Trial Statistical Analysis Plan

c15782943-02

BI Trial No.:	1336.6
Title:	Phase I, non-randomized, open-label, multi-center dose escalation trial of BI 836880 administered by weekly repeated intravenous infusions in patients with advanced solid tumors Including Protocol Amendment #1 [c03124055-01]
Investigational Product(s):	BI 836880
Responsible trial statistician(s):	Phone: Fax:
Date of statistical analysis plan:	20 JUN 2017
Version:	Final

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2. LIST OF ABBREVIATIONS

Include a list of all abbreviations used in the TSAP

Term	Definition / description
ADA	Anti-Drug Antibodies
AP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
aPTT	Activated Partial Thromboplastin Time
AE	Adverse Event
AUC	Area Under the Curve
AUEC	Area under the effect curve
BLRM	Bayesian Logistic Regression Model
BSA	Body Surface Area
BMI	Body Mass Index
BRPM	Blinded Report Planning Meeting
CRF	Case Report Form
CTC	Common Terminology Criteria
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
DCE-MRI	Dynamic Contrast-Enhanced Magnetic Resonance Imaging
DLT	Dose Limiting Toxicity
DM&SM	Boehringer Ingelheim Data Management and Statistics Manual
DRA	Drug Regulatory Affairs
DMG	Dictionary Maintenance Group
DSB	Data Safety Board
eCRF	Electronic Case Report Form
EMEA	European Agency for the Evaluation of Medicinal Products
FAS	Full Analysis Set
$IAUC_{60}$	Initial area under contrast agent concentration–time curve at 60 s
ICH	International Conference on Harmonisation
INR	International Normalised Ratio
K_{trans}	Volume transfer constant obtained from DCE-MRI data
LOCF	Last Observation Carried Forward

Term	Definition / description
MedDRA	Medical Dictionary for Regulatory Activities
MQRM	Medical Quality Review Meeting
MTD	Maximum Tolerated Dose
O*C	Oracle Clinical
PK	Pharmacokinetics
PLT	Platelets
PPS	Per Protocol Set
PSTAT	Project Statistician
PT	Prothrombin Time
PT	Preferred Term
PV	Protocol Violation
Q1	Lower Quartile
Q3	Upper Quartile
RECIST	Response Evaluation Criteria In Solid Tumors
REP	Residual Effect Period
SA	Statistical Analysis
SD	Standard Deviation
SMQ	Standardised Meddra Query
SOC	System Organ Class
TCM	Trial Clinical Monitor
TESS	Treatment Emergent Signs And Symptoms
ToC	Table Of Contents
TMW	Trial Medical Writer
TSAP	Trial Statistical Analysis Plan
WBC	White Blood Cell Count

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, randomization.

SAS® Version 9.4 will be used for all analyses.

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

Section 7.3.5.3 of the CTP stated that "The exploratory statistical analyses of the biomarker data will be performed separately and results will be covered in a separate report." However, the team has now decided to include the biomarker analyses as a part of CTR and section 5.4.1 and section 9 of this TSAP covers a list of the biomarkers to be analyzed and section 7.8.5 provides further details on their analysis.

5. ENDPOINT(S)

5.1 PRIMARY ENDPOINT(S)

The objective of this study is to determine the safety and tolerability of BI 836880. 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 first treatment cycle. The DLT is defined in section 5.3 of the CTP.

The MTD is defined as the highest dose with less than 25% risk of the true DLT probability being above 33%, and may be considered reached if the probability that the true DLT rate is in target interval (16%-33%) is sufficiently large during the MTD evaluation period.

The MTD evaluation period is defined as the time within 3 weeks after first administration of study treatment.

Patients who have not completed one cycle of treatment will be replaced. Patients who were replaced during the MTD evaluation period will not be considered for MTD determination. Those patients that have completed the MTD evaluation period without having been replaced will be referred to as patients evaluable for MTD.

5.2 SECONDARY ENDPOINT(S)

5.2.1 Key secondary endpoint(s)

There were no key secondary endpoints for this study.

