TRIAL STATISTICAL ANALYSIS PLAN

c34073963-01

BI Trial No.:	1381.0003
Title:	An open label Phase I PET imaging study to investigate the biodistribution and tumor uptake of [^{89}Zr]Zr-BI 754111 in patients with advanced non-small cell lung cancer and head and neck squamous cell carcinoma treated with BI 754111 in combination with BI 754091 Including Protocol Amendments 1 and 2
Investigational Product(s):	[^{89}Zr]Zr-BI 754111, ezabenlimab (BI 754091) and BI 754111
Responsible trial statistician(s):	[redacted] Phone: [redacted] Fax:
Date of statistical analysis plan:	15 FEB 2021 SIGNED
Version:	1

1. TABLE OF CONTENTS

[redacted]

LIST OF TABLES

2. LIST OF ABBREVIATIONS

See Medicine Glossary:
http://glossary

Term	Definition / description
AE	Adverse Event
C1	Cycle 1
C2	Cycle 2
CR	Complete Response
CTC	Common Terminology Criteria
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
DBL	Database Lock
DM&SM	Boehringer Ingelheim Data Management and Statistics Manual
DRA	Drug Regulatory Affairs
DMG	Dictionary Maintenance Group
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
FL	Follicular Lymphoma
ICH	International Conference on Harmonisation
iPD	Important Protocol Devations
LOCF	Last Observation Carried Forward
MedDRA	Medical Dictionary for Regulatory Activities
MQRM	Medical Quality Review Meeting
MTD	Maximum Tolerated Dose
O*C	Oracle Clinical
OR	Objective Response
PD	Progression of Disease
PK	Pharmacokinetics
PR	Partial Response
PSTAT	Project Statistician
PT	Preferred Term
Q1	Lower Quartile

Term	Definition / description
Q3	Upper Quartile
RECIST	Response Evaluation Criteria in Solid Tumours
iRECIST	Immune Response Evaluation Criteria in Solid Tumours
REP	Residual Effect Period
RPM	Report Planning Meeting
SA	Statistical Analysis
SAE	Serious Adverse Event
SD	Stable Disease
StD	Standard Deviation
SMQ	Standardised MedDRA query
SOC	System Organ Class
SUVmean	Average Standard uptake value
SUVpeak	Standard uptake value in a 1ml sphere around highest SUV pixel
TESS	Treatment Emergent Signs and Symptoms
ToC	Table of Contents
TMW	Trial Medical Writer
TS	Treated Set
TSAP	Trial Statistical Analysis Plan

3. INTRODUCTION

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

This Trial Statistical Analysis Plan (TSAP) assumes familiarity with the Clinical Trial Protocol (CTP), including Protocol Amendments. In particular, the TSAP is based on the planned analysis specification as written in CTP Section 7 “Statistical Methods and Determination of Sample Size”. Therefore, TSAP readers may consult the CTP for more background information on the study, e.g., on study objectives, study design and population, treatments, definition of measurements and variables, planning of sample size, and randomization.

In the following, study medication always refers to [^{89}Zr]Zr-BI 754111, ezabenlimab (BI 754091) and BI 754111.

SAS® Version 9.4 or a newer version and Phoenix TM WinNonlin ® version 8.1 will be used for PK analyses. SAS® Version 9.4 or newer version will be used for all analyses.

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

This is the initial version of TSAP and there is no change in the analysis plan since the finalization of the protocol version 3.0.

The study was prematurely terminated by the sponsor.

Other than specified in the CTP, the following analyses will not be performed by BI:

[redacted]

5. ENDPOINTS(S)

5.1 PRIMARY ENDPOINT(S)

The main objective of this study is to determine the biodistribution and intra-tumor accumulation of [^{89}Zr]Zr-BI 754111 at baseline and its change upon treatment.

The primary endpoint of this study is:

- Standardized uptake values (SUVs) of [^{89}Zr]Zr-BI 754111 for tumor uptake at baseline (Cycle1) and post BI 754111 dose (up to Cycle2 Day8).

