TRIAL STATISTICAL ANALYSIS PLAN

c35274648-01

BI Trial No.:	1336-0012
Title:	An open label, Phase I study of BI 836880 monotherapy and combination therapy of BI 836880 and BI 754091 in Japanese patients with advanced solid tumors Including Protocol Amendment #2[c25769893-03]
Investigational Product(s):	BI 836880 Ezabenlimab (BI 754091)
Responsible trial statistician(s):	[redacted] Telephone: [redacted] Fax: [redacted]
Date of statistical analysis plan:	14 April 2021 SIGNED
Version:	Final

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2. LIST OF ABBREVIATIONS

Term	Definition / description
AE	Adverse Event
ADA	Anti-Drug Antibodies
ALQ	Above the Limit of Quantification
[redacted]	
AUC	Area under the curve
BLQ	Below Lower Limit of Quantification
BRPM	Blinded Report Planning Meeting
C_{max}	Maximum Concentration
CTC	Common Terminology Criteria
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
DCE-MRI	Dynamic Contrast-Enhanced Magnetic Resonance Imaging
DM&SM	Boehringer Ingelheim Data Management And Statistics Manual
DLT	Dose Limiting Toxicity
DRA	Drug Regulatory Affairs
DMG	Dictionary Maintenance Group
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic Data Capture
EMEA	European Agency For The Evaluation Of Medicinal Products
EOT	End of Treatment
FAS	Full Analysis Set
ICH	International Conference On Harmonisation
LLOQ	Lower Limit of Quantification
LOCF	Last Observation Carried Forward
LVEF	Left Ventricular Ejection Fraction
MedDRA	Medical Dictionary For Regulatory Activities
MQRM	Medical Quality Review Meeting
MTD	Maximum Tolerated Dose
Pd	Pharmacodynamics
PD	Progressive disease

Term	Definition / description
PD	Protocol deviation
[redacted]	
PK	Pharmacokinetics
PPS	Per Protocol Set
PSTAT	Project Statistician
PT	Preferred Term
Q1	Lower Quartile
Q3	Upper Quartile
RECIST	Response Evaluation Criteria In Solid Tumors
REP	Residual Effect Period
RP2D	Recommended Phase 2 Dose
SA	Statistical Analysis
SD	Standard Deviation
SMQ	Standardised MedDRA Query
SOC	System Organ Class
$t_{1/2}$	Half Life Time
t_{max}	Time to reach Maximum Plasma Concentration
TCPK	Trial Clinical PharmacokineticsPharmacokineticist
TESS	Treatment Emergent Signs And Symptoms
ToC	Table of Contents
TMW	Trial Medical Writer
TSAP	Trial Statistical Analysis Plan
ULOQ	Upper Limit of Quantification

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

SAS® Version 9.4 will be used for all analyses.

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

This section is not applicable.

5. ENDPOINT(S)

This is a phase I study, containing two parts: Part I (dose escalation of BI 836880) and part II (dose escalation of BI 836880 in combination with ezabenlimab) in Japanese patients with advanced solid tumors.

The objective of part I is to determine MTD and/or RP2D and safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (Pd) of BI 836880 monotherapy.

The objective of part II is to determine MTD and/or RP2D and safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (Pd) of the combination therapy of BI 836880 and ezabenlimab.

5.1 PRIMARY ENDPOINT

Part I:

The primary endpoint is the determination of the maximum tolerated dose (MTD) of BI 836880 based on the number of patients with dose-limiting toxicities (DLTs) during the MTD evaluation period. The definition of DLTs for solid tumor patients is provided in Section 4.1.7 of the CTP.

The MTD is 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, and may be considered reached if one of the following criteria is fulfilled:

1. The posterior probability of the true DLT rate in the target interval [0.16–0.33) of the MTD is above 0.5, OR

2. At least 9 patients have been treated in this part, of which at least 6 at the MTD.

The MTD evaluation period is defined as the first treatment cycle.

Part II:

The primary endpoint is the determination of maximum tolerated dose (MTD) of the combination of BI 836880 and ezabenlimab, based on the number of patients with dose-limiting toxicities (DLTs) during the MTD evaluation period. The definition of DLTs for solid tumor patients is provided in Section 4.1.7 of the CTP.

The MTD is 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, and may be considered reached if one of the following criteria is fulfilled:

1. The posterior probability of the true DLT rate in the target interval [0.16 – 0.33) of the MTD is above 0.5, OR

2. At least 9 patients have been treated in this part, of which at least 6 at the MTD.

The MTD evaluation period is defined as first treatment cycle.

5.2 SECONDARY ENDPOINTS

5.2.1 Key secondary endpoint

Not applicable.