5.2.2 (Other) Secondary endpoint(s)

The following secondary endpoints related to safety and PK, were specified:

- Drug related AEs leading to dose reduction or discontinuation during the treatment period

6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENT(S)

The starting dose of the study is BI 836880 40 mg every week, and dose escalation decision will be made by Data Safety Board (DSB).

The following treatment period will be defined:

- Screening: from the date of informed consent to the date of 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 + residual effect period (REP).
- Post-study: from the last day of on-treatment period + 1 day onwards

6.2 IMPORTANT PROTOCOL VIOLATIONS

A protocol violation (PV) is important if it affects the rights or safety of the study patients, or if it can potentially influence the primary outcome measurements in a non-negligible way. Patients with important PVs that could potentially impact the evaluation of the primary endpoint(s) will be excluded.

A list of important PVs is given in Table 6.2: 1 below. Important PVs will be reviewed at Medical Quality Review Meetings (MQRMs) conducted periodically during the trial. A list of protocol deviations will be discussed at the blinded report planning meetings (BRPMs).

If the data show other important PVs, this table will be supplemented accordingly at MQRMs or BRPMs 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 BRPM prior to DBL.

Table 6.2: 1 Important protocol violations

Category / Code		Description	Requirements	Excluded from
A		**Entrance criteria not met**		
	A1	Inclusion criteria not met		
	A1.1	Requirements on age or birth control not met	Inclusion criteria 1 or 8	None
	A1.2	Disease severity not met	Inclusion criteria 2	None
	A1.3	Adequate health condition not met	Inclusion criteria 3, 4, 6, or 7	None
	A2	Exclusion criteria not met		
	A2.1	Hypersensitivity to the trial drug	Exclusion criteria 1	None
	A2.2	Previous anti-cancer therapy washout period not met	Exclusion criteria 2	None
	A2.3	Clinically relevant concomitant or history of disease, pre-existing conditions	Exclusion criteria 3, 4, 5, 6, 7, 8, 9, 10, or 11	None

Table 6.2: 1 Important protocol violations (cont.)

Category / Code		Description	Requirements	Excluded from
A		**Entrance criteria not met**		
	A2.4	Under judicial protection and legally institutionalized	Exclusion criteria 12	None
	A2.5	Requirement of adherence to protocol not met	Exclusion criteria 13	None
	A2.6	Pregnancy / breast feeding related	Exclusion criteria 14	None
B		**Informed consent**		
	B1	Informed consent not available/not done	Informed consent date missing	All
	B2	Informed consent too late	Informed consent date was after screening visit date	None
C		**Trial medication and randomisation**		
	C1	Incorrect trial medication taken	To be determined on a case by case basis. Listing will be created and decision will be made at MQRM / BRPM, e.g., incorrect dose taken, dose in course 1 not following dose escalation scheme, overdose, use of expired medication etc.	None
	C3	Non-compliance	Study drug not taken according to protocol. To be determined on a case by case basis. Listing will be created and decision will be made at MQRM / BRPM e.g., outside of dosing schedule window, unreasonable drug administration time, etc.	None
	C5	Re-treatment criteria not met	Re-treatment criteria was not met according to CTP section 4.1.4	None
D		**Concomitant medication**		
	D2	Prohibited medication use	Refer to CTP section 4.2.2.1.	None
Z		**Other**		
	Z3	Missing critical safety information in cycle 1	Essential safety information for the evaluation of DLT is missing	None

6.3 PATIENT SETS ANALYSED

Treated set:
This patient set includes all patients enrolled in the trial who were documented to have taken at least one dose of study medication.

Dose finding cohort treated set:

This patient set includes all patients enrolled in dose finding and confirmation of MTD cohort of the trial who were documented to have taken at least one dose of study medication and were evaluable for the MTD determination.

MTD Expansion cohort treated set:

This patient set includes all patients enrolled in expansion cohort of the trial who were documented to have taken at least one dose of study medication.

Tumor type expansion treated cohort set

This patient set includes all patients with selected tumor type enrolled in expansion cohort of the trial who were documented to have taken at least one dose of study medication.

6.5 POOLING OF CENTRES

This section is not applicable.

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") (3). Missing data and outliers of PK data are handled according to (2). Please refer to section 7.5 of the CTP for more details.

