Radiological (CT Scan) tumor shrinkage, defined as the difference between the minimum post-baseline sum of longest diameters of target lesions and the baseline sum of longest diameters of the same set of target lesions according to RECIST 1.1.
- The duration of OR is measured from the time measurement criteria are first met for CR/PR (whichever is first recorded) until the first date that recurrent or PD is objectively documented (taking as reference for PD the smallest measurements recorded on study) according to RECIST 1.1.
- Disease control, defined as CR, PR, or stable disease (SD) lasting at least 16 weeks according to RECIST 1.1 from the start of treatment until the earliest of PD, death or last evaluable tumor assessment and before start of subsequent anti-cancer therapy.
- The following PK parameters will be calculated after study treatment administration, as measured during the first cycle and after multiple cycles:
  - C_{max}: Maximum measured plasma concentration of BI 905711 in plasma.
  - AUC_{0-t2}: Area under the concentration-time curve for BI 905711 in plasma.

A detailed definition of objective response and PFS is given in appendix 10.1.

[redacted]



6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENT(S)

This is a phase Ia/b, open label, multicentre, dose escalation study of BI 905711 in combination with chemotherapy (with or without bevacizumab) followed by expansion cohorts in patients with advanced or metastatic CRC and PDAC. The study will consist of two phases: a dose-escalation phase (Phase Ia) and a dose-expansion phase (Phase Ib). For the main analysis the phase Ia and phase Ib data will be pooled together.

In phase Ia, CRC patients will be administered BI 905711 + FOLFIRI + Bevacizumab biweekly with 20 planned patients. In phase Ib dose expansion, CRC patients will be randomized into two cohorts in a 2:1 ratio. Patients in cohort 1 (arm A with 40 planned patients) will be administered BI 905711 + FOLFIRI + Bevacizumab and patients in cohort 2 (arm B with 20 planned patients) will be administered FOLFIRI + Bevacizumab only. In addition there will be a separate single arm cohort with patients 2nd line PDAC that will be administered BI 905711 + FOLFIRI (or Liposomal Irinotecan + 5-FU/Leucovorin) with 20 planned patients.

The following "analyzing treatment" (Table 6.1:1) will be used for reporting treatment emergent adverse events (AEs) and safety laboratory variables and the timeline criteria "start date ≤ onset date of AE < stop date" will be used to determine if an AE will be assigned to be "analyzing treatment" or not. Detailed rule for assigning AEs to these time periods are listed below:

- If the date of informed consent ≤ AE onset date < date/time of the first administration of BI 905711, then the AE is assigned to "Screening";
- If the date/time of the first administration of BI 905711 ≤ AE onset date < min{date of the late administration of BI 905711 + 35 days, DBL date}, then the AE is assigned to "On-treatment";
- If AE onset date ≥ date of the last administration of BI 905711 + 35 days, then the AE is assigned to "Follow-up".

AEs that have onset date during the screening or follow-up periods will be displayed in separate subject listings from those occurred during the on-treatment period. For the on-treatment and follow-up periods, AE frequency tabulations will contain a "total" column, representing all doses of BI 905711. Subject data listings of AEs will not have a "total" column. To justify the MTD determination, DLTs occurring during the MTD evaluation period and the entire on-treatment period will be displayed separately.

Table 6.1:1 Analyzing Treatments

Analyzing Treatment Period	Start Date (including)	Stop Date (excluding)
Screening	Date of informed consent	Date of the first administration of BI 905711 or chemotherapy whichever comes first
On-treatment	Date of the first administration of BI 905711 or chemotherapy whichever comes first	Date of the last administration of BI905711 + 35 days (for discontinued patients); or DBL date (for on-going patients)
Follow-up	Date of the last administration of BI 905711 + 35 days Note: on-going patients do not have follow-up periods	Date of the last per protocol visit or DBL date, whichever comes first
MTD evaluation period	Date of the first administration of BI 905711	Date of the second administration of study BI 905711 + 29 days; or DBL date; or the start date of the third treatment cycle, whichever is earlier

Note: a 35-day residual effect period is defined for this study. DBL = database lock. 29 days is from the criteria of DLT since any drug-related AE that causes a > 28 days of drug free interval is a DLT.

The actual treatment codes and decodes, the labels for the analyzing treatment, and the analysis numbers are defined in the technical TSAP document of ADS Plan and Data Guide and stored in the same location with this document in Boehringer Ingelheim Regulatory Documents for Submission (BIRDS).

