TRIAL STATISTICAL ANALYSIS PLAN

Document No.:	**c44138015-01**
BI Trial No.:	**1426-0001**
Title:	Phase I, first in human trial evaluating BI 1387446 alone and in combination with ezabenlimab (BI 754091) in solid tumours Including global protocol amendments 1 - 4
Investigational Product(s):	BI 1387446 Ezabenlimab (BI 754091)
Responsible trial statistician(s):	[redacted] Phone: [redacted] Fax: [redacted]
Date of statistical analysis plan:	8 Apr 2024
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1. TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

2. LIST OF ABBREVIATIONS

See Medicine Glossary:
http://glossary

Term	Definition / description
ADA	Anti-Drug Antibody
AE	Adverse Event
AESI	Adverse Event of Special Interest
BLRM	Bayesian Logistic Regression Model
BMI	Body Mass Index
CR	Complete Response
DLT	Dose Limiting Toxicity
ECOG	Eastern Cooperative Oncology Group
EOT	End of Treatment
EoT	End-of-Text
RECIST	Response Evaluation Criteria in Solid Tumours
itRECIST	Response Criteria for Intratumoural Immunotherapy in Solid Tumours
iRECIST	Immune Response Evaluation Criteria In Solid Tumours
MTD	Maximum Tolerated Dose
OR	Objective Response
ORR	Objective Response Rate
PKS	Pharmacokinetic parameter set
PR	Partial Response
RECIST	Response Evaluation Criteria In Solid Tumours
REP	Residual Effect Period
SCS	Screened Set
TS	Treated Set
ULN	Upper Limit of Normal

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 (or a newer version) and Phoenix TM WinNonlin® Version 8.1 (or a newer version) will be used for PK analyses. R version 4.0.1 (or a newer version) and Stan will be used for all analyses related to BLRM. SAS® Version 9.4 (or a newer version) will be used for all other analyses.

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

As development of BI 1387446 has been terminated, the following further endpoints will not be analysed for the CTR:

5. ENDPOINTS(S)

5.1 PRIMARY ENDPOINT(S)

The main objective of this trial is to determine the maximum tolerated dose (MTD) for BI 1387446 as single agent (Arm A) and for BI 1387446 in combination with ezabenlimab (Arm B). The number of patients with Dose Limiting Toxicities (DLTs) during the MTD evaluation period will be used to determine the MTD in each arm.

The primary endpoints are:
- MTD based on number of Dose-limiting toxicities (DLTs)
- Number of patients with DLT in the MTD evaluation period

The MTD is defined as the highest dose with less than 25% risk of the true DLT rate being above 33% during MTD evaluation period. For definition of DLTs, see CTP Section 4.1.4.4.

The MTD evaluation period is defined as the first treatment cycle including echocardiographic/MUGA scan measurements acquired on Day 1 of Cycle 2.

For analyses, the MTD evaluation period will be derived as the time from the first administration of study drug to the start of the second treatment cycle, i.e. in more detail as the time from the first administration of (any) trial medication to the start of the 2nd administration of ezabenlimab or 4th administration of BI 1387446 (whatever from the latter two comes first). In the case that the 2nd administration of ezabenlimab and/or the 4th administration of BI 1387446 are not given, the MTD evaluation period ends 90 days after the last administration.
Patients who were replaced during the MTD evaluation period will not be considered for MTD determination. Patients who experience a DLT will not be replaced. The decision on replaced patients will be collected in a separate file and stored in the TMF. Patients that have not been replaced will be referred to as patients evaluable for MTD determination (MTD set).

5.2 SECONDARY ENDPOINT(S)

5.2.1 Key secondary endpoint(s)

Not applicable, no key secondary endpoints have been specified in the CTP.

