TRIAL STATISTICAL ANALYSIS PLAN
MODULE C (BI 754091+ BI 836880) c39700100-01

BI Trial No.:	1381.9
Title:	An open-label, Phase II trial evaluating the safety and efficacy of BI 836880 in combination with ezabenlimab in PD-(L)1 naïve and PD-(L)1 pretreated patient populations with advanced and/or metastatic solid tumours who have had at least one line of systemic therapy
Investigational Product(s):	Ezabenlimab (BI 754091 [anti-PD-1]) BI 836880 (anti-VEGF/Ang2)
Responsible trial statistician(s):	[redacted] Phone: [redacted]
Date of statistical analysis plan:	20 JUL 2022 SIGNED
Version:	Final
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1. TABLE OF CONTENTS

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2. LIST OF ABBREVIATIONS

Term	Definition / description
AE	Adverse Event
BHM	Bayesian Hierarchical Model
CR	Complete Response
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
DC	Disease Control
DoR	Duration of Response
ICH	International Conference on Harmonisation
IPD	Important Protocol Divations
MedDRA	Medical Dictionary for Regulatory Activities
MQRM	Medical Quality Review Meeting
MTD	Maximum Tolerated Dose
OR	Objective Response
OS	Overall Survival
PD	Progression of Disease
PFS	Progression-Free Survival
PK	Pharmacokinetics
PR	Partial Response
PSTAT	Project Statistician
PT	Preferred Term
RECIST	Response Evaluation Criteria in Solid Tumours
REP	Residual Effect Period
SA	Statistical Analysis
SAE	Serious Adverse Event
SD	Stable Disease
SOC	System Organ Class
ToC	Table of Contents
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 TSAP assumes familiarity with the Master and Module C Clinical Trial Protocol (CTP), including Protocol Amendments. In particular, the Module C TSAP is based on the planned analysis specification as written in Master and Module C CTP Section 7 “Statistical Methods and Determination of Sample Size”. Therefore, Module C TSAP readers may consult the Master and Module C 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 the latest version will be used for analyses.

R v3.5.1 and JAGS v4.3.0 or the latest versions will be used for BHM analysis.

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

Refer to the Master TSAP.

5. ENDPOINT(S)

5.1 PRIMARY ENDPOINT(S)

Refer to the Master TSAP.

5.2 SECONDARY ENDPOINT(S)

5.2.1 Key secondary endpoint(s)

This section is not applicable because no key secondary endpoints have been defined in the CTP.

5.2.2 Secondary endpoint(s)

Refer to the Master TSAP.

5.3 FURTHER ENDPOINT(S)

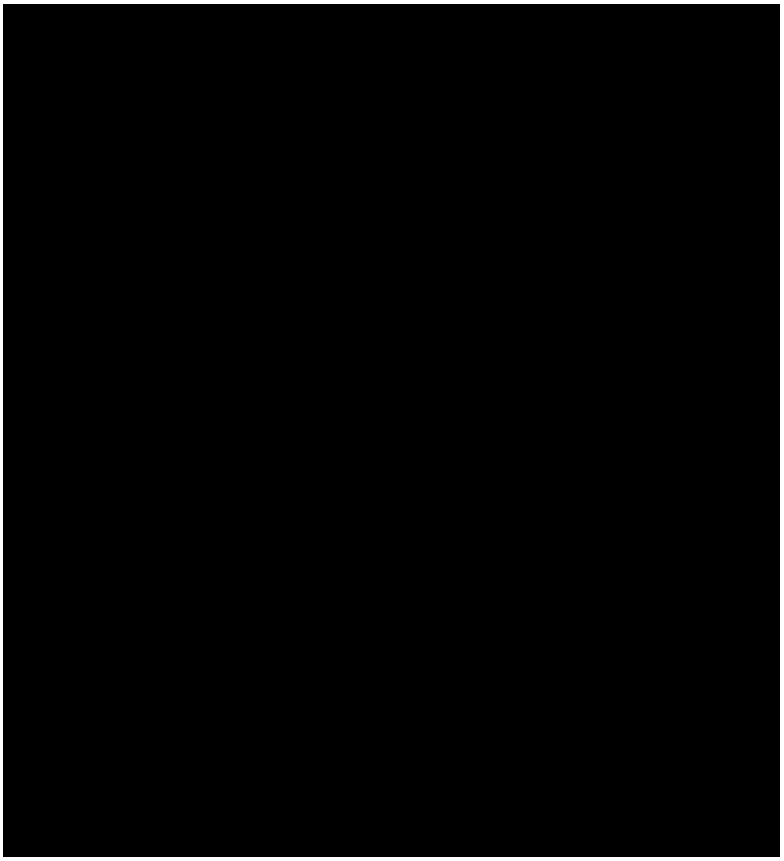
Refer to the Master TSAP.