6.2 IMPORTANT PROTOCOL DEVIATIONS

According to (5), important safety protocol deviations (PDs) are those that potentially affect the rights or safety of study subjects. Important PDs (IPDs) are those that can potentially influence the primary outcome measure(s) for the respective patients in a way that is neither negligible nor in accordance with the study objectives.

Handling of iPDs in analysis is included in the DV domain specifications and stored within the trial master file (TMF) in the electronic document management system (EDMS). The final list of iPDs will be confirmed at the last report planning meeting (RPM) before the database

lock for the primary analysis of the primary endpoint (based on blinded central independent review).

Important PDs will be documented in the DV template domain with input from clinical. The DV template domain will then be sent to data management that will convert to a data base for analysis.

6.3 SUBJECT SETS ANALYSED

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

- Treated set (TS): This includes all subjects who were dispensed study medication and were documented to have been treated with at least one dose of BI 905711 or chemotherapy. This TS is used for both safety and efficacy analyses.

- MTD evaluation set (MTDS): This includes all patients in the TS who were not replaced for the MTD determination. The MTDS is used for the primary analyses of DLTs and MTD determination. Rules for replacement of patients are defined in the CTP Section 3.3.4.1.1. The list of replaced patients will be provided by the Trial Clinical Monitor no later than the last RPM and should be documented in the RPM minutes.

- Pharmacokinetic parameter analysis set (PKS): This includes all subjects in the treated set (TS) who provide at least one PK endpoint and was not excluded due to a protocol deviation relevant to the evaluation of PK or due to PK non-evaluability (as specified in the following subsection Pharmacokinetics). Descriptive and potential model based analyses of PK parameters will be based on the PKS.

6.5 POOLING OF CENTRES

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

6.6 HANDLING OF MISSING DATA AND OUTLIERS

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

Missing or incomplete AE dates are imputed according to BI standards in (3) (see “Handling of missing and incomplete AE dates”).

Missing data and outliers of PK data are handled according to BI standards. PK parameters that cannot be reasonably calculated based on the available drug concentration-time data will not be imputed.

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

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

Unless otherwise specified, baseline is defined as the time point closest to and prior to the first administration of any study treatment of either BI 905711 or chemotherapy. Note that for some study procedures (e.g. body weight, vital signs, laboratory tests), baseline may be the measurement made on the same day the study treatment was started. In such cases, these measurements will be assumed to have been taken according to the protocol, i.e. prior the first administration of BI 905711.

For laboratory parameters for which not only the examination date but also the sampling time was recorded, examination time should be taken into consideration when defining baseline. That is a laboratory measurement on the same date as the first administration of BI 905711 is considered as baseline if and only if the examination time of the laboratory measurement is before the first administration of BI 905711.

7. PLANNED ANALYSIS

The following standards for End-Of-Text tables are defined:

- The set of summary statistics for continuous data 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, standard deviation, minimum, and maximum. If not otherwise specified, the abbreviation Pxx should be used for displaying the xx^{th} percentile. Other than the Min and Max, all statistics will be presented to one more decimal place than the raw data.

- 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). The precision for percentages will be one decimal place. The category "missing" will be displayed only if there are actually missing values.

- 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 25th percentile (P25), median, 75th percentile (P75) and number of patients censored [N(%)]. If not specified otherwise the duration as well as the time to event will be displayed in months.

Where 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.

General aspects for PK

Descriptive data analysis of PK endpoints and concentrations will be performed according to BI procedures.

Plasma concentration data and parameters of a subject will be included in the statistical pharmacokinetic (PK) analyses if they are not flagged for exclusion due to a protocol deviation relevant to the evaluation of PK (to be decided no later than in the Report Planning Meeting) or due to PK non-evaluability (as revealed during data analysis, based on the criteria specified below). Exclusion of a subject's data will be documented in the CTR.

Important protocol deviations may be

- Incorrect trial medication taken, i.e. the subject received at least one dose of trial medication the subject was not assigned to
- Incorrect dose of trial medication taken
- Use of restricted medications

Plasma concentrations and/or parameters of a subject will be considered as non-evaluable, if for example.

- Missing samples/concentration data at important phases of PK disposition curve.

Plasma concentration data and parameters of a subject which are flagged for exclusion will be reported with its individual values but will not be included in the statistical analyses. Only concentration values within the validated concentration range and actual sampling times will be used for the calculation of pharmacokinetic parameters. Concentrations used in the pharmacokinetic calculations will be in the same format as in the bioanalytical report (that is to the same number of decimal places provided in the bioanalytical report).