5.2.2 Secondary endpoint(s)

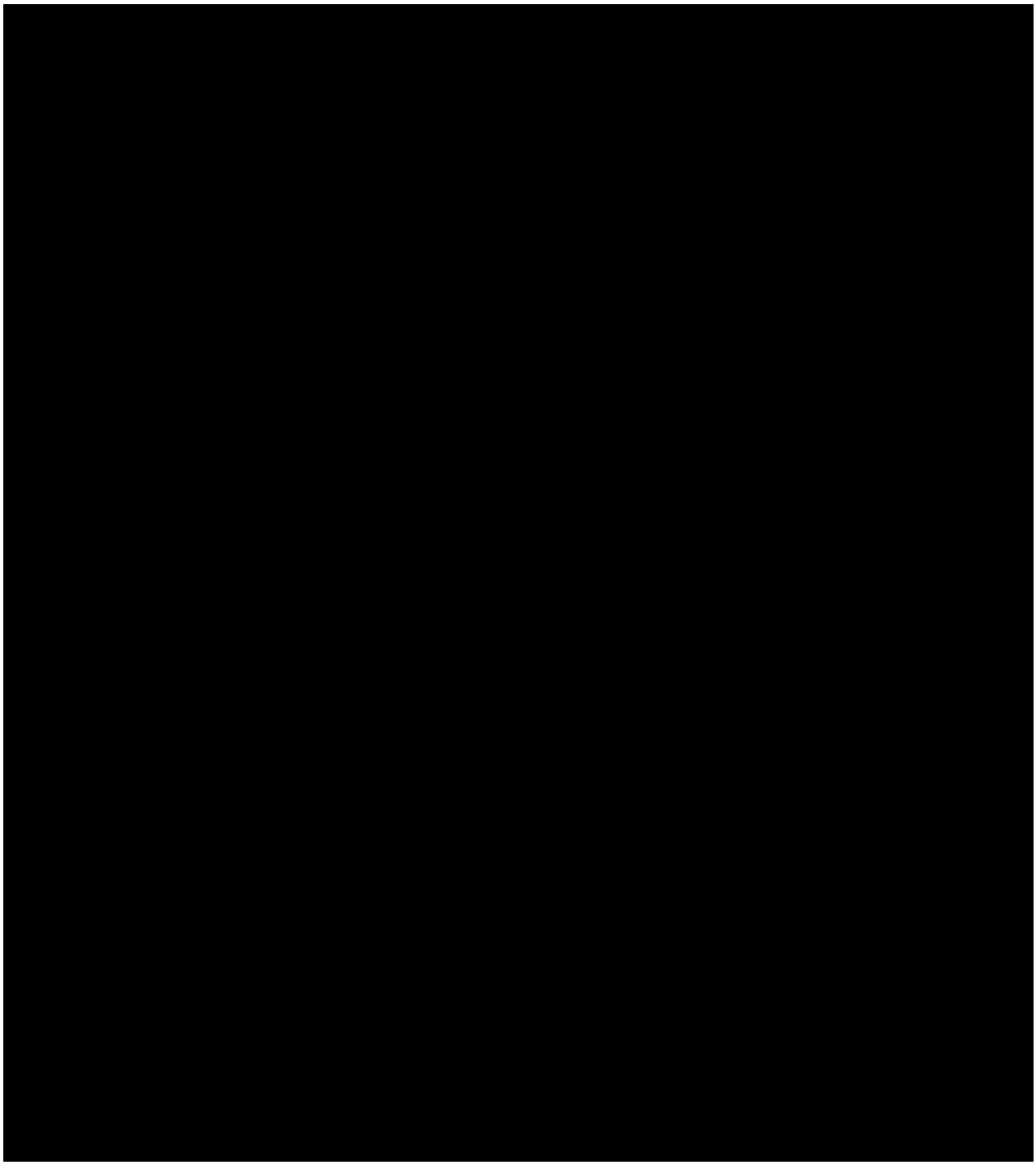
The secondary endpoints of this trial are:

For CTP Version 1 and 2:
- Objective response based on Response Evaluation Criteria in Solid Tumors (RECIST)
- Best percentage change from baseline in size of injected lesions
- Best percentage change from baseline in size of target lesions

For CTP Version 3 and later:

- Objective response based on Response Criteria for Intratumoural Immunotherapy in Solid Tumours (itRECIST)
- Best percentage change from baseline in size of injected target lesions
- Best percentage change from baseline in size of non-injected target lesions

All secondary endpoints will be assessed separately for Arm A and Arm B.