[redacted]

5.4.1 Demographics and baseline characteristics

Refer to the Master TSAP.

[redacted]



6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENT(S)

Patients in this Module of the clinical trial will receive BI 836880 combined with BI 754091 by i.v. infusion after signing the Master and Module C informed consent forms and completing the screening processes. Treatment will be administered every 3 weeks (1 cycle = 21 days).

For definition of treatment periods refer to the Master TSAP.

6.2 IMPORTANT PROTOCOL DEVIATIONS

Refer to master TSAP for definition of iPD criteria listed in Table 6.2: 1.
The module C specific iPD criteria are listed in Table 6.2: 1 below.

Table 6.2: 1 Module C Important protocol deviations

Category / Code		Description	Comment / Example	Excluded from	Automatic/ Manual
A		**Entrance criteria not met**			
	A1a	**Inclusion criteria not met**			
	A1a.1	No measurable lesions according to RECIST 1.1	Inclusion criterion (IN) 3 not met	None	Automatic
	A2a	**Exclusion criteria met**			
	A2a.1	Unresolved toxicity from previous treatment.	Exclusion criterion (EX) 2 met	None	Automatic
	A2a.2	Significant cardiovascular/ cerebrovascular disease.	Exclusion criterion (EX) 3 met	None	Automatic
	A2a.3	Severe haemorrhagic or thromboembolic event in past 12 months	Exclusion criterion (EX) 4 met	None	Automatic
	A2a.4	Known inherited predisposition to bleeding or to thrombosis	Exclusion criterion (EX) 5 met	None	Automatic
	A2a.5	Patients who require full-dose anticoagulation	Exclusion criterion (EX) 6 met	None	Automatic
	A2a.6	Prior anti-angiogenic therapy (with the exception of CRC Cohort)	Exclusion criterion (EX) 7 met	None	Automatic

6.3 SUBJECT SETS ANALYSED

Module C Screened Set:
This patient set includes all patients who have signed the informed consent for the study and module C. The screened set will be used for patient disposition tables.

Module C Treated Set (TS):
This patient set includes all patients who were documented to have received at least one dose of trial medications in Module C. The TS is used for both efficacy analysis and safety analyses.

Module C Pharmacokinetic Set (PKS):
This patient set includes all patients in the TS with at least one valid plasma concentration. PKS will be used for all pharmacokinetic analyses.

6.5 POOLING OF CENTRES

This section is not applicable because centre/country is not included in the statistical analyses.

6.6 HANDLING OF MISSING DATA AND OUTLIERS

Refer to the Master TSAP.

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

Baseline values will be the measurements taken most recently prior to first administration of study drug in Module C.

Study day will be calculated relative to the date of the first administration of study drug in Module C. 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.

In order to identify whether consecutive imaging time points are missing for a given patient in this module, a nominal time point (i.e. Week 6, 12, 18 … etc.) will be assigned to each and every image. This is achieved by creating windows for every radiological response assessment. These windows are defined in Table 6.7: 1.

Table 6.7: 1 Nominal time points and windows for imaging

Nominal time point (weeks from start of study drug)	**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

If a patient does not have an image in one of the windows described above, he/she will be said to have missed an assessment for that time point.