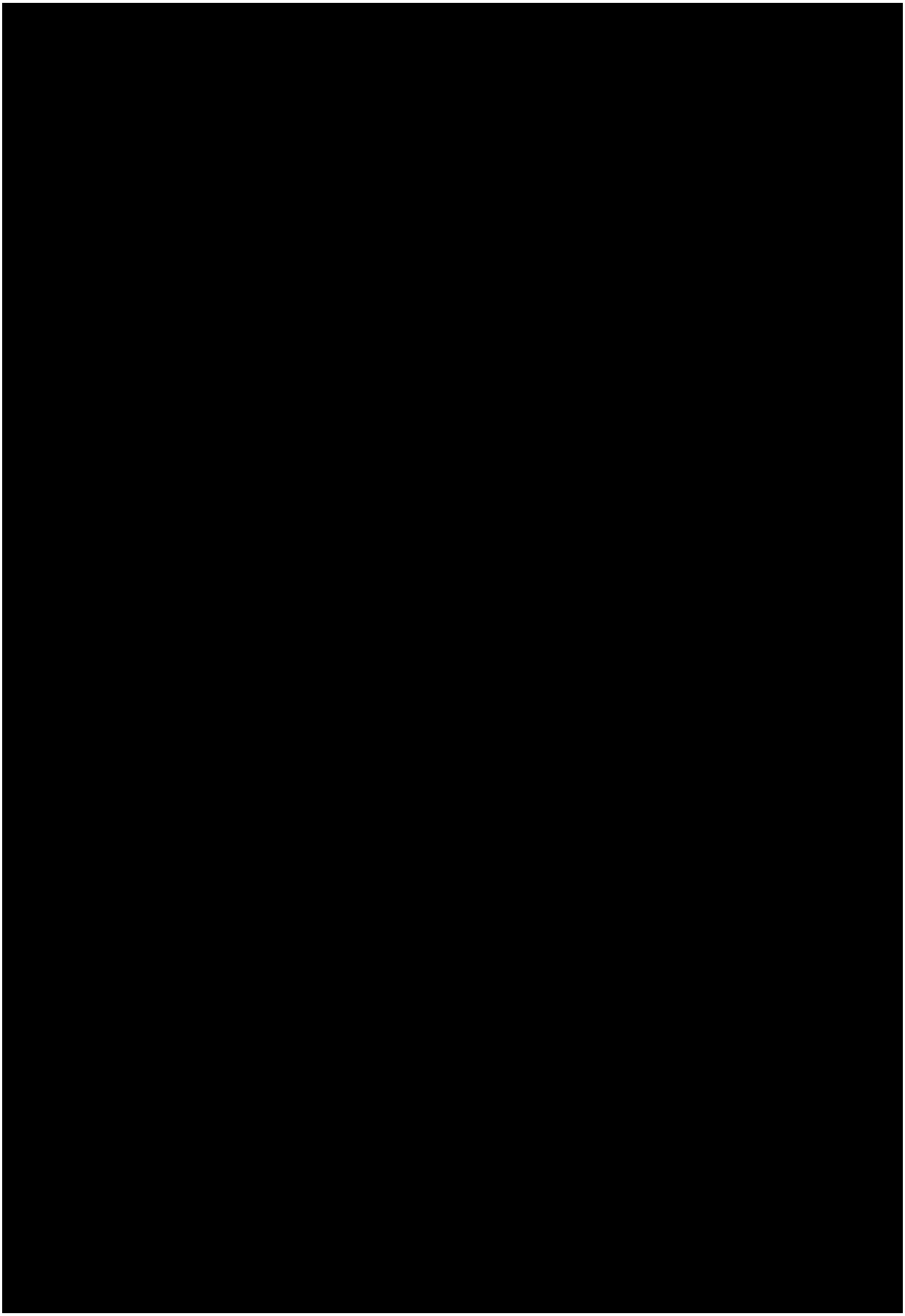
5.2.2 Secondary endpoints

Part I:

- The following PK parameters of BI 836880 will be calculated in cycles 1, 2 and 4:
  - C_{max}: maximum measured concentration of BI 836880 in plasma
  - $AUC_{0\text{-}504h}$: area under the concentration-time curve of BI 836880 in plasma over the time interval from 0 to 504 hours.

Part II:

- The following PK parameters of BI 836880 and ezabenlimab will be calculated in cycles 1 and 4:
  - C_{max}: maximum measured concentration of BI 836880 and ezabenlimab in plasma.
  - $AUC_{0\text{-}504h}$: area under the concentration-time curve of BI 836880 and ezabenlimab in plasma over the time interval from 0 to 504 hours.