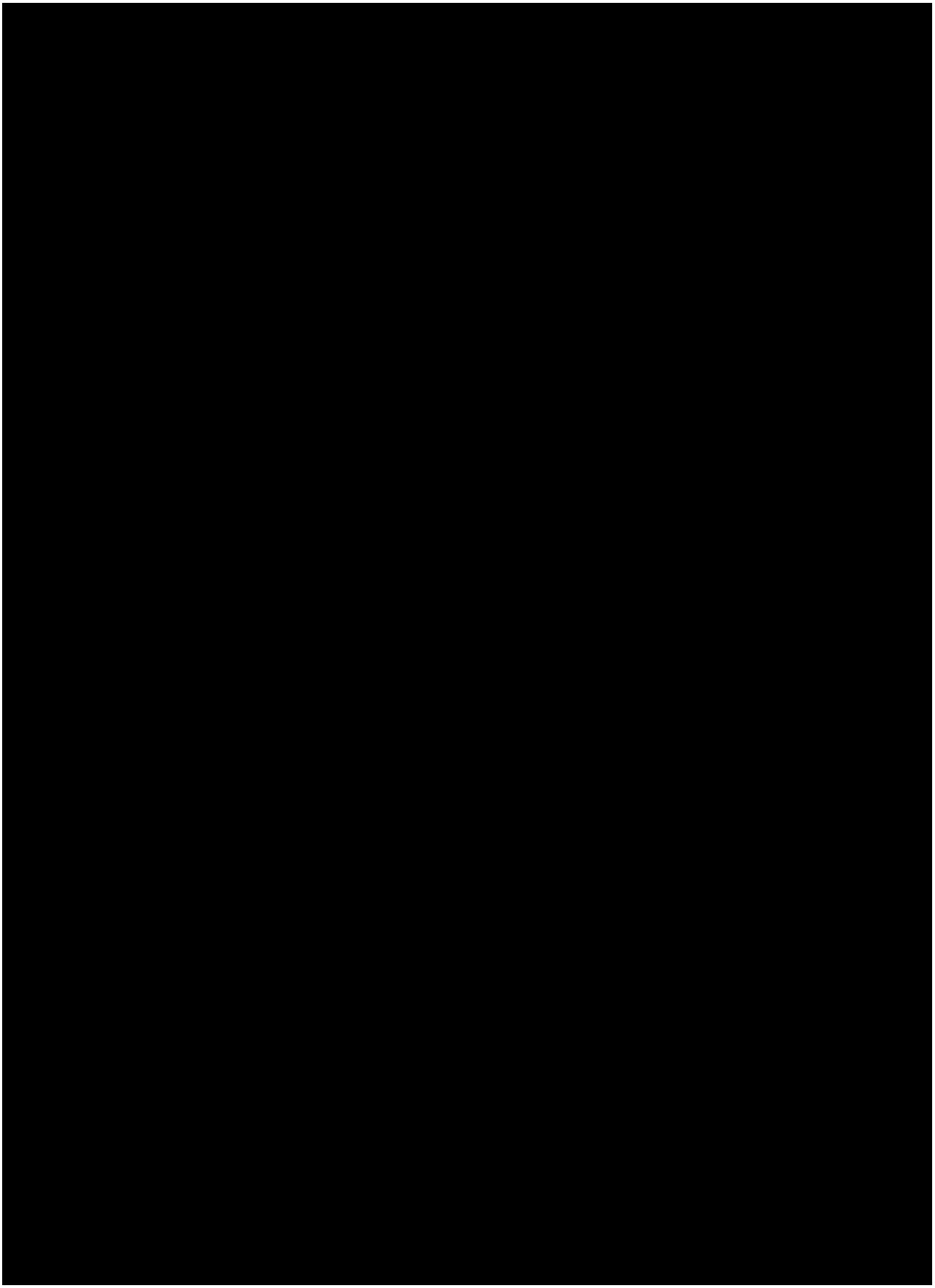
5.2 SECONDARY ENDPOINT(S)