6.7 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, baseline is the one observed closest but prior to or on the first day of drug intake.

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 6 weeks i.e.: Week 6, 12, 18… etc. The number of weeks will be calculated using their relative day (from start of treatment) using a ±3 week window (images taken in the first 3 weeks from start of treatment will be

assigned to Week 6). Imaging not older than 28 days at start of treatment will suffice as screening images and do not need to be repeated.

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.

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.

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 for first treatment cycle will be calculated as mean of "per visit" compliance at visit Day 1, Day 8 and Day 15.

Overall Compliance for second treatment cycle onwards (from Day 22 onwards) will be calculated as mean of "per visit" compliance at each visit within the cycle. 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(S)

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 5.3.1 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 course 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 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.

7.5.2 (Other) Secondary endpoint(s)

Drug related AEs leading to treatment discontinuation or dose reduction will be analysed as part of safety analysis as described in section 7.8.1.

7.7 EXTENT OF EXPOSURE

Treatment exposure will be primarily summarized by the total on-treatment time and has been defined in section 5.4 of this TSAP.
Treatment interruptions before permanent discontinuation will not be excluded. Summary statistics for treatment time by each dose level and the dosage of BI 836880 over time will also be provided.

7.8 SAFETY ANALYSIS

All safety analyses 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. The first analysis of safety will be performed for the first part of the trial (determination of the MTD, first cycle only (3-week treatment), treatment regimen = initial dose at the start of the treatment, treated set). This descriptive analysis will evaluate the MTD for the monotherapy of BI 836880. 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 'Handling and summarization of adverse event data for clinical trial reports and integrated summaries' (5).

For patients treated with the test drug, that means that all adverse events occurring between first drug intake and 42 days after last drug intake or death, whichever occurs first, will be assigned to the on-treatment period. All adverse events occurring before any study drug intake will be assigned to ‘screening’ and all adverse events occurring after last study drug intake + 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’ and ‘Other significant AEs’ but will include additional rows for ‘AEs leading to dose reduction’, ‘AEs leading to death’ and ‘AEs by highest Common Terminology Criteria (CTC) grade’.

The frequency of patients with adverse events will be summarised 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:

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

- Drug-related AEs leading to treatment discontinuation
- Drug related AEs leading to dose reduction
- 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
- DLTs

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 5.3.8.1 and dose limiting toxicities as defined by 5.3.1), 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 v4.0 (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 last value on treatment.

Summaries will be produced of laboratory data recorded prior to treatment, on-treatment and post-treatment. For details on the treatment definition, see section 6.1.

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

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

7.8.4 ECG

ECG data will be collected as described in CTP section 5.3.4. Clinically significant findings in ECG data will be reported under "Adverse events" if applicable and will be analysed accordingly. In addition patients with notable findings in QTcF or QT interval at any time on treatment will be summarised in a descriptive manner.

7.8.5 Others

8. REFERENCES

1	*CPMP/ICH/363/96:* "Statistical Principles for Clinical Trials", ICH Guideline Topic E9, Note For Guidance on Statistical Principles for Clinical Trials, current version.
2	*001-MCS 36-472*: "Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics", current version; IDEA for CON.
3	*001-MCG-156_RD-01:* "Handling of missing and incomplete AE dates", current version; IDEA for CON.
4	001-MCG-420: “Statistical Methods for Pharmacokinetics”, Version 3.0, IDEA for CON
5	*001-MCG-156*: "Handling and summarization of adverse event data for clinical trial reports and integrated summaries", current version; IDEA for CON.
6	Common terminology criteria for adverse events (CTCAE): version 4.0, published: May 28, 2009 (v4.03: June 14, 2010) (NIH publication no. 09-5410, revised June 2010, reprinted June 2010). http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf (access date: 5 June 2012) ; U.S. Department of Health and Human Services, National Institutes of Health, National Cancer Institute 2010
7	*001-MCG-157*: "Handling, Display and Analysis of Laboratory Data", current version; IDEA for CON.

10. HISTORY TABLE

Table 10: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
Final	**20-JUN-17**		None	This is the final TSAP without any modification