6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENT

In this open label Phase I trial, consisting of 2 parts, treatments are not randomized. In part I, the starting dose is BI 836880 360 mg every three weeks. In part II, the starting dose combination is BI 836880 120 mg + ezabenlimab 240 mg every three weeks. Dose escalation decision will be made by Safety Monitoring Committee (SMC) based on the available safety data (including DLTs, AEs that are not DLTs, and AE information), as well as the recommendations from the BLRM.

The following treatment period will be defined:

- Screening: from the date of informed consent to the date of the first study medication intake -1 day.
- On-treatment: from the date of first intake of study drug to the date of last study drug administration + 42 days. i.e., actual on-treatment period + REP
- Post-study: from the last day of on-treatment period+1 day

This will be applied both for adverse events and immune-related adverse events. Referring to CTP section 5.2.9 for details of AE collection and reporting.

6.2 IMPORTANT PROTOCOL DEVIATIONS

A protocol deviation (PD) is important if it affects the rights or safety of the study subjects, or if it can potentially influence the primary outcome measurement(s) in a non-negligible way. Patients with important PDs that could potentially impact the evaluation of the primary endpoint(s) will be excluded.

A list of important PDs is given in Table 6.2:1 below. Important PDs will be reviewed at Medical Quality Review Meeting (MQRM) conducted periodically during the trial. A list of protocol deviations will be discussed at the report planning meetings (RPMs).

If the data show other important PDs, this table will be supplemented accordingly at MQRMs or RPMs or through team review of the manual PV log. The decision whether a patient will be excluded from the analysis will be made at the final RPM prior to DBL.

Table 6.2:1 Important Protocol Deviations

Category/ Code		Description	Requirements	Excluded from	Automatic/ Manual
A		**Entrance criteria**			
	A1.1	Requirements on age or agreement on birth control not met	Inclusion criteria 1, 3 not met	None	Automatic
	A1.2	Protocol specified disease stage / condition not met	Inclusion criteria 4, 5 not met	None	Automatic

	A1.3	Adequate health condition not met	Inclusion criteria 6, 7, 8 not met	None	Automatic
	A2.1	Hypersensitivity to the trial drug	Exclusion criteria 1 met	None	Automatic
	A2.2	Previous anti-cancer therapy washout period not met	Exclusion criteria 6 met	None	Automatic
	A2.3	Clinically relevant concomitant or history of disease, pre-existing conditions	Exclusion criteria 2, 3, 4, 7, 8, 9, 10, 11, 12, 13, 14,15, 16 met	None	Automatic
	A2.5	Requirement of adherence to protocol not met	Exclusion criteria 18 met	None	Automatic
	A2.6	Pregnancy / breast feeding related	Exclusion criteria 21 met	None	Automatic
	A2.9	Immunosuppressive corticosteroid use within 4 weeks	Exclusion criteria 5 met	None	Automatic
	A2.13	Previous enrolment in this trial	Exclusion criteria 19 met	None	Automatic
	A2.14	Patients who must or wish to continue the use of restricted medications	Exclusion criteria 17 met	None	Automatic
	A2.20	Haematological malignancies	Exclusion criteria 20 met	None	Automatic
B		**Informed consent**			
	B1	Informed consent (initial and re-consent) not available/not done	Informed consent date missing	All	Automatic
	B2	Informed consent (initial and re-consent) too late	Informed consent date was later than the initiation of treatment	None	Automatic
C		**Trial medication**			
	C1	Incorrect trial medication taken	Decision at MQRM (e.g., incorrect dose taken, overdose, use of expired medication etc.)	None	Automatic and manual
	C3	Administration not according to protocol	Decision at MQRM (e.g. outside of dosing schedule window, unreasonable drug administration time, etc.)	None	Automatic and manual
	C6	Administration of study medication which exceeded the limit of in-use stability	Decision at MQRM	None	Automatic and manual
	C5	Retreatment criteria were not met but the patient is treated (Cycle 2~)	Retreatment criteria was not met according to CTP section 4.1.6	None	Manual

	C7	Dose reduction not done even though patient meets the dose reduction criteria.	Dose reduction not done according to CTP section 4.1.7	None	Manual
	C8	Treatment is not discontinued even though patient meets the discontinuation criteria	Treatment is not discontinued according to CTP section 3.3.4.1	None	Manual
D		**Concomitant medication**			
	D2	Prohibited medication use	Refer to CTP section 4.2.2.1	None	Manual
E		**Incorrect procedure**			
	E1	Certain deviations from procedures used to measure secondary data	Decision at MQRM (e.g. incorrect usage of sampling tube, store at wrong temperature, etc.)	None	Manual
Z		**Missing Data**			
	Z1	Important PK time points not taken	Blood sample not taken at important time point (e.g. end of infusion sample not taken, sample at elimination phase not taken, etc.)	None	Automatic
	Z3	Missing critical safety information in cycle 1	Essential safety information not taken	None	Automatic and manual

6.3 SUBJECT SETS ANALYSED

Treated set (TS) in monotherapy:
This patient set includes all patients enrolled in the trial who were documented to have administrated at least one dose of BI 836880 monotherapy. The TS is used for both efficacy analysis and safety analyses.