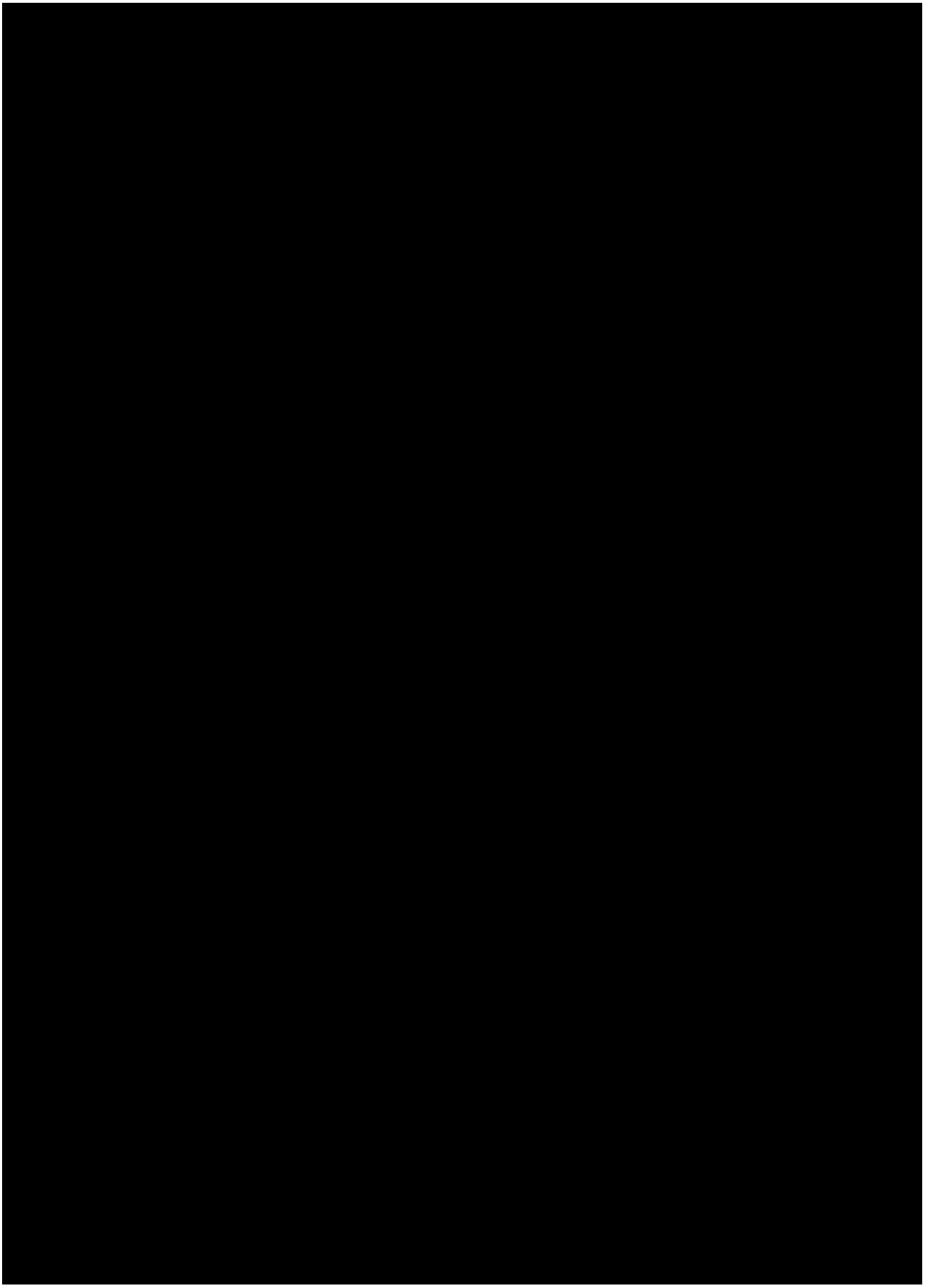
5.2.1 Key secondary endpoint(s)

Not applicable; there is no secondary endpoint in this study.

5.2.2 Secondary endpoint(s)

Not applicable; there is no secondary endpoint in this study.





6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENT(S)

In this Phase I trial treatments are not randomised.

Patients will receive combination treatment of BI 754111 (600 mg) and ezabenlimab (240 mg). Data of study parts 1 and 2 will be reported together, grouped by (cold) blocking dose of BI 754111 (cohorts).