6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENT(S)

In this Phase I trial treatments are not randomized. In Arm A and Arm B, different dose levels of BI 1387446 alone (Arm A) or of BI 1387446 in combination with 240 mg of ezabenlimab (Arm B) are being administered.

If not specified otherwise, all analyses will be performed for each treatment arm separately. Data will be presented by initial treatment, i.e. within each treatment arm for all dose cohorts separately and in total over all dose cohorts of that arm.

For safety summaries, events that start from the first administration of any trial medication until 90 days after the last administration of any trial medication (residual effect period, REP) will be assigned to the on-treatment period for evaluation. If not specified otherwise, all safety tables will be based on the on-treatment period. Adverse events that have an onset during the screening or the follow-up period will be displayed in separate listings from those that occurred during the on-treatment period.

The MTD evaluation period will be derived as the time from the first administration of study drug to the start of the second treatment cycle, i.e., in more detail as the time from the first administration of (any) trial medication to the start of the 2nd administration of ezabenlimab or 4th administration of BI 1387446 (whatever from the latter two comes first). In the case that the 2nd administration of ezabenlimab and/or the 4th administration of BI 1387446 are not given, the MTD evaluation period ends 90 days after the last administration.

Handling of cross-over patients:

Patients with progressive disease on BI 1387446 monotherapy (Arm A) may cross over to the combination (Arm B) after completion of cycle 1 and will be treated at the highest dose level declared to be safe by the SMC at this time. Instead of completing the REP after monotherapy, these patients will continue treatment in combination by re-starting treatment at Cycle 1 Day 1 in Arm B (with limited set of screening assessments).

After crossing over from Arm A to Arm B, patients will be considered in the safety and efficacy analyses in Arm B. That is, if not specified otherwise, they will be included in the tabulation of safety and efficacy data of both arms. A footnote will be used in the outputs to indicate that cross-over patients are depicted in Arm A and Arm B.

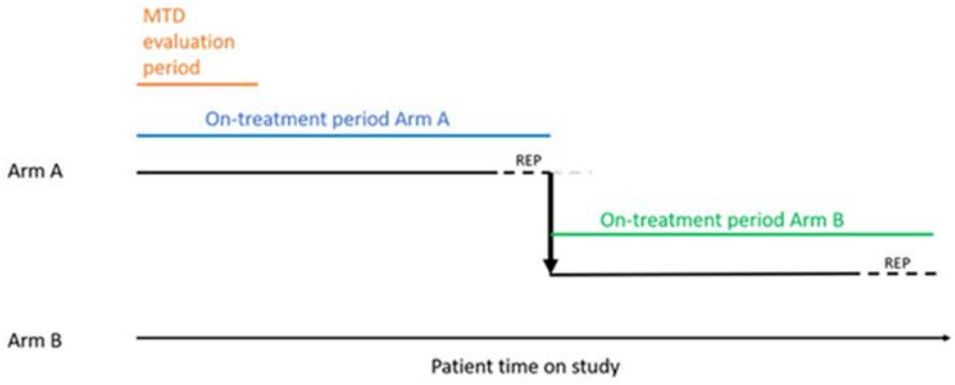
In particular, for patients who cross over from Arm A to Arm B, two on-treatment periods will be defined, one for Arm A and a separate one for Arm B: The on-treatment period in Arm A will be derived as the time from first administration of BI 1387446 in Arm A until 90 days after the last administration in Arm A (including) or until the first administration of any trial drug in Arm B (excluding), whatever is first. The on-treatment period in Arm B will be derived as the time from first administration of study drug in Arm B until 90 days after the last administration of any trial medication. Figure 6.1: 1 provides a visualization of the two

on-treatment periods for a patient who crosses over to Arm B without completing the REP in Arm A.

The analyses of Arm A data will be presented by the patient's initial treatment in Arm A, the analyses of arm B data will be presented by the treatment the patient receives first after the crossover to Arm B.

For cross-over patients, the MTD evaluation period will only be defined for their treatment in Arm A.

Figure 6.1: 1 On-treatment periods and MTD evaluation period for cross-over patients



6.2 IMPORTANT PROTOCOL DEVIATIONS

The documentation of the iPD categories and how to handle iPDs in the analysis are done in the DV domain specifications, which is stored within the TMF in EDMS.