Treated set (TS) in combination therapy:
This patient set includes all patients enrolled in the trial who were documented to have administrated at least one dose of BI 836880 and ezabenlimab combination therapy. The TS is used for both efficacy analysis and safety analyses.

Dose escalation cohort treated set in monotherapy:
This patient set includes all patients enrolled in dose escalation cohort of monotherapy who were documented to have administrated at least one dose of study medication and were evaluable for the MTD determination. This set is used for dose finding and MTD determination in Part I.

Dose escalation cohort treated set in combination therapy:
This patient set includes all patients enrolled in dose escalation cohort of combination therapy who were documented to have administrated at least one dose of study medication and were evaluable for the MTD determination. This set is used for dose finding and MTD determination in Part II.

PK parameter analysis set (PKS)
The PK parameter analysis set (PKS) includes all subjects from the TS who provide at least one PK parameter that is not excluded.

[redacted]

6.5 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") (3). Missing data and outliers of PK data are handled according to (2). Please refer to Section 7.4 of the CTP for more details. According to (2), missing biomarker data (NOS - no sample, NOR - no valid result, NOA - not analyzed) will not be imputed. Handling of data below or above the limit of quantification, e.g. the myriad panel data:

- BLQ data will be replaced by ½ LLOQ
- ALQ data will be replaced by ULOQ, if ULOQs are available.

Otherwise, ALQ data will be excluded from the analysis.

[redacted]

6.6 BASELINE, TIME WINDOWS AND CALCULATED VISITS

Baseline values will be the measurements taken most recently prior to first administration of study drug (same dates are allowed). If not available, then the values reported at the screening visit will be considered. For lab values, not only the examination date but also time is recorded, examination time has to be taken into account when defining baseline. That is, a laboratory value on the same date as the first study drug administration is considered as baseline value if and only if the time of laboratory value is before or the same as the time of study drug administration.

Time windows and visits will be calculated to determine the planned day of tumour measurement and response status, based on the protocol-specified tumour imaging schedule. Imaging data will be displayed as screening, and then every 2 cycles i.e.: Week 6, 12, 18, 24, for the first 6 months of treatment, then every 3 cycles thereafter (Week 33, 42, 51… etc.). In order to identify whether consecutive imaging time points are missing for a given patient, a nominal time point will be assigned to each and every image. This nominal time points and windows is defined in Table 6.6:1. Images which are not older than 28 days at start of treatment will be suffice as screening images and do not need to be repeated.

Table 6.6: 1 Nominal time points and windows for imaging

Nominal time point (weeks from start of study medication)	Due date of scans (days)*	Window (days)
6	43	1 to ≤ 64
12	85	65 to ≤ 106

18	127	107 to ≤ 148
24	169	149 to ≤ 200
33	232	201 to ≤ 263
42	295	264 to ≤ 326
51	358	327 to ≤ 389
Etc., 9 week interval	Etc.	Etc.

* The date of the first dose of study medication is Day 1

7. PLANNED ANALYSIS

For End-Of-Text (EoT) tables, the set of summary statistics is: N / Mean / SD / Min / Q1 (lower quartile) / Median / Q3 (upper quartile) / Max.

Tabulations of frequencies for categorical data will include all possible categories and will display the number of observations in a category as well as the percentage (%) relative to the respective treatment group (unless otherwise specified, all patients in the respective patient set whether they have non-missing values or not). Percentages will be rounded to one decimal place. The category missing will be displayed only if there are actually missing values.

[redacted]

For PK, [redacted]
For analyte concentrations, the following descriptive statistics will additionally be calculated:

Nobs	Number of observations
CV	arithmetic coefficient of variation
gMean	geometric mean
gCV	geometric coefficient of variation

For PK parameters, the following descriptive statistics will additionally be calculated:

Nobs	Number of observations
CV	arithmetic coefficient of variation
gMean	geometric mean
gCV	geometric coefficient of variation
P10	10th percentile
Q1	1st quartile
Q3	3rd quartile
P90	90th percentile

The data format for descriptive statistics of concentrations will be identical with the data format of the respective concentrations. The descriptive statistics of PK parameters will be calculated using the individual values with the number of decimal places as provided by the evaluation program. Then the individual values as well as the descriptive statistics will be reported with three significant digits in the CTR.

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

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

7.2 CONCOMITANT DISEASES AND MEDICATION

Descriptive statistics are planned for concomitant diseases. Concomitant therapies will be displayed in listing.