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

Analysing Treatment Period	**Start Date**	**Stop Date**
Screening	Date of informed consent	Date/Time of the first administration of trial medication
On-treatment	Date/Time of the first administration of trial treatment	Date of the last administration of trial medication + 30 days (residual effect period)
Follow-up	Date of the last administration of trial treatment + 31 days	Date of the last per protocol visit

Note: a 30-day safety follow-up period is defined for this trial.

For safety analyses, adverse events (AEs) will be classified to one of the following time periods: “Screening”, “On-Treatment” or “Follow-up”. This will be applied for all adverse events. Detailed rule for assigning AEs to these time periods are listed below:

- If the date of informed consent ≤ AE onset date < date/time of first administration of [^{89}Zr]Zr-BI 754111, ezabenlimab or BI 754111, then the AE is assigned to “Screening”;
- If date/time of first administration of ezabenlimab or BI 754111 ≤ AE onset date ≤ date of last administration of [^{89}Zr]Zr-BI 754111, ezabenlimab or BI 754111 + 30 days, then the AE is assigned to “On-Treatment”;
- If AE onset date > date of last administration of [^{89}Zr]Zr-BI 754111, ezabenlimab or BI 754111 + 30 days, then the AE is assigned to “Follow-up”

For the on-treatment period, the nominal trial medication assigned at the beginning of the first treatment cycle (Cycle 3) will be used as label of the analysing treatment. In cases where patients stop treatment before Cycle 3, the actual treatment doses applied in Cycles 1 and 2 will be used as label. Tables for the on-treatment period will contain a “total” column, representing all doses of trial medication combined.

The first treatment cycle starts with the first administration of any trial medication and lasts for 21 days. Treatment cycles generally consist of 21 days.

Adverse Events (AEs) that have onset date during the Screening or Follow-Up periods will be displayed in separate listings from those occurred during the on-treatment period. Listings of AEs will not present a "total" category.

Labels of each analysing treatment period, analysis numbers, the labels used for display in the tables and listings in the CTR, as well as codes, decodes, sort order and labels for each trial medication used in this trial are provided in the technical document "ADS Plan".

6.2 IMPORTANT PROTOCOL DEVIATIONS

According to (3) important safety protocol deviations (iPDs) are those that potentially affect the rights or safety of study subjects. Important PDs 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.

No per protocol set is defined for this phase I trial, but patients with important protocol deviations (iPD) will be identified and reported in the clinical trial report (CTR). Potential IPDs are defined in Table 6.2: 1. The final list of IPDs will be confirmed at the last report planning meeting (RPM) before DBL.

Data discrepancies and deviations from the CTP will be identified for all treated patients. Listings of protocol deviations and of unresolved discrepancies will be provided to be discussed at the medical quality review meetings (MQRMs), e.g. deviations in drug administration, in blood sampling etc. At these meetings, it will be decided whether the discrepant data can be used as they are or whether the data have to be corrected in the clinical database.

Each protocol deviation must be assessed to determine whether it is an important protocol deviation. A protocol deviation (PD) is important if it affects the rights or safety of the study patients or if it can potentially influence the primary outcome measure(s) for the respective patients in a way that is neither negligible nor in accordance with the study objectives. PDs that do not influence the patient's rights and safety or the evaluability of the patients for the main study objectives are called non-important PDs. These are only considered when checking the trial quality in general.

If any manual iPDs are identified, they are to be summarised into categories and will be captured in the MQRM/RPM minutes via an accompanying Excel spreadsheet (3). The following table (Table 6.2: 1) contains the categories which are considered to be possible iPDs in this trial.

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		None	Automatic
	A2	Patient has laboratory assessment that may cause additional risk		None	Automatic
	A3	Patient is unable to comply with the protocol		None	Automatic
	A4	Patient does not have trial diagnosis or is not part of the target population		None	Automatic
	A5	Patient has condition that may interfere with evaluation of safety and/or efficacy		None	Automatic
B		**Informed consent**			
	B1	Informed consent not available, not done		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.)	None	Automatic
C		**Trial medication**			
	C1	Incorrect treatment administered	Study medication dispensing error leading to change in actual treatment	Decision at MQRM	Automatic
	C2	Continuation/Discontinuation of study medication not according to protocol		Decision at MQRM	Automatic
D		**Concomitant medication**			
	D1	Prohibited medication	Based on restrictions regarding concomitant treatment as specified in CTP Section 4.2.2.1	None	Manual
E		**Trial specific violations**			
	E1	Incorrect study procedures performed	Any deviation from the protocol not defined above but deemed important to be documented in the CTR	Decision at MQRM	Manual