6.3 INTERCURRENT EVENTS

The expected intercurrent events of interest in this trial are:

- Treatment discontinuation during the MTD evaluation period due to DLT
- Treatment discontinuation during the MTD evaluation period due to other reason than DLT
- Dose reduction during the MTD evaluation period due to a DLT
- Dose reduction during the MTD evaluation period due to other reason than DLT
- Progressive disease during the MTD evaluation period
- Death during the MTD evaluation period where the death event is not a DLT
- Any events other than DLT that cause missed visits during the MTD evaluation period

The strategy for handling intercurrent events in this trial is as follows:

Modified principal stratum: This is the effect of the treatment in the principal stratum of patients who do not discontinue treatment, miss visits, progress, or die during the MTD evaluation period for any reason other than DLT. That means patients experiencing one of the

following intercurrent events are excluded from the analysis: “Treatment discontinuation during the MTD evaluation period due to other reason than DLT”, “Dose reduction during the MTD evaluation period due to other reason than DLT”, “Progressive disease during the MTD evaluation period”, “Death during the MTD evaluation period where the death event is not a DLT”, “Any events other than DLT that cause missed visits during the MTD evaluation period”. The intercurrent events “Treatment discontinuation due to DLT” and “Dose reduction due to DLT” will be handled using a composite strategy, that is, patients experiencing the intercurrent events “Treatment discontinuation due to DLT” and “Dose reduction due to DLT” are included in the analysis.

Refer to ICH E9 R1 (9.2) for definitions of the principal stratum strategy and the composite strategy. Table 6.3: 1 provides an overview of the intercurrent events and the respective handling strategies. The modified principal stratum strategy is applied to the primary analysis of this trial.

Table 6.3: 1 Overview of intercurrent event handling strategies for the primary analysis of the MTD

Intercurrent event	**Modified principal stratum strategy**
Treatment discontinuation during the MTD evaluation period due to DLT	Composite
Treatment discontinuation during the MTD evaluation period due to other reason than DLT	Principal stratum
Progressive disease during the MTD evaluation period	Principal stratum
Death during the MTD evaluation period where the death event is not a DLT	Principal stratum
Dose reduction during the MTD evaluation period due to a DLT	Composite
Dose reduction during the MTD evaluation period due to other reason than DLT	Principal stratum
Any events other than DLT that cause missed visits during the MTD evaluation period	Principal stratum

6.4 SUBJECT SETS ANALYSED

- Screened set (SCR):

This patient set includes all patients who signed the main 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 any study medication. The treated set will be used for all demographic and baseline analyses as well as all safety and efficacy analyses (besides the MTD determination).

- MTD set:

The MTD set includes all treated patients who are considered evaluable as per CTP, that is, all patients who have completed the required number of administrations of BI 1387446 (and ezabenlimab in arm B) in cycle 1 and who underwent the Echo/MUGA scan in cycle 2 visit 1. In case a patient has not completed the required number of study drug administrations due to DLT(s), he/she will be considered evaluable and included in the MTD set. Patients who cross over from Arm A to Arm B will only be included in the MTD set if they are evaluable in Arm A. The MTD set will be used for the main analysis of the MTD.

- PK parameter set (PKS):

This patient set includes all patients in the treated set who provide at least one evaluable observation for at least one PK endpoint and no PK relevant protocol deviations. The PK parameter analysis set will be used for all PK analyses.

- Biomarker analysis set:

This patient set includes all patients in the treated set who provide at least one evaluable observation for at least one biomarker endpoint. The biomarker analysis set will be used for any biomarker analysis.

[redacted]

6.6 HANDLING OF MISSING DATA AND OUTLIERS

No imputation will be performed on missing efficacy data. Missing baseline laboratory values will be imputed by the respective values from the screening visit. Every effort will be made to obtain complete information on all adverse events, with particular emphasis on potential DLTs.

Potential outliers will be reported and analysed as observed.

Missing or incomplete AE dates will be imputed according to BI standards (9.3).

Handling of missing PK data will be performed according to the current relevant BI standards (9.4). PK parameters that cannot be reasonably calculated based on the available drug concentration time data will not be imputed.