7.3 TREATMENT COMPLIANCE

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

Compliance will be calculated for subjects having attended the visit. A subject is considered having attended the visit if the indicated visit is captured in the eCRF database. In particular, if a subject attended the visit, but is not treated at the visit, the compliance of this visit is considered as 0%.

Compliance with trial medication will be based on the drug infusion/administered eCRF data and calculated as amount of drug infused/administered divided by the amount of drug to be infused/administered expressed as a percentage, see calculations below.

"Per Visit" Compliance to trial medication will be calculated as follows:

$$\frac{(\text{Amount of drug infused/administered at Visit X(n)})}{(\text{Amount of drug planned to be infused/administered at Visit X(n)})} \times 100$$

Overall Compliance to trial medication will be calculated as mean of the "per visit" compliance.

The compliance will be based on the total volume infused in mL (eCRF data) compared to total volume prepared (eCRF data).

7.4 PRIMARY ENDPOINT

In part I and II, the primary endpoint is to assess the MTD based on the number of patients presenting DLTs during the MTD evaluation period. The primary analysis is for the determination of the MTD. The purpose of this analysis is to summarize and document the data that led to the selection of the MTD. Therefore, an overall summary of DLTs (see CTP Section 4.1.7 for the definition of DLTs) which occurred during the MTD evaluation period will be provided for each dose cohort from the dose finding cohort treated set. Patients, if any, who did not complete the MTD evaluation period for reasons other than DLT will be excluded from the analysis of the primary endpoint.

A summary of the number of patients with DLTs overall in any cycle will be also given by initial treatment and displayed in a similar format to the summary of DLTs occurring in the MTD evaluation period.

The analysis of the MTD is based on a Bayesian logistic regression model (BLRM) guided by the escalation with overdose control principle. The MTD is defined as the highest dose for a given schedule 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 during the dose escalation phase of the study 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. The model to be used is specified in CTP Section 7.

The posterior probabilities that the toxicity rates of each dose level fall into the categories specified in CTP Section 7 will be displayed.

7.5 SECONDARY ENDPOINTS

7.5.1 Key secondary endpoint

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

7.5.2 Secondary endpoints

The analysis of standard PK parameters will be performed according to (2) and (4). In general, all dose levels from Part I and Part II will be analysed separately.

7.7 EXTENT OF EXPOSURE

Treatment exposure will be primarily summarized by the total treatment exposure time and has been defined in Section 5.4 of this TSAP.

Treatment interruptions before permanent discontinuation will not be excluded. In part I, summary statistics for treatment time by each dose level, dosage of BI 836880 overtime and total treatment cycles initiated will also be provided. In part II, summary statistics for treatment time by each combination dose level, dosage of BI 836880 and ezabenlimab overtime and total treatment cycles initiated will also be provided. Dose reduction will be summarized by each dose levels from Part I and Part II separately. The maximum treatment delay in days will be summarized by each dose level for both parts.

7.8 SAFETY ANALYSIS

All safety analysis will be performed on the treated set.

7.8.1 Adverse events

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. Two analyses will be performed in part I and part II, respectively. The first analysis of safety will be performed for the first cycle of the trial (determination of the MTD, first cycle only, dose level = initial dose at the start of the treatment, dose escalation cohort treated set). This descriptive analysis will evaluate the MTD. The second analysis will be performed with respect to all cycles and will act as a support for the determination of the MTD (treated set).

For analysis of duration, severity etc. of multiple AE occurrences, data on the case report form (CRF) will be collapsed into AE episodes provided that all of the following applies:

- The same MedDRA lowest level term was reported for the occurrences.
- The occurrences were time-overlapping or time-adjacent (time-adjacency of two occurrences is given if the second occurrence started on the same day or on the day after the end of the first occurrence).
- Treatment did not change between the onset of the occurrences or treatment changed between the onsets of the occurrences, but no deterioration was observed for the later occurrence.

For further details on summarization of AE data, please refer to the guideline 'Analysis and Presentation of Adverse Event Data from Clinical Trials' (5).

For patients treated with the test drug, that means that all adverse events occurring between first drug infusion and 42 days after last drug infusion or death, whichever occurs first, will be assigned to the on-treatment period. All adverse events occurring before any study drug infusion will be assigned to ‘screening’ and all adverse events occurring after last study drug infusion + 42 days will be assigned to ‘post-study’ (for listings only). For details on the treatment definition, see Section 6.1.

An overall summary of adverse events will be presented. This summary will exclude the rows ‘Severe AEs’, ‘Significant AEs’, ‘AEs of special interest’ and ‘Other significant AEs’ but will include additional rows for ‘AEs leading to dose reduction’ and ‘AEs by highest Common Terminology Criteria (CTC) grade’.

The frequency of patients with adverse events will be summarized by highest CTC grade (grades 1, 2, 3, 4, 5 and all grades), treatment, primary system organ class and preferred term for each of the following AE tables as well as relatedness of AEs to treatment and seriousness:

For Part I and Part II:

- All AEs
- Drug-related AEs
- AEs leading to dose reduction
- Drug-related AE leading to dose reduction
- AEs leading to treatment discontinuation
- Drug-related AEs leading to treatment discontinuation
- Drug-related AEs leading to treatment discontinuation or dose reduction

- AEs leading to death
- Serious AEs
- Drug-related serious AEs
- Non-serious AE with higher than 5% occurrence rate
- Adverse Events of Special Interest (AESIs)
- DLTs

Part II only:

- Immune-related AEs
- Immune-related AEs leading to dose reduction
- Immune-related AEs leading to treatment discontinuation
- Immune-related AEs leading to treatment discontinuation or dose reduction

All tables will be sorted by system organ classes (SOC) according to the standard sort order specified by the European Medicines Agency (EMA). Preferred terms (PTs) will be sorted by frequency (within SOC).

The above tables will be repeated with the project defined grouping of AE terms. Details of the project defined groupings are defined in the technical TSAP. In these tables the grouped AEs will replace the original PTs for all AEs that are included within the grouped term. The grouped AE categories will then be tabulated along with all remaining MedDRA PTs, sorted by descending frequency.

A reference table presenting the entire project defined groupings and MedDRA PTs within each grouping will also be produced.

Additional AE tables will be produced for AEs of special interest (hepatic injury as defined in CTP Section 5.2.9.1.4 and dose limiting toxicities as defined by 4.1.7), providing further details on highest CTC grade, action taken with study drug and time to first onset of AE.

7.8.2 Laboratory data

The analyses of laboratory data will be descriptive in nature and will be based on BI standards "Display and Analysis of Laboratory Data" (7). CTC grade for applicable lab parameters will be calculated according to CTCAE v5.0 (6).

Descriptive statistics of all converted laboratory values by visit will be provided including changes from baseline. Frequency tables of transitions relative to the reference range and of possible clinically significant abnormalities will be produced. For those parameters that have CTC grading possible clinically significant abnormalities are defined as those laboratory values with a CTC grade ≥ 2 that have had an increase of ≥ 1 grade from baseline. For those parameters for which no CTC grade has been defined standard BI project definitions will be used to decide on clinical significance. Further frequency table will show the transition of CTC grade from baseline to worst value and from baseline to last value on treatment.

Summaries will be produced of laboratory data recorded at screening, on-treatment and post-study periods. For details on the treatment definition, see Section 6.1.

Differential blood counts will be displayed in absolute value. In case a subject's differential blood count is reported in percentage, the following conversion will be applied:

Differential blood count [10^9/L]:
Differential [10^9/L] = Differential [%] *white blood cell count / 100

The corresponding reference ranges of the converted differential blood values are not allowed to be converted like the individual laboratory measurements. The reference range is taken from BI standard reference range definition.

The focus of the laboratory data analysis will be on the following laboratory parameters:

- Low values: Activated Partial Thromboplastin Time (aPTT), Prothrombin Time (PT), International Normalised Ratio (INR), White Blood Cell Count (WBC) with differential, Platelets (PLT)
- High values: Aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT), bilirubin, Alkaline Phosphatase (AP), Activated Partial Thromboplastin Time (aPTT), Prothrombin Time (PT), International Normalised Ratio (INR), Protein levels in urine

7.8.3 Vital signs

Descriptive statistics of all vital signs measurement by visits are planned for each dose levels.

The frequency of patients with increased blood pressure by highest CTC grade (grades 1, 2, 3 and all grades) and prior history of hypertension will be summarized. For the patients with hypertensive blood pressure measurements, frequency will be summarized by time to onset of hypertensive episode after infusion for each dose levels. Their duration and outcome of first hypertensive episode will also be reported. Any hypertension defined as grade 2 or higher will be shown with detailed increase date and administration information.

7.8.4 ECG

ECG data will be collected as described in CTP section 5.2.5. Clinically significant findings in ECG data will be reported under "Adverse events" if applicable and will be analysed accordingly.

7.8.5 Echocardiography

Descriptive statistics are planned for this section. A table shows LVEF at screening, EOT visit and percent change from baseline to final will be provided.