Table 6.7: 2 Time windows for assignment of safety lab measurements to visits for statistical analysis

Window No.	Nominal visit	Nominal day	Interval
0	Cycle 1	1	NA
1	Cycle 1	8	[2,11]
2	Cycle 1	15	[12,18]
3	Cycle 2	22	[19,32]
4	Cycle 3	43	[33,53]
n+1	Cycle n	21*(n-1)+1	[21*(n-1)-9, 21*(n-1)+11]
18	EOT	21*16+1	[327, 351]
19	Safety Follow up	21*16+31	[352, ∞]

Note: n=3,4,5,…,16.

For patients discontinuing treatment before Cycle 16 or receive treatment beyond Cycle 16, identify the last treatment cycle n (>=3) and time windows of EOT and Safety Follow up will be derived according to Table 6.7: 3.

Table 6.7: 3 Time windows for patients discontinuing treatment before Cycle 16 or receive treatment beyond Cycle 16

Window No.	Nominal visit	Nominal day	Interval
n+1	Cycle n	21*(n-1)+1	[21*(n-1)-9, 21*(n-1)+11]
n+2	EOT	21*n+1	[21*n-9, 21*n+15]
n+3	Safety Follow up	21*n+31	[21*n+16, ∞]

7. PLANNED ANALYSIS

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Refer to the Master TSAP.

7.2 CONCOMITANT DISEASES AND MEDICATION

Refer to the Master TSAP.

7.3 TREATMENT COMPLIANCE

Only descriptive statistics are planned for this section.

7.4 PRIMARY ENDPOINT(S)

7.4.1 Primary analysis

Refer to the Master TSAP for BHM [2] approach description for the primary analysis of ORR.

For the BHM approach, a non-informative normal distribution with mean 0 and standard deviation of 2 is specified for the mean μ. For the inter-cohort heterogeneity parameter τ, a half normal distribution with parameter 1 is used which is a very conservative assumption regarding between-cohort variability and hence leads to only little borrowing of data across patient cohorts because there is little prior information on the strength of the correlation between the treatment effects across cohorts in Module C.

Prior to the primary analysis, the interim futility analysis is planned (section 7.4.2).

7.4.2 Interim analysis

Interim analysis will be performed when deemed necessary. Final/primary analysis for a specific treatment combination or cohort will be considered as interim analysis. A cohort or Module may be closed, if determined to be appropriate based on results of interim analyses. Note that interim analysis will not lead to any modifications within the running trial unless otherwise stated in a Module.

Refer to section 7.4 of the Master protocol and Module C protocol for details.

7.5 SECONDARY ENDPOINT(S)

7.5.1 Key secondary endpoint(s)

This section is not applicable because no key secondary endpoints have been defined in the CTP.

7.5.2 (Other) Secondary endpoint(s)

Refer to the Master TSAP.

[redacted]

7.7 EXTENT OF EXPOSURE

The numbers of cycle initiated will be summarized descriptively for each cohort.

7.8 SAFETY ANALYSIS

All safety analyses will be performed on the treated set (TS). Analysis will be performed as defined in Section 7.3.4 of the CTP.

7.8.1 Adverse events

Refer to the Master TSAP.

7.8.2 Laboratory data

Refer to the Master TSAP.

7.8.3 Vital signs

Refer to the Master TSAP.