In general, missing data not discussed in the BI standards will not be imputed unless required for the following analyses and definitions. Then the rules as described below apply.

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.

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.

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

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

For the analysis of ‘Best percentage change from baseline in size of injected lesions’ (CTP version 1 and 2) and ‘Best percentage change from baseline in size of injected target lesions’ (CTP version 3 and later) the derivation of baseline will follow the itRECIST publication, details are given in Section 7.5.2.

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

7. PLANNED ANALYSIS

The labelling and display format of statistical parameters will follow the BI guideline (9.5).

For End-Of-Text (EoT) tables, the set of summary statistics is: N / Mean / Standard deviation (StD) / Min / Median / Max.

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

For plasma concentrations as well as for all PK parameters the set of summary statistics will also include: arithmetic coefficient of variation (CV), geometric mean (gMean), geometric coefficient of variation (gCV). Furthermore, for PK parameters the following descriptive statistics will be calculated in addition: 10th percentile (P10), 1st quartile (Q1), 3rd quartile (Q3), 90th percentile (P90). For PK parameters, summary statistics will be calculated using the individual values with the number of decimal places as provided by the evaluation program. The individual values as well as the summary statistics will then be reported with three decimal places.

For Bayesian logistic regression model (BLRM) analysis tables, the set of summary statistics is: Mean, StD, Median and quartiles.

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 dose cohort (unless otherwise specified, all patients in the respective patient set whether they have non-missing values or not). Percentages will be rounded to one decimal place. The category missing will be displayed only if there are actually missing values.

Sort order for general categorical variables: If categories correspond to the collected categories in 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. categorized continuous data) are to be displayed in ascending order.

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

If applicable, conversion from days to weeks, months and years will be as follows:
- Weeks = Days / 7
- Months = (Days * 12) / 365.25
- Years = Days / 365.25

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

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 report.

Concomitant diseases will be coded similarly as adverse events based on the most current Medical Dictionary for Regulatory Activities (MedDRA) version. Concomitant therapies (CTs) will be coded according to World Health Organization Drug Dictionary (WHO DD). CTs will be classified according to the Anatomical Therapeutic Chemical (ATC) classification system. The third ATC level will be used to categorize CTs by therapy type. In situations where a medical product may be used for more than one equally important indication, there are often several classification alternatives. As appropriate, patients receiving CTs with more than one possible ATC level 3 category will be counted more than once. Footnotes will clarify this possible double counting in tables.

7.3 TREATMENT COMPLIANCE

Not applicable as compliance is not recorded in the eCRF. Drug administration is supervised by the study personnel and will be assessed via drug concentrations (PK data) and exposure data.

7.4 PRIMARY OBJECTIVE ANALYSIS

7.4.1 Main analysis

The primary endpoints of the trial are the MTD of BI 1387446 as single agent and the MTD of BI 1387446 in combination with ezabenlimab, and the respective number of patients with DLTs in the MTD evaluation period.

The number of patients with DLTs during the MTD evaluation period at each dose level will be presented. Patients who were replaced during the MTD evaluation period will be excluded from the evaluation of the MTD.

The analysis of the MTD in each treatment arm is based on a joint BLRM for both arms guided by the escalation with overdose control principle.

The MTD in each arm is defined as the highest dose that is expected to cause less than 25% risk of the true DLT rate being above or equal to 33% during the MTD evaluation period. Estimation of the MTD will be based upon the estimation of the posterior probability of the incidence of DLT in toxicity categories during the MTD evaluation period for all evaluable patients, i.e. patients in the MTD set as defined in Section 6.4.

Using the joint BLRM model specified in CTP Section 7, tables and bar charts displaying for each dose the posterior probabilities of the true DLT rates being in either the under-toxicity interval, the targeted toxicity interval or the over-toxicity interval will be produced.

The modified principal stratum strategy as defined in Section 6.3 will be applied for handling intercurrent events in the primary objective analysis. The MTD set will be used for the analysis of the primary endpoint.

The primary analysis is aligned with the estimands described in the Table 7.4.1: 1 below.