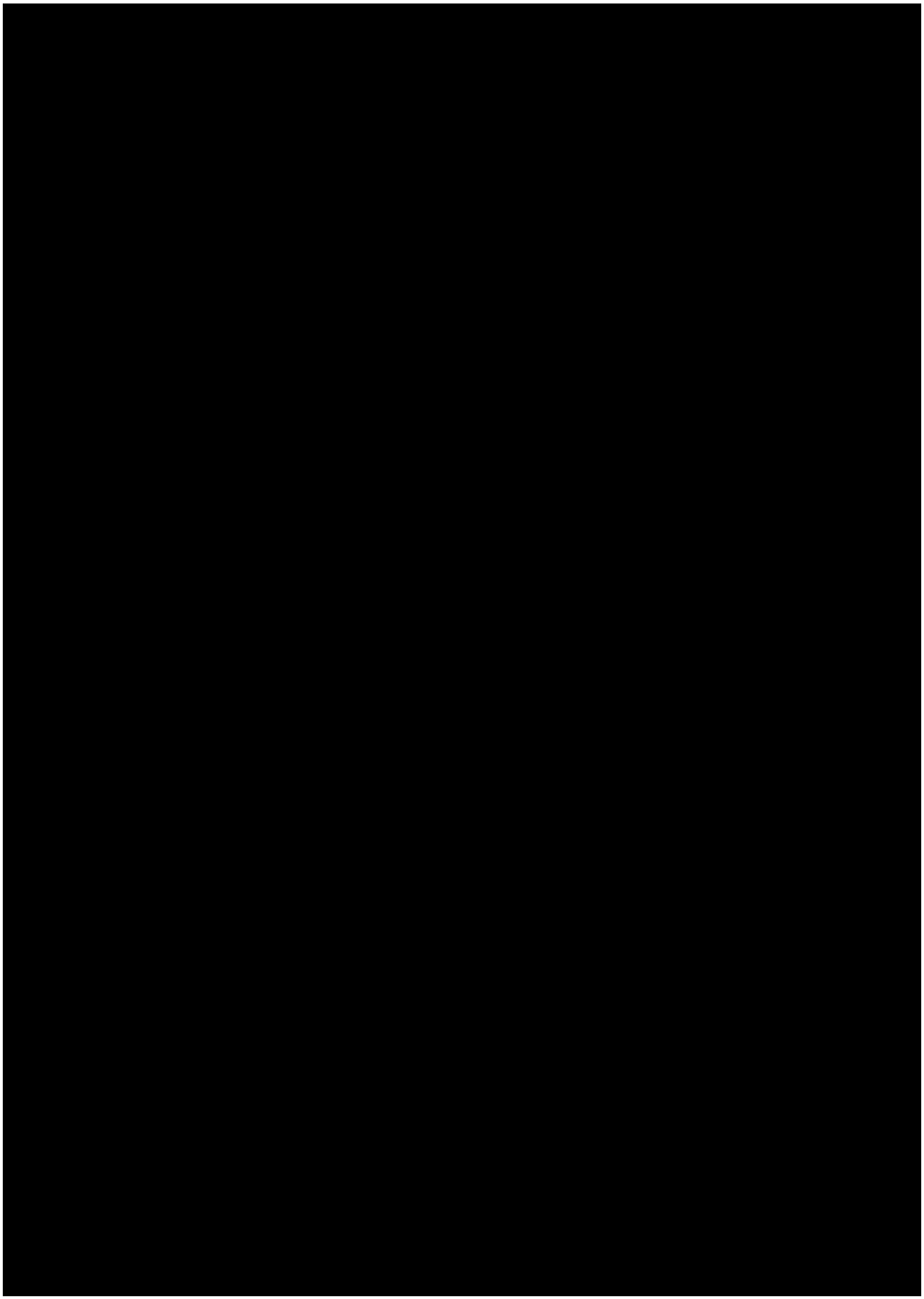
7.8.6 ECOG performance status

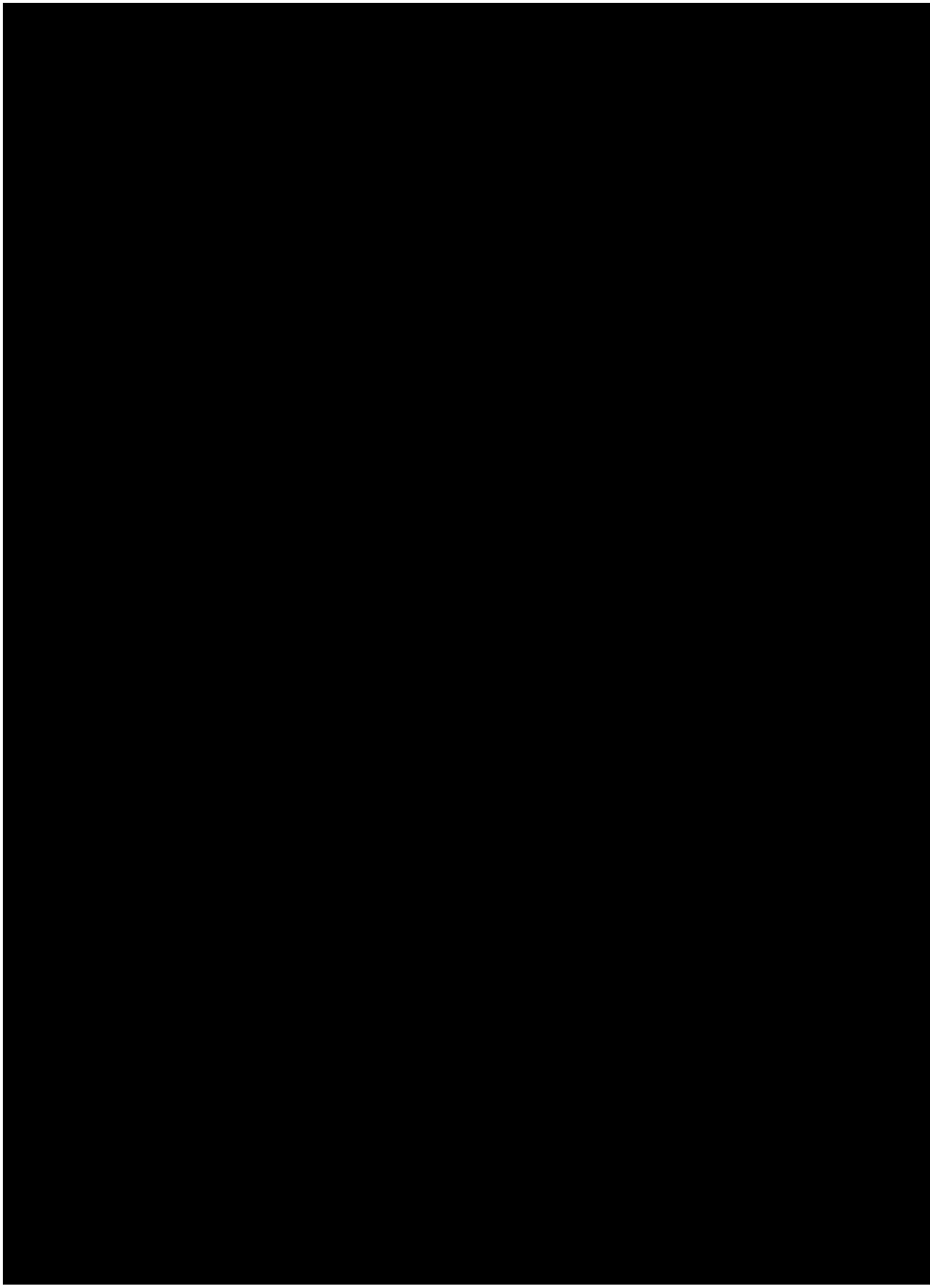
The best, worst and last ECOG performance status during treatment will be summarized by treatment and baseline status for Part I and Part II separately.

[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	*BI-KMED-TMCP-MAN-0014: "Noncompartmental PK/PD Analyses of Clinical Studies", current version; KMED.*
3	*001-MCG-156_RD-01: "Handling of missing and incomplete AE dates", current version; IDEA for CON.*
4	*BI-KMED-TMCP-MAN-0012: "Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics", current version; KMED.*
5	*BI-KMED-BDS-HTG-0041: "Analysis and Presentation of Adverse Event Data from Clinical Trials", current version.*
6	*Common terminology criteria for adverse events (CTCAE): version 5.0, published: November 27, 2017 - https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf; U.S. Department of Health and Human Services, National Institutes of Health and Human Services, National Cancer Institute 2017*
7	*BI-KMED-BDS-HTG-0042: "Handling, Display and Analysis of Laboratory Data", current version.*
8	*R09-0262 Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009; 45:228-247.*





10. HISTORY TABLE

Table 10: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
Final	14-04-2021	[redacted]	None	This is the final TSAP without any notification

APPROVAL / SIGNATURE PAGE

Document Number: c35274648 **Technical Version Number:1.0**

Document Name: 8-01-tsap-core

Title: An open label, Phase I study of BI 836880 monotherapy and combination therapy of BI 836880 and BI 754091 in Japanese patients with advanced solid tumors

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Author-Trial Clinical Pharmacokineticist	[redacted]	14 Apr 2021 10:43 CEST
Approval-Clinical Trial Leader		14 Apr 2021 10:47 CEST
Approval-Clinical Program Leaders		14 Apr 2021 10:49 CEST
Author-Trial Statistician		14 Apr 2021 10:49 CEST
Approval-Medical Writer		14 Apr 2021 10:59 CEST
Approval-Project Statistician		15 Apr 2021 16:32 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	**Signed by**	**Date Signed**