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

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

7.2 CONCOMITANT DISEASES AND MEDICATION

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

Concomitant diseases will be coded using the most current version of Medical Dictionary for Regulatory Activities (MedDRA).

Concomitant medications will be coded using the most current version of 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 therapies 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 3 category will be counted more than once. Explanatory footnotes will clarify the possible double counting.

Separate summaries of concomitant medications started prior to and after first administration of trial medication will be produced.

7.3 TREATMENT COMPLIANCE

Only descriptive statistics on the treated set are planned for this section of the CTR. The actual dose versus the planned dose for infusion drug administration for each patient will be listed.

7.4 PRIMARY OBJECTIVE ANALYSIS

This trial will be performed as an open label.

7.4.1 Main analysis

The primary objective in phase Ia is to determine the MTD and the recommended dose for expansion (RDE) of BI 905711 in combination with FOLFIRI plus bevacizumab. MTD is defined as the highest dose with less than 25% risk of the true DLT rate being equal or above 0.33 (EWOC criterion). Dose-escalation for each group will be guided by a two-parameter Bayesian Logistic Regression Model (BLRM), escalating with overdose control (EWOC).

In phase Ia, in order to identify the MTD of the trial, the number of patients at each dose level that had DLT during the MTD evaluation period will be presented, excluding patients who discontinue during the first treatment cycle for reasons other than a DLT. The BLRM as described in Section 7.2.3 of the CTP will be analyzed using the number of patients at each dose that had DLTs during the MTD evaluation period among the patients in the MTD set. The prior defined in Table 7.2.3: 2 of the CTP will be used for the analysis. The resulting posterior distribution of the DLT rates of the 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) (under dosing), [0.16, 0.33) (target dosing), and [0.33, 1] (overdosing) will be computed and listed for each dose. The posterior probabilities of under dosing, target dosing, and overdosing of the tested dose levels will additionally be visualized in a bar diagram that further displays which of the dose levels satisfy the EWOC criterion. In addition, the number of patients with DLTs that occurred during the entire treatment period will be summarized at each dose level.

In phase Ib the objective response will be analyzed in terms of objective response rate (ORR), defined as the proportion of patients with best overall response of complete response (CR) or partial response (PR). For each dose level, the proportion of patients with objective response (CR and PR) will be calculated with 95% confidence interval.

The primary endpoints in the dose-expansion part are objective response (OR).

7.4.4 Supplementary analysis

Not applicable.

7.5 SECONDARY OBJECTIVE ANALYSIS

7.5.1 Key secondary objective analysis

There is no key secondary analysis as no key secondary endpoint has been specified in the protocol.

7.5.1.1 Main analysis

Not applicable.

7.5.1.4 Supplementary analysis

Not applicable.

7.5.2 Secondary objective analysis

Descriptive analysis of the following pharmacokinetic parameters will be performed for BI 905711 in phase Ia and phase Ib as outlined in section 7.2.5 in CTP and according to BI standards if applicable and feasible

- C_{max} : maximum measured concentration of BI 905711 in plasma
- $AUC_{0\text{-}t2}$: area under the concentration-time curve of BI 905711 in plasma

These parameters will be calculated after study treatment administration, as measured during the first cycle and after multiple cycles.

Other secondary endpoints in phase Ib include PFS, radiological (CT scan) tumor shrinkage, duration of OR and disease control and rate.

Kaplan-Meier estimates will be used to display the distribution of PFS for each treatment group on a Kaplan-Meier curve. To support the plot, estimated survival probabilities at specific time points of interest (scheduled imaging time points) will be tabulated along with 95% CIs using Greenwood's variance estimate. In addition, the Kaplan-Meier estimates will be used to provide estimates of the median, 25^{th}, and 75^{th} percentiles.

Duration of overall response and disease control will be analyzed by descriptive statistics. Disease control rate will be analyzed the same way as ORR. Tumor shrinkage will be analyzed by descriptive statistics and by treatment. Waterfall and spider plots will be provided.

For the abbreviated report there will be limited analyses provided from statistics and programming for PK and this will only include specific checks of PK data. The PK group (TMCP) will provide analyses for Cmax and AUC.

7.6 FURTHER OBJECTIVE ANALYSIS

PK and PD parameters will be analyzed by descriptive statistics and using standard methods. The Number of patients with treatment emergent AEs will be analyzed by descriptive

statistics. The analysis of OS will use the same methods as secondary endpoint PFS in Phase Ib.

ADA

ADA will be analyzed descriptively. A potential effect of ADA on PK, PD, safety and efficacy may be evaluated.

The abbreviated report will include listing of ADA titer. The PK group (TMCP) will provide analyses for ADA titer.

For the abbreviated report there will be no analysis of PRO data and PRO-CTCAE questionnaires.

Additional exploratory analyses of biomarker may be performed on the CDH17 expression as follows.

- Protein expression (IHC) levels for CDH17 compared to PFS (CRC)
- Gene expression levels for CDH17 and TRAILR2 compared to PFS (CRC)
- Protein expression (IHC) levels for CDH17 compared to cCasp (CRC)
- Gene expression levels for CDH17 and TRAILR2 compared to cCasp (CRC)
- Correlation between cCasp activity and PFS.

As of March 2023, the study was terminated due to lack of efficacy signal and it was decided to produce an abbreviated CTR. The abbreviated CTR would include a limited amount of biomarker outputs.

7.7 EXTENT OF EXPOSURE

Treatment exposure will be primarily summarized by the total on-treatment time and has been defined in section 5.4.2 of this TSAP.

7.8 SAFETY ANALYSIS

All safety analyses will be performed on the treated set.

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 35 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, i.e. all adverse events occurring between start of treatment and end of the residual effect period. Adverse events that start before first drug intake and deteriorate under treatment will also be considered as 'treatment-emergent.'

The analyses of adverse events (AE) will be descriptive in nature. All analyses of AEs will be based on the number of patients with AEs and not on the number of AEs. Frequency of patients with AEs will be tabulated by treatment dose, highest CTCAE grade, system organ class (SoC) and preferred term after coding according to the current version of MedDRA at the database lock. In addition, AEs will be tabulated by preferred terms only. The SoC will be sorted alphabetically. In tables displaying AEs by preferred terms, this will be sorted by descending frequency of AEs in the "Total" BI 905711 group.

Summary tables and listings of AEs, SAEs, related AEs, related SAEs, AEs of special interest, AEs leading to dose reduction, AEs leading to treatment discontinuation and AEs leading to deaths will be provided. In addition the number of DLTs in the MTD period and during the study will be provided.

7.8.2 Laboratory data

The analysis of laboratory data will be descriptively in nature and will follow standard procedures. The analysis of laboratory data will use the same "analyzing treatments" as described for AEs, except for that the baseline laboratory values will be included in the "on treatment" period. 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 value will be displayed in the category "Missing CTCAE grade at baseline".
Descriptive statistics, including change from baseline, frequency of patients with transitions relative to the references range, will be provided for laboratory assessments at scheduled visits. Data collected during potential unscheduled laboratory assessments will be listed. No post-study laboratory values will be considered. CTCAE grade for applicable laboratory parameters will be calculated according to CTCAE v5.0. The following outputs will be presented:

- Baseline, last value and difference from baseline
- Worst CTCAE grade experienced during the on-treatment period
- Transitions of the CTCAE grade from baseline to the worst lab values, from baseline to the last lab values, and from the worst to last values during the on-treatment period
- Possible clinically significant laboratory values
- Transitions for laboratory values without CTCAE grade based on reference ranges

Note: For calculating the change in CTCAE grade from baseline, patients with a CTCAE grade of -9 (no CTCAE grade defined) or CTCAE grade of -5 (overlapping reference ranges) will be treated as a CTCAE grade 0 for all analyses. In laboratory listings, the CTCAE grade is displayed as -9 and -5, respectively.

For Uric Acid, Hypokalemia, amylase, bicarbonate, eosinophils, glucose (high direction), INR of prothrombin time, lipase, methemoglobin, sodium (low direction) the CTCAE grade cannot

always be assigned by the laboratory parameter itself as two different CTCAE grades have the same laboratory constellation, but are distinguished by additional clinical parameter. In this case a CTCAE grade of -1 will be assigned. These will not be considered for laboratory analyses. In laboratory listings, the CTCAE grade is displayed as -1, respectively.

7.8.3 Vital signs

Vital signs and physical examination, at Screening, baseline, during the course of the trial and at the end-of-trial evaluation will be listed with regard to possible changes compared to findings before start of treatment.

7.8.4 ECG

ECG data will be collected as described in CTP Section 5.2.4. Clinically significant findings in ECG data will be reported under “Adverse events” if applicable and will be analyzed accordingly. In addition, patients ECG assessments will be listed for all time points.

7.8.5 Others

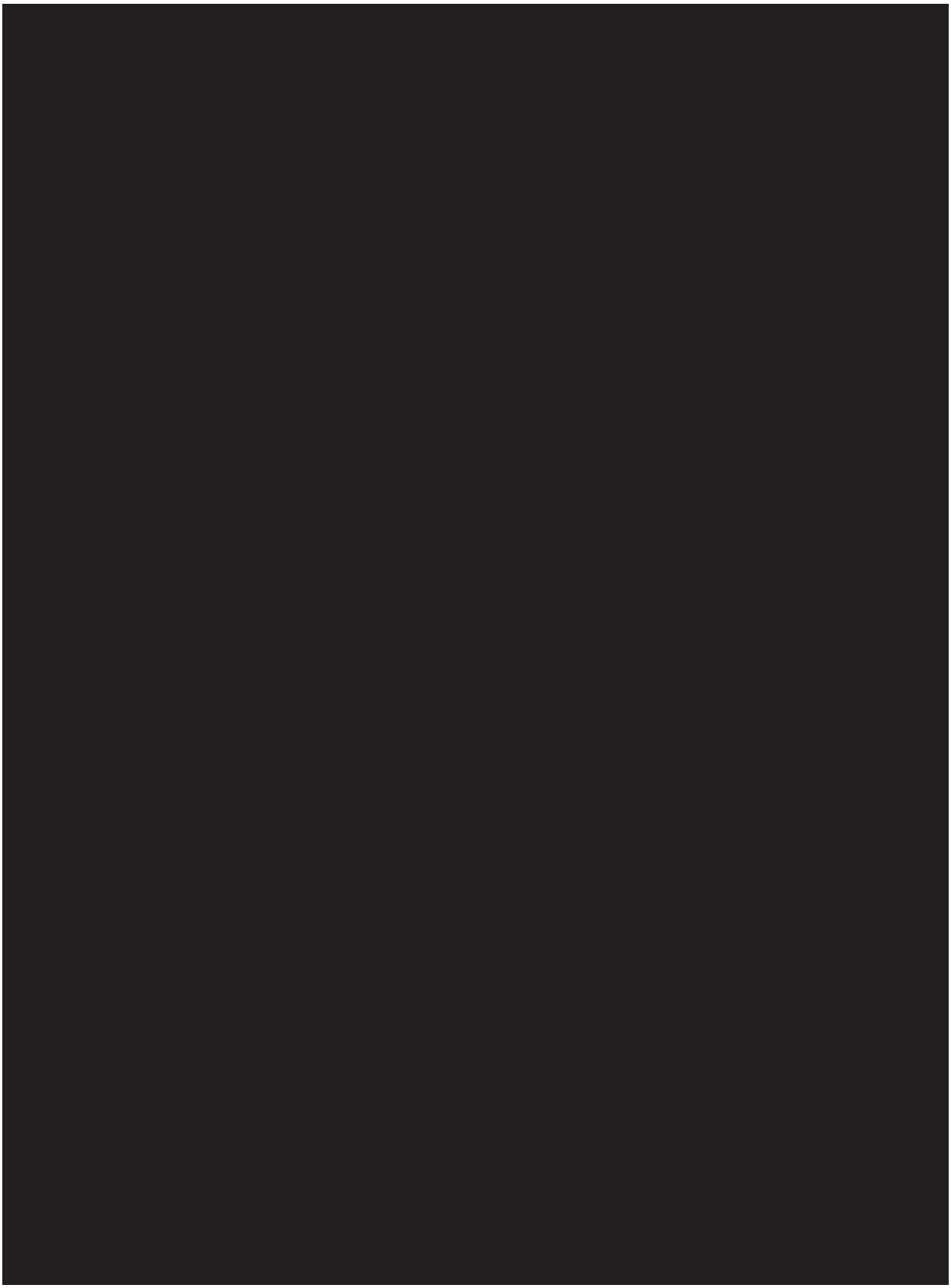
Details on interim analysis are described in section 7.2.8 in CTP as follows.

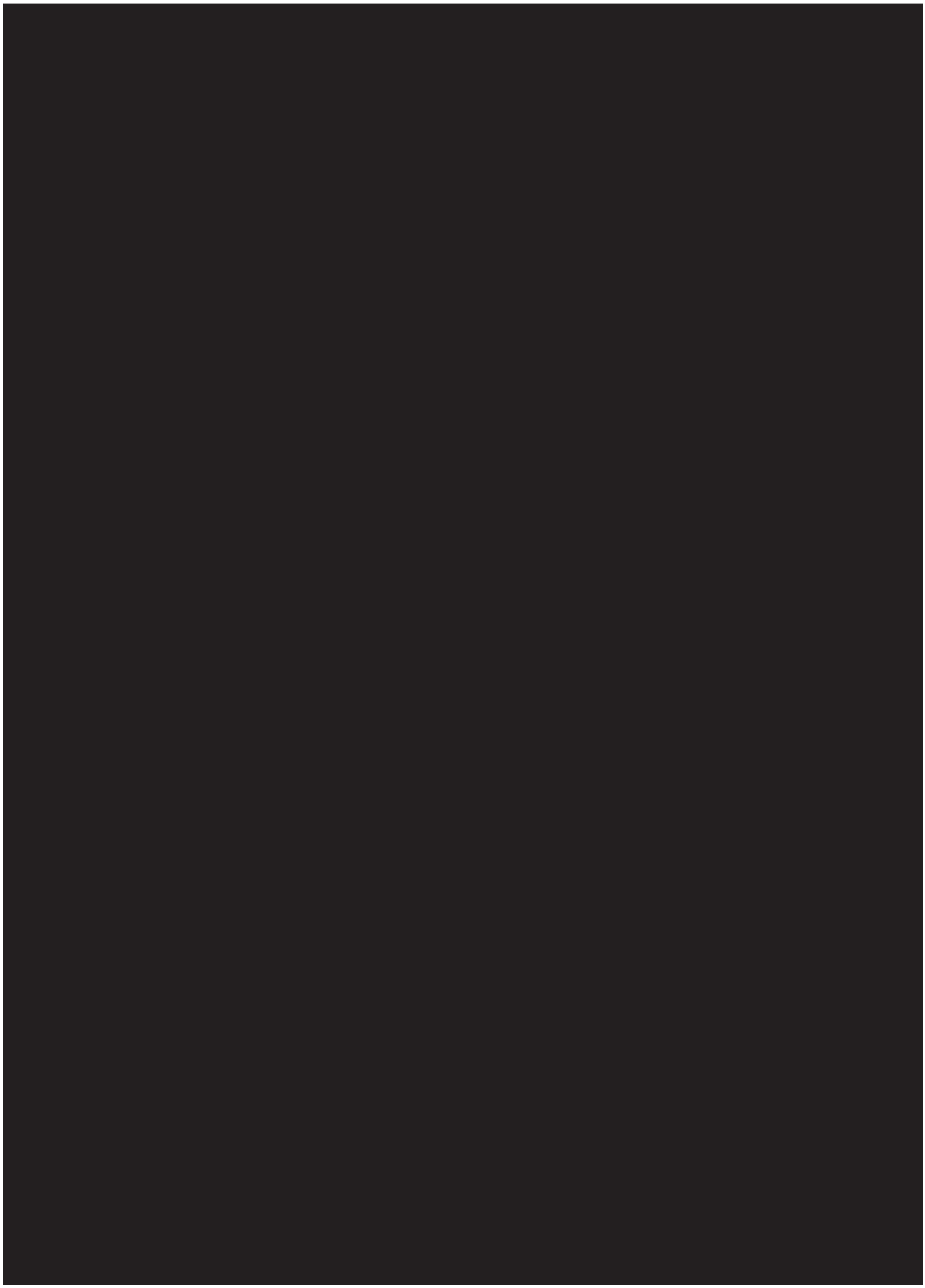
No formal interim analysis is planned for PK and immunogenicity. Preliminary, exploratory analysis of PK and if applicable of immunogenicity will be performed prior to database lock during study conduct based on all evaluable data at the time of analysis. This will be performed to support dose escalations and e.g. in case the information is needed to inform other activities during the development of substance such as concomitant treatment restrictions in other trials. In contrast to the final calculations, the preliminary, exploratory analysis will be based on planned sampling times rather than on actual times, regardless of whether actual times were within the time windows or not. Therefore, minor deviations of preliminary and final results may occur. No formal preliminary PK and immunogenicity report will be written.

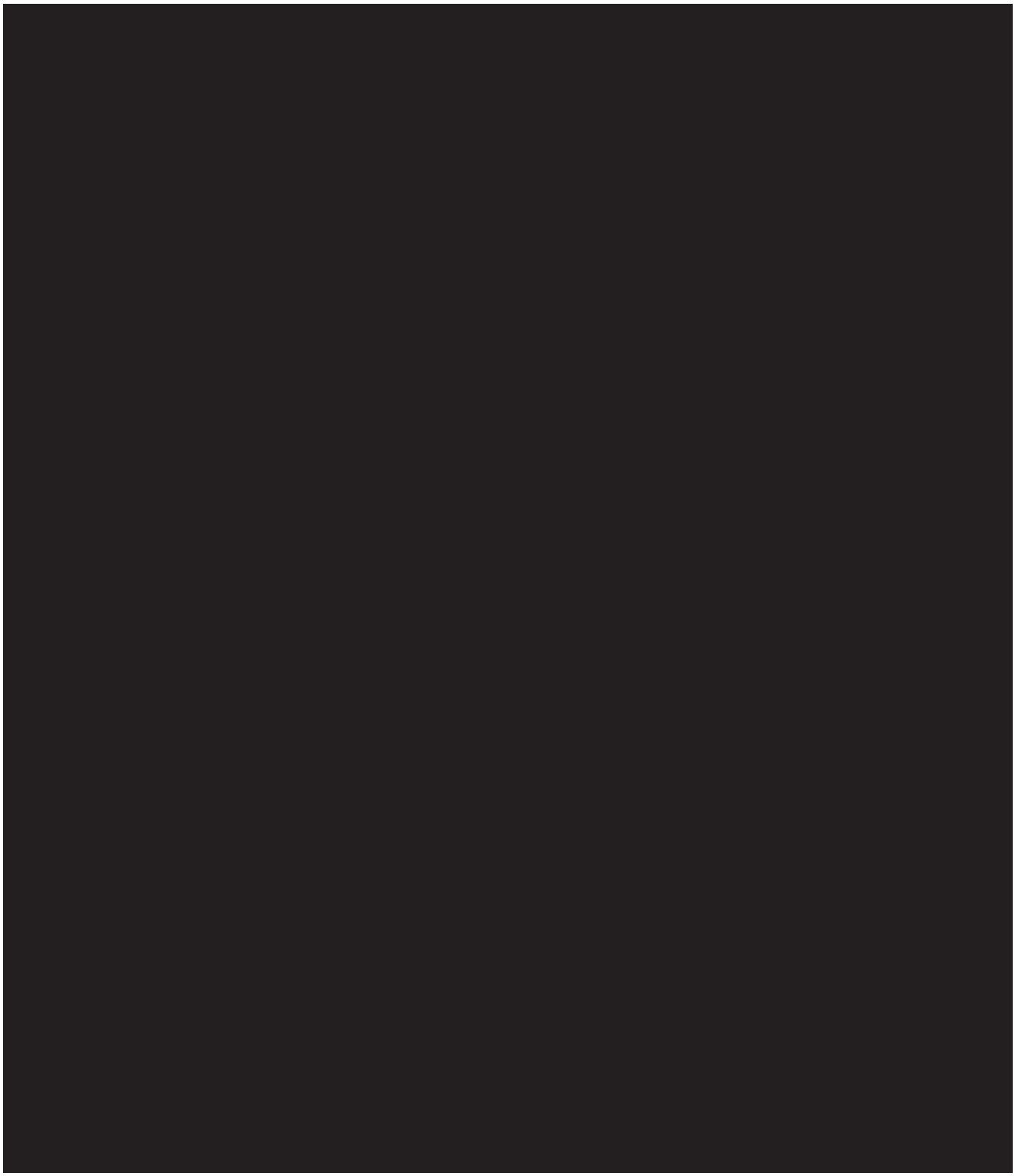
In Phase Ib there will be a continuous monitoring of the efficacy in terms of OR (and PD-modulation). Tumor marker (CEA, CA19-9) modulations will be monitored continuously. An arm may be terminated early due to lack of efficacy.