Table 7.4.1: 1 Estimands table for primary objective analysis

Estimand attribute	
Population	Patients with different types of advanced or metastatic cancer (solid tumours)
Treatment condition(s)	BI 1387446 monotherapy or BI 1387446 in combination with ezabenlimab
Variable (outcome)	Occurrence of DLTs in the MTD evaluation period
Handling of intercurrent events	• Treatment discontinuation or dose reduction during the MTD evaluation period due to DLT: Composite – patients will be included in the analysis contributing to the analysis with their DLT • Treatment discontinuation or dose reduction during the MTD evaluation period due to other reason than DLT: Principal stratum – patients will be excluded from the analysis and replaced • Progressive disease during the MTD evaluation period: Principal stratum – patients will be excluded from the analysis and replaced • Death during the MTD evaluation period where the death event is not a DLT: Principal stratum – patients will be excluded from the analysis and replaced • Any events other than DLT that cause missed visits during the MTD evaluation period: Principal stratum – patients will be excluded from the analysis and replaced
Summary measure	Posterior probability of the incidence of DLT in toxicity categories during the MTD evaluation period per dose level for all evaluable patients

7.4.4 Supplementary analysis

As a supplementary analysis, the joint BLRM may be analyzed using DLT data from the whole on-treatment period instead of DLT data from the MTD evaluation period. This analysis will include all treated patients, including 'backfill' patients and cross-over patients.

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.

7.5.1.1 Main analysis

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

7.5.1.4 Supplementary analysis

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

7.5.2 Secondary objective analysis

OR based on RECIST 1.1: (CTP version 1 and 2)
Objective response (OR) by RECIST 1.1 will be presented in terms of objective response rate (ORR), which is defined as the rate of patients whose best overall response is confirmed CR or PR as determined by the Investigator's assessment according to RECIST 1.1 from date of first treatment administration until the earliest of disease progression, death or last evaluable tumor assessment before start of subsequent anti-cancer therapy, loss to follow-up or withdrawal of consent.

OR based on itRECIST: (CTP version 3 and later)
Objective response (OR) by itRECIST will be presented in terms of objective response rate (ORR), which is defined as the rate of patients whose best overall response is confirmed itCR or itPR as determined by the Investigator's assessment according to itRECIST from date of first treatment administration until the earliest of confirmed disease progression, death or last evaluable tumor assessment before start of subsequent anti-cancer therapy, loss to follow-up or withdrawal of consent.

Each patient treated under CTP version 1 or 2 will be assigned to one of the following best overall response categories according to RECIST 1.1: CR, PR, stable disease (SD), progressive disease (PD), not evaluable (NE).

Each patient treated under CTP version 3 or later will be assigned to one of the following best overall response categories according to itRECIST: intratumoral CR, intratumoral PR, intratumoral SD, intratumoral unconfirmed PD, intratumoral confirmed PD, not evaluable (NE).

A best overall response of CR and PR (RECIST 1.1) or intratumoral CR and intratumoral PR (itRECIST) must be confirmed by a subsequent tumor assessment, i.e. a confirmed response requires a repeated observation on two occasions at least 4 weeks apart.

For a best overall response of SD (RESIST 1.1) or intratumoral SD (itRECIST), a minimal duration of 35 days (6 weeks +/-1 week to account for the imaging time window) is required.

ORR according to RECIST v1.1 and ORR according to itRECIST will be summarized descriptively with 95% confidence intervals using the Wilson method. Patients' time to tumor response and duration of response will be visualized by swimmer plots.

Best percentage change from baseline in size of target lesions (CTP version 1 and 2) and Best percentage change from baseline in size of non-injected target lesions (CTP version 3 and later) will be analyzed using descriptive statistics as well as waterfall plots. All lesion measurements recorded from start of trial treatment until the earliest of progression (confirmed intratumoral PD with CTP version 3 and later), start of subsequent anti-cancer therapy, loss to follow-up or withdrawal of consent will be taken into account when calculating the best percentage change from baseline.

Similarly, Best percentage change from baseline in size of injected lesions (CTP version 1 and 2) and Best percentage change from baseline in size of injected target lesions (CTP version 3 and later) will be analyzed using descriptive statistics as well as waterfall plots. All lesion measurements recorded from start of trial treatment until the earliest of progression (confirmed intratumoral PD with CTP version 3 and later), start of subsequent anti-cancer therapy, loss-to follow-up or withdrawal of consent will be taken into account when calculating the best percentage change from baseline.