6.3 SUBJECT SETS ANALYSED

Screened Set (SCS)

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

Treated Set (TS)

This patient set includes all patients who were documented to have received at least one dose of [^{89}Zr]Zr-BI 754111, BI 754111, or ezabenlimab. The TS will be used for all safety and efficacy analyses including the primary analysis.

Pharmacokinetic Analysis Set (PKS)

All evaluable patients in the TS which provide at least one evaluable observation for at least one PK endpoint and no PK relevant protocol violation. PKS is used for pharmacokinetical analysis.

[redacted]

6.5 POOLING OF CENTRES

This section is not applicable, because the study was performed in only one center.

6.6 HANDLING OF MISSING DATA AND OUTLIERS

Missing or incomplete AE dates are imputed according to BI standards (see "Handling of missing and incomplete AE dates") (4).

Potential outliers will be reported and analyzed as observed. In general, missing data not discussed in (4) and (2) 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. This is in line with the imputation of partial dates for the analysis of AEs.

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 flowchart of the CTP. For nominal time points and windows of tumor imaging, see Table 6.7: 1.

Unless otherwise specified, baseline is defined as the time point closest but prior to the very 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.

Note that for some trial procedures (for example Eastern Co-operative Oncology Group (ECOG) performance score, body weight, vital signs, laboratory tests) this may be the value measured on the same day when trial medication was started. In these cases it will be assumed that the measurements were taken prior to the intake of any study medication.

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

[redacted]

[redacted]

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.

7. PLANNED ANALYSIS

The labelling and display format of statistical parameters will follow the guideline “Reporting of Clinical Trials and Project Summaries” (7).

For End-Of-Text (EoT) tables, the set of summary statistics is: N / Mean / SD / 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.

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.

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.

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(%)]" to be displayed only for the main category.

If a table includes only categorical data, "N[(%)]" is to be displayed in the column header only.

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

Only descriptive statistics are planned for this section of the report. Demographic parameters collected and to be presented include

- Sex (Male, Female)
- Race and ethnicity (as defined in the eCRF)
- Age [years]
- Height [cm]
- Weight [kg]
- Body mass index [kg/m^2] (defined as weight [kg]/(height [cm]/100)^2)
- Smoking history (Never, Current, Former)
- Baseline ECOG
- Site
- Country

Descriptive statistics are planned for disease history, prior anti-cancer therapies, medical history and baseline disease assessment.

7.2 CONCOMITANT DISEASES AND MEDICATION

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

Concomitant diseases will be coded similarly as AEs 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

Not applicable in this study.

7.4 PRIMARY ENDPOINT(S)

All evaluations will be based on the treated set (TS), unless otherwise stated. Patients who might not be evaluable for the assessment of [^{89}Zr]Zr-BI 754111 (Cycle1 and Cycle2) will be excluded from the primary endpoint analysis. Exclusion of a subject's data will be documented in the clinical trial report (CTR).

The primary endpoint will be analyzed descriptively.

7.4.1 Primary analysis of the primary endpoint(s)

The primary endpoint is defined as:

Mean relative change (ΔSUV_{peak}) of the standardized uptake values (SUV_{peak}) from baseline (Cycle1 / C1) to on-treatment (Cycle2 / C2) PET assessments in all evaluable, metabolic active lesions.

Two PET imaging time points (PET assessments) will be considered for the calculation (2 time points for CTP v1/v2; 3 time points CTP v3/not applicable); the time point leading to the maximum effect (max. reduction from baseline) will be reported.

Calculation:
The primary endpoint is derived for each patient as follows:

- Calculate the relative change from baseline for each selected lesion at each time point (e.g. 96h, 144h):
  $\mathbf{100 * (SUV_{peak,lesion,timepoint,C2} - SUV_{peak,lesion,timepoint,C1}) / SUV_{peak,lesion,timepoint,C1}}$
- Calculate the mean over all evaluable lesions (at each time point)
- Select the lower mean, i.e. choose the time point with maximum average effect/reduction in tumor uptake from baseline (= ΔSUV_{peak})

The minimum mean ΔSUV_{peak} will be summarized per cohort (dose group of BI 754111 in Cycle2) as: N / Mean / SD / Min / Median / Max.

A similar analysis of minimum mean ΔSUV_{peak} will be presented for each patient as: N / Mean / SD / Min / Median / Max.

Tumor uptake at baseline:
The mean tumor uptake at baseline will be summarized per cohort (blocking dose of BI 754111 in Cycle2) separately for each imaging time point (96h, 144h) as the mean $SUV_{peak,C1}$ over all selected lesions as: N / Mean / SD / Min / Median / Max.

A similar analysis of mean tumor uptake (SUV_{peak}) at baseline (Cycle1) will be presented for each patient as: N / Mean / SD / Min / Median / Max.

Impact of CTP amendments:
As per CTP v3, the assessment of the primary endpoint was changed from 2 to 3 PET scans (imaging time points) to assess tumor uptake. The changes are not considered to impact on the primary endpoint; the reported effect is assumed to be fully captured in the time window.
No patients were actually imaged as per CTP v3.

7.4.2 Sensitivity analysis, subgroup analysis, exploratory analysis of the primary endpoint(s)

No sensitivity or further exploratory analyses of the primary endpoint will be performed.

7.5 SECONDARY ENDPOINT(S)

7.5.1 Key secondary endpoint(s)

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

Primary analysis of the key secondary endpoint(s)

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

Sensitivity analysis, subgroup analysis, exploratory analysis of the key secondary endpoint(s)

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

7.5.2 (Other) Secondary endpoint(s)

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

[redacted]

7.7 EXTENT OF EXPOSURE

The total number of cycles initiated of BI 754111 / ezabenlimab will be summarized descriptively. This analysis will be based on all patients in the TS who received at least one cycle of nominal combination treatment of BI 754111 (600 mg) and ezabenlimab (240 mg).

7.8 SAFETY ANALYSIS

All safety analyses will be performed on the treated set (TS). Treated patients will be analyzed according to their initial treatment.

Analyses will be performed as defined in Section 7.3.3 of the CTP. In general, safety analyses will be descriptive in nature and will be based on BI standards. No hypothesis testing is planned.

Safety data recorded during the Residual Effect Period (REP) of 30 days will be considered as on-treatment.

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 and not on the number of AEs. The analysis will be based on current BI standards (5). AEs will be coded using the most recent version of MedDRA. The severity of

AEs was assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. AEs will be analyzed as reported by the investigator and pooled independent of CTCAE version used if applicable.

For analysis multiple AE occurrence data on the CRF will be collapsed into an AE provided that all of the following applies:

- All AE attributes are identical (Low Level term (LLT), severity, action taken, therapy required, seriousness, reason for seriousness, relationship, outcome, AE of special interest (AESI) **)**.
- The occurrences were time-overlapping or time-adjacent (time-adjacency of 2 occurrences is given if the second occurrence started on the same day or on the day after the end of the first occurrence).

Unless otherwise specified, 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. For a definition of treatment refer to Section 6.1. 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 listed separately.

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.

An overall summary of AEs will be presented.

Adverse events will be displayed by the initial dose of study medication administered on the first day of treatment.

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

- AEs by highest CTCAE grade
- Serious AEs (SAEs) by highest CTCAE grade
- Investigator assessed drug-related AEs by highest CTCAE grade
- Investigator assessed drug-related SAEs by highest CTCAE grade
- Investigator assessed AEs of special interest (AESIs) by highest CTCAE grade
- irAEs through the whole trial (i.e. including irAEs occurring after residual effect period) by highest CTCAE grade
- Investigator assessed infusion-related AEs by highest CTCAE grade
- AEs leading to treatment discontinuation by highest CTCAE grade

- AEs leading to death

For the definition of irAEs and AESIs refer to the CTP Section 5.2.6.1

The SOC will be sorted by frequency, and preferred terms will be sorted by frequency (within SOC).