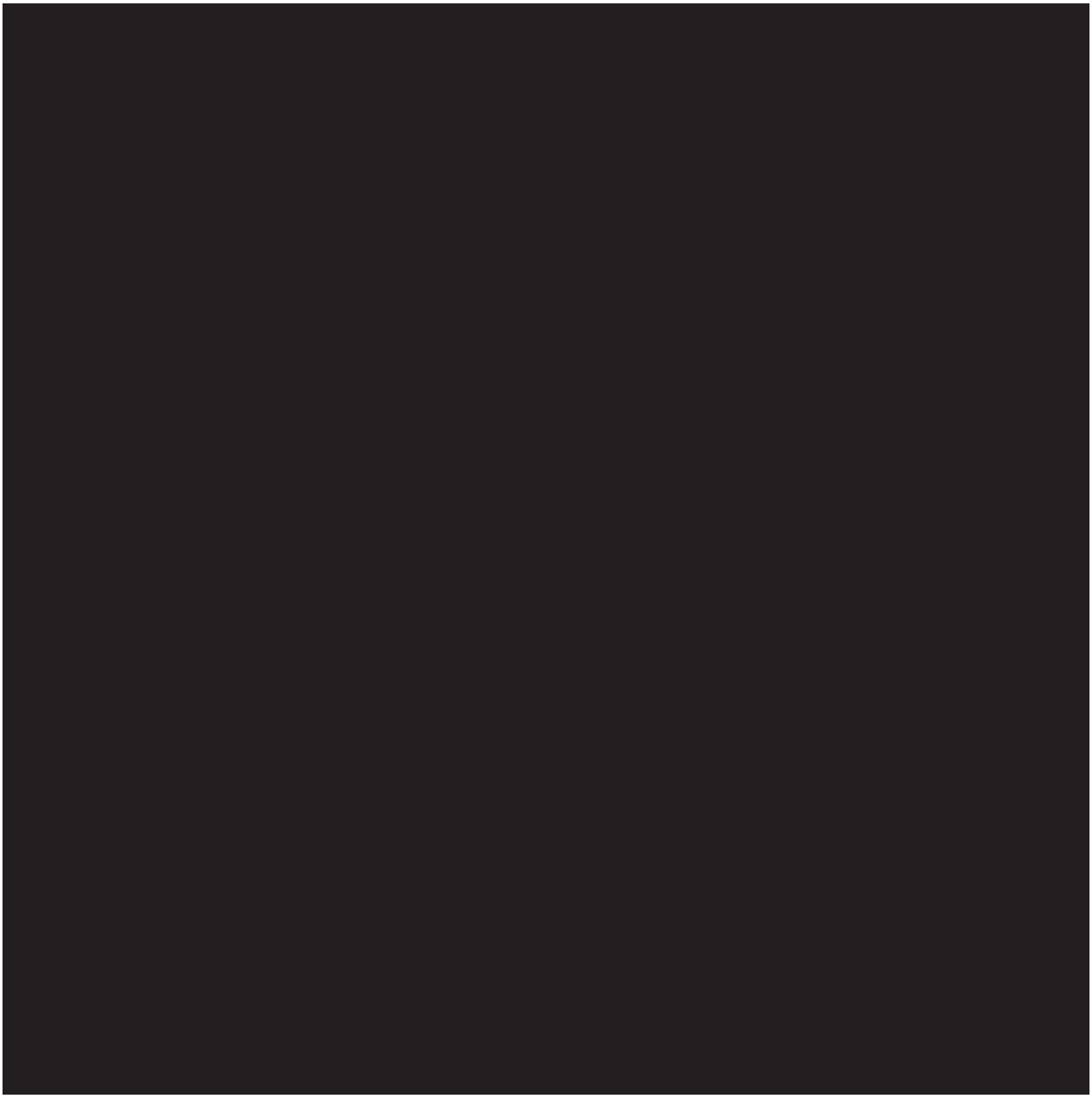
8. REFERENCES

	1. *CPMP/ICH/363/96:* "Statistical Principles for Clinical Trials", ICH Guideline Topic E9, Note For Guidance on Statistical Principles for Clinical Trials, current version.
	2. *001-MCS-36-472:* “Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics”, current version, Group “Biostatistics & Data Sciences”, IDEA for CON.
	3. *001-MCG-156_RD-01:* "Handling of missing and incomplete AE dates", current version; IDEA for CON.
	4. *001-MCG-156*: "Handling and summarization of adverse event data for clinical trial reports and integrated summaries", current version; IDEA for CON.
	5. *CPMP/ICH/137/95*: “Structure and Content of Clinical Study Reports”, ICH Guideline Topic E3; Note For Guidance on Structure and Content of Clinical Study Reports, current version, EMA webpage.
	6. *001-MCG-157*: "Handling, Display and Analysis of Laboratory Data", current version; IDEA for CON.









10. HISTORY TABLE

Table 10: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
Draft	**03-MAY-2023**	[redacted]	None	This is the draft TSAP
Version 1	**24-JUL-2023**		3, 4, 5.3, 6.1, 6.6, 6.7, 7.6, 10.1	Final based on reviewers comments.
Version 1.1	**09-OCT-2023**		7.4,7.5,7.6	Align sections 7.4,7.5,7.6 heading titles with version 4 TSAP template as applicable.
Final	**30-NOV-2023**		2, 5.4.2, 7.4.1 and 7.5.2	Update TSAP according to final comments.