However, for the last two endpoints, special attention should be paid to the derivation of baseline, which will be determined according to the itRECIST publication:
For each injected (target) lesion, the baseline is its diameter just before it is first injected, and the baseline SOD for injected lesions is the sum of these diameters, which may originate from different time points. The best response SOD is the SOD of these lesions at each lesion's smallest size after injection, again, possibly at different time points.

All secondary endpoints will be presented dose cohort, separately for Arm A and Arm B.

[redacted]

[redacted]

[redacted]

7.7 EXTENT OF EXPOSURE

Duration of treatment with BI 1387446 and Duration of treatment with ezabenlimab will be summarized descriptively.

The Cumulative total dose for both trial drugs and the Number of cycles initiated will also be summarized.

The Number of patients with at least one dose reduction of BI 1387446 will be displayed.

7.8 SAFETY ANALYSIS

All safety analyses will be performed on the treated set, besides the analyses for MTD determination. These will be performed on the MTD set. Treated patients will be analyzed separately for each treatment arm and according to their initial planned treatment.

Patients who cross over from Arm A to Arm B will be considered for both treatment arms: in Arm A according to their initial planned treatment and in Arm B according to their planned combination treatment at cross-over to Arm B. See Section 6.1 for details.

Safety data recorded during the Residual Effect Period (REP) of 90 days will be considered as on-treatment.

7.8.1 Adverse Events

The analyses of AEs will be descriptive in nature. All analyses of AEs will be based on the number of subjects with AEs and NOT on the number of AEs. The analysis will be based on BI standards (9.6). AEs will be coded using the most recent version of MedDRA. The severity of AEs will be scaled according to the Common terminology Criteria for Adverse Events (CTCAE) version 5.0.

The analysis of AEs will be based on the concept of treatment emergent AEs. That means that all AEs occurring between first administration of trial medication until 90 days after last administration of trial medication will be considered treatment-emergent and assigned to the initial planned treatment.

All AEs occurring before first administration of trial medication will be assigned to ‘screening’ and all AEs occurring after last administration of trial medication + 90 days will be assigned to ‘follow-up’ (for listings only). For details on the treatment definition, see Section 6.1.

AEs will be reported with start day and end day as calculated from the first day of treatment with trial 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.

AEs will be displayed by the initial planned dose of trial medication administered on the first day of treatment. Patients who undergo a cross-over from Arm A to Arm B during the trial will be displayed in both treatment arms: by the initial planned dose of study medication in Arm A and by the planned combination dose in Arm B.

The frequency of patients with AEs during the on-treatment period will be summarized by treatment, primary system organ class (SOC) and preferred term (PT) for each of the following AE tables:

The frequency of patients with AEs during the on-treatment period will be summarized by treatment, primary system organ class (SOC) and preferred term (PT) for each of the following AE tables:

- DLTs
- All AEs by highest CTCAE grade
- Serious AEs by highest CTCAE grade
- Investigator assessed BI 1387446 related AEs by highest CTCAE grade
- Investigator assessed ezabenlimab related AEs by highest CTCAE grade
- Investigator assessed BI 1387446 related SAEs by highest CTCAE grade
- Investigator assessed ezabenlimab related SAEs by highest CTCAE grade
- Investigator assessed Adverse Events of Special Interest (AESI) by highest CTCAE grade
- Investigator assessed infusion-related AEs by highest CTCAE grade
- Investigator assessed immune-related AEs by highest CTCAE grade
- Investigator assessed procedural complication (biopsy/injection) AEs by highest CTCAE grade
- AEs leading to treatment discontinuation of BI 1387446 by highest CTCAE grade
- AEs leading to treatment discontinuation of ezabenlimab by highest CTCAE grade
- AEs leading to dose reduction of BI 1387446 by highest CTCAE grade
- AEs leading to death

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

Listings of DLTs, fatal AEs, serious AEs, AEs leading to treatment discontinuation of BI 1387446, AEs leading to treatment discontinuation of ezabenlimab and AEs leading to dose reduction of BI 1387446 will be provided.

7.8.2 Laboratory data

The analysis of laboratory data will be descriptive in nature and will be based on BI standards (9.7). The same on-treatment period as considered for the analysis of AEs will be applied for laboratory values. Patients having at least one post-baseline laboratory value will be displayed in the descriptive analyses.

CTCAE grades for applicable laboratory parameters will be calculated according to CTCAE v5.0. Patients with missing CTCAE grade at baseline or no baseline value but with post-baseline values will be displayed as "Missing" for those laboratory parameters where CTCAE grading is applicable. For some laboratory parameters which cannot be assigned a CTCAE grade at baseline, CTCAE shift tables will be replaced by shift tables of pre-defined categories based on Upper Limit of Normal (ULN) values. A similar approach will also be adopted for creatinine due to the ambiguity of CTCAE grading for grade 2 and 3. The predefined categories will follow BI standards (9.8).

The following outputs will be presented:

- Descriptive statistics, including baseline and change from baseline
- Frequency of patients with shifts from baseline:
  - Transitions of CTCAE grade from baseline to worst laboratory value,
  - Transitions of CTCAE grade from baseline to last laboratory value
- Frequency of patients with possible clinically significant abnormalities (according to the BI standard definitions)

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, BI standard definitions 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 (or CTCAE grading at baseline cannot be assigned) 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 will be considered as possibly clinically significant.

Corrected calcium:
The grading of hypocalcaemia 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.

Hepatic enzyme elevations (potential Hy's law cases):
These are defined as those cases where a combination of all of the following events occurred: any on-treatment value of ALT and/or AST > 3ULN (upper limit of normal) with total bilirubin ≥ 2ULN and ALKP < 2ULN. The events can occur in any order, but must occur within 30 days of the previous event, i.e. the second event must occur within 30 days of the first event, and the third event must occur within 30 days of the second event, etc. Patients with missing laboratory values for liver enzymes will be excluded from these analyses, but presented separately.

A listing of patients with hepatic injuries according to CTP Section 5.2.7.1.4 will be provided.

7.8.3 Vital signs

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

7.8.4 ECG

Analyses of ECG will be descriptive in nature. Newly emergent abnormalities will be recorded and analyzed as adverse events. As outlined in Section 4, centrally evaluated ECG recordings will not be analyzed.

7.9 OTHER ANALYSIS

[redacted]

7.9.3 Eastern Cooperative Oncology Group performance status

The best, worst and last ECOG performance status during treatment will be summarized by dose cohort and baseline ECOG status.

8. TIMEPOINT OF RELEASE OF TREATMENT INFORMATION

The treatment information will be loaded into the trial database at trial initiation.

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.
9.2	Committee for Medicinal Products for Human Use: ICH E9 (R1) addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials: step 5 (17 February 2020, EMA/CHMP/ICH/436221/2017) [R21-0743]
9.3	*BI-KMED-BDS-HTG-0035:* "Handling of missing and incomplete AE dates", current version, Group “Med Biostatistics & Data Sciences”, KMED.
9.4	*BI-KMED-TMCP-MAN-0014:* “Noncompartmental PK/PD Analyses of Clinical Studies”, current version; KMED.
9.5	*BI-KMED-BDS-HTG-0045:* "Standards for Reporting of Clinical Trials and Project Summaries", current version, Group “Med Biostatistics & Data Sciences”; KMED.
9.6	*BI-KMED-BDS-HTG-0066:* "Analysis and Presentation of Adverse Event Data from Clinical Trials", current version, Group “Med Biostatistics & Data Sciences”; KMED.
9.7	*BI-KMED-BDS-HTG-0042:* "Handling, Display and Analysis of Laboratory Data", current version, Group “Med Biostatistics & Data Sciences”; KMED.
9.8	*BI-KMED-BDS-HTG-0036:* “CTCAE Grading for Laboratory Values”, current version, Group “Med Biostatistics & Data Sciences”; KMED.
9.9	*BI-KMED-TMCP-MAN-0010:* “Description of Analytical Transfer Files and PK/PD Data Files”; KMED.

11. HISTORY TABLE

Table 11:1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
1.0	**08-APR-24**	[redacted]	None	This is the final TSAP.