Adverse events that are immune mediated can potentially begin more than 30 days after treatment. Additional tables will summarize all immune related events, including events with onset more than 30 days after the last treatment.

AEs leading to death during the on-treatment period will be tabulated by SOC and PT. Reported fatal AEs during follow-up period will be listed. All deaths during the study will be summarized by primary cause of death (death due to disease, death due to AE, death cause unknown, other).

7.8.2 Laboratory data

The analysis of laboratory data will be descriptive in nature and will be based on BI standards (6). 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 Version 5.0.

The following outputs will be presented:
- Worst CTCAE grade experienced during the on-treatment phase
- Transitions of CTCAE grade from baseline to worst laboratory value

For lab tests for which CTCAE grades are not sued for at least one direction of interest, frequency of patients with shifts from baseline as defined in the Project Safety Statistical Analysis Plan (SSAP (8)) will be followed.

Analysis

The Laboratory tests will be classified into the following categories:

- Primary- full analysis
- Secondary- listing of possible clinically significant values
- Diagnostic- listing of all observed values
- Not analyzed

The following outputs will be presented for primary laboratory tests:

- Descriptive statistics, including changes from baseline
- Frequency of patients with shifts from baseline
    - Shifts will be defined in terms of
        - CTCAE grades will be used for laboratory tests with CTCAE grades defined
        - The upper and lower reference limits will be used for laboratory tests without CTCAE grades
- Frequency of patients with possible clinically significant abnormalities

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

Possible clinically significant abnormal laboratory values:
Possible clinically significant abnormal laboratory values are defined as those laboratory values that are of CTCAE Grade ≥ 2 and show an increase from baseline value by at least one CTCAE grade. For those parameters for which no CTCAE grade has been defined, definition in SSAP (8) will be used to determine possible clinical significance. Frequency of patients with possible clinically significant abnormal laboratory values will be provided whenever applicable. If no baseline value is available but the patient has a post-baseline laboratory value of CTCAE Grade ≥ 2 an increase from baseline will be assumed, i.e. the laboratory value considered as possible clinically significant.

Laboratory tests classified as “diagnostic” are recorded as a follow-up to abnormalities of associated lab tests for diagnostic purposes i.e. amylase and lipase would be measured to investigate possible pancreatitis. These values will be presented in a separate listing. No other analyses will be performed.

Analyses 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.

Baseline for safety laboratory parameters will be the last available measurement before the start of study drug. Laboratory measurements taken up to 30 days after the last administration of study drug will be considered as on-treatment.

[redacted]

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.

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 (mg/dL) = Total Calcium (mg/dL) – 0.8[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.

Liver Function tests and potential Hy's Law

A listing of all liver function tests will be provided for all patients who meet the following criteria at any time:

- ALT or AST ≥3xULN and elevation of total bilirubin ≥2xULN at the same time

In addition, tables of liver function test abnormalities will be provided.

7.8.3 Vital signs

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

7.8.4 ECG

Patients with abnormal ECG data will be provided.

7.8.5 Others

Other parameters relevant for safety as height, weight, and ECOG score will be analyzed descriptively and displayed in patient listings.

ECOG
A shift table from worst, best and last ECOG performance status on treatment from baseline will be provided.

[redacted]

[redacted]

[redacted]

[redacted]

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 30-476*: "TMCP Data Analysis", current version; IDEA for CON.
3	*001-MCS-50-413*: "Handling of Protocol Violations in Clinical Trials and Projects", current version; group: Study Conduct; IDEA for CON.
4	*BI-KMED-BDS-HTG-0035*: "Handling of missing and incomplete AE dates", current version; IDEA for CON.
5	*BI-KMED-BDS-HTG-0066*: " Analysis and presentation of adverse event data from clinical trials", current version; IDEA for CON.
6	*BI-KMED-BDS-HTG-0042*: "Handling, Display and Analysis of Laboratory Data", current version; IDEA for CON.
7	*BI-KMED-BDS-HTG-0045*: ”Reporting of Clinical Trials and Project Summaries”, current version; IDEA for CON.
8	1381.P1 Safety SAP, current version; BIRDS.

10. HISTORY TABLE

Table 10: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
1	**15-FEB-21**	[redacted]	None	This is the final TSAP.