7.8.4 ECG

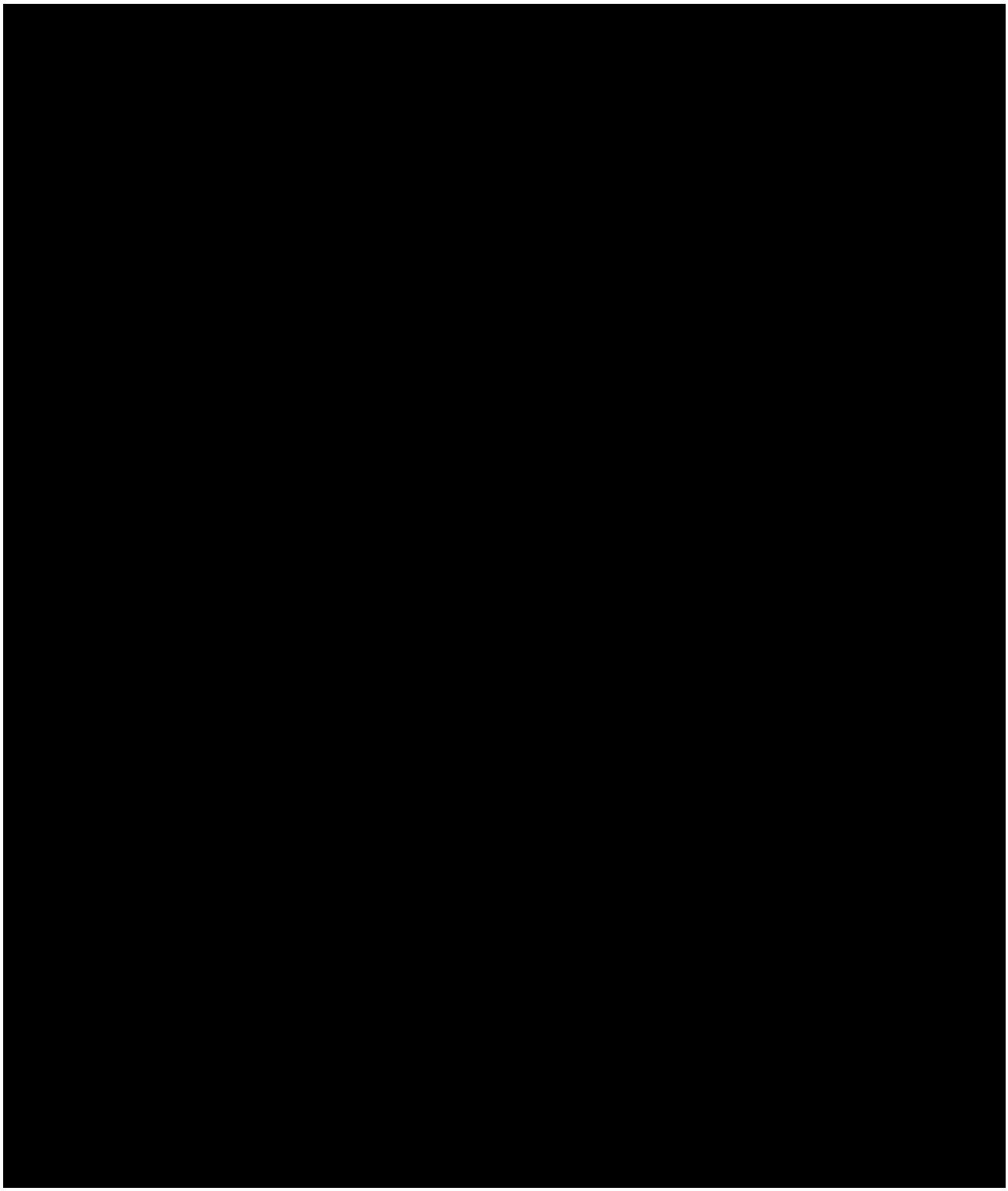
N/A

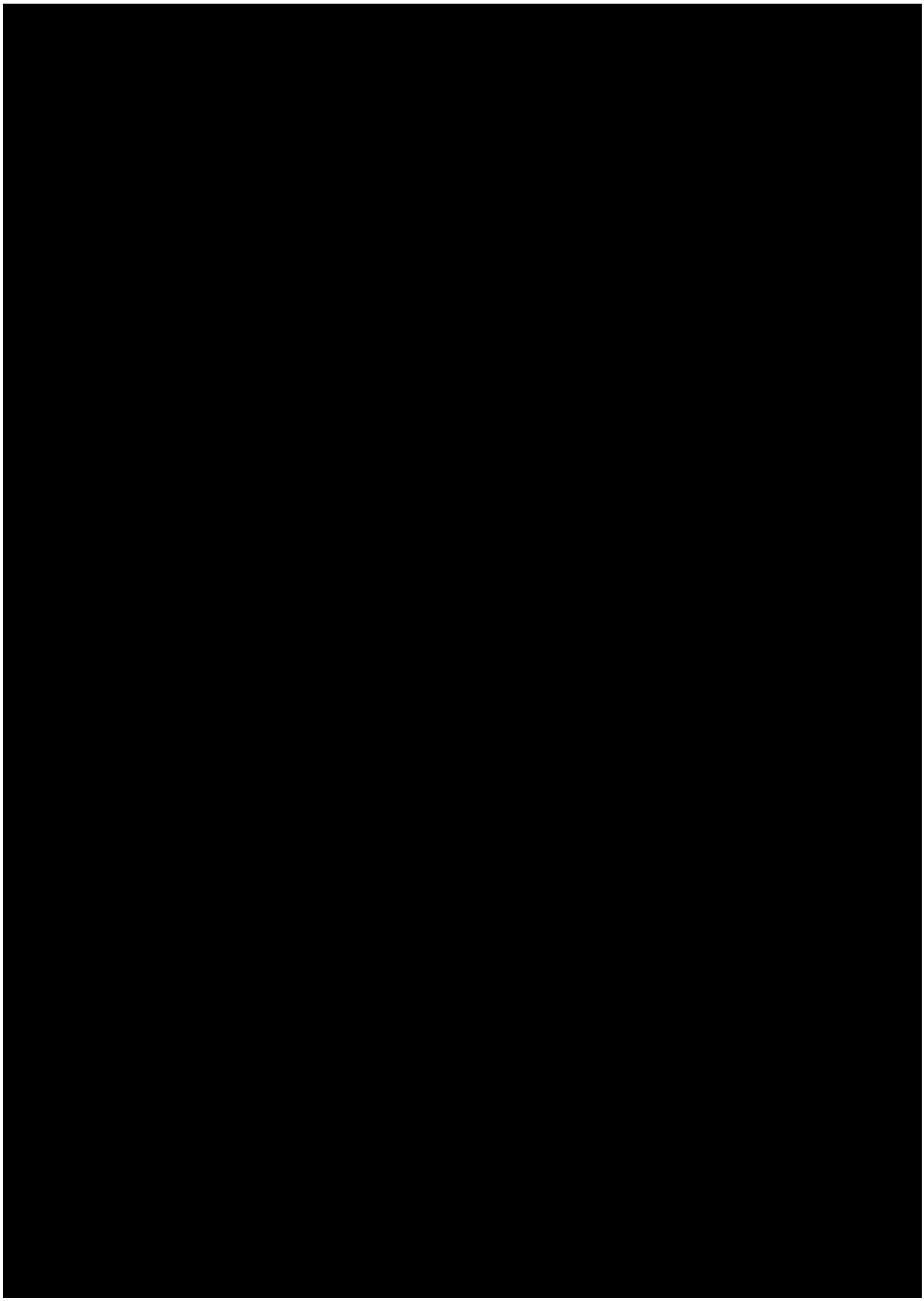
7.8.5 Others

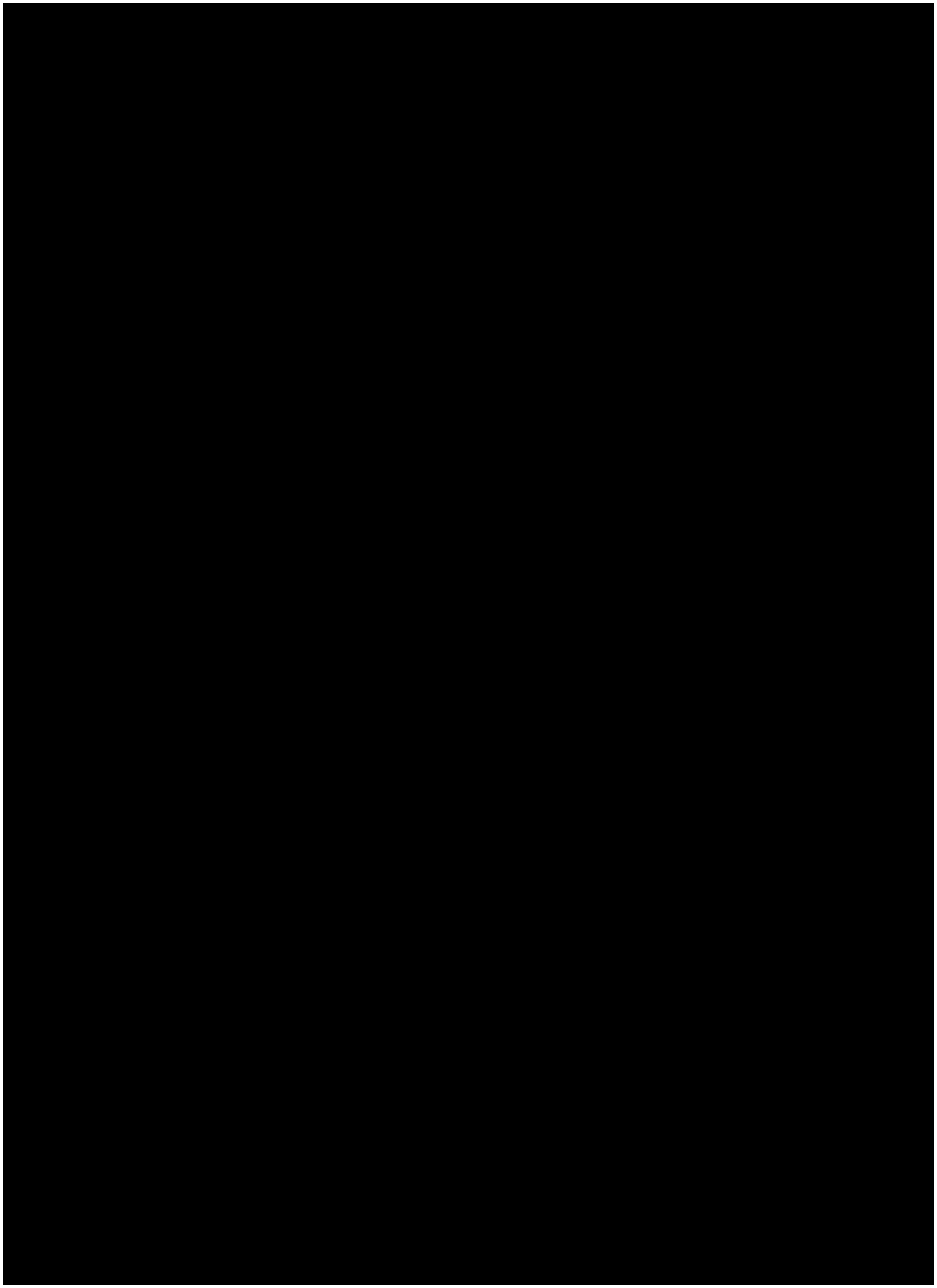
7.8.5.1 PK parameters

For ezabenlimab as well as for BI 836880 actual sampling times will be listed. Raw concentration values will be summarized descriptively per nominal time point. The derived PK parameters will be summarized descriptively.

As described in Section 5.3.1 of the Module C CTP, plasma concentration values will be used to support an exploratory model based analysis, using pooled data from other studies. These analyses will be done and reported outside of the CTR.







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.	Berry SM, Broglio KR, Groshen S, Berry DA. Bayesian hierarchical modeling of patient subpopulations: Efficient designs of Phase II oncology clinical trial. Clinical Trials 10 (5), 720-734 (2013) [R18-2260].

10. HISTORY TABLE

Table 10: 1 History table

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

APPROVAL / SIGNATURE PAGE

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Title: An open-label, Phase II trial evaluating the safety and efficacy of BI 836880 in combination with ezabenlimab in PD-(L)1 naïve and PD-(L)1 pretreated patient populations with advanced and/or metastatic solid tumours who have had at least one line of systemic therapy

Signatures (obtained electronically)

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Author	[redacted]	04 Aug 2022 15:43 CEST
Approval-Biostatistics		04 Aug 2022 15:47 CEST
Approval-Team Member Medicine		04 Aug 2022 15:52 CEST
Approval-Clinical Trial Leader		12 Aug 2022 17:30 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed