Trial Statistical Analysis Plan

c02325889-03

BI Trial No.:	1325.1
Title:	An open label phase I dose finding study of BI 860585 administered orally in a continuous dosing schedule as single agent and in combination with exemestane or with paclitaxel in patients with various advanced and/or metastatic solid tumours Including Protocol Amendment 2 (c01837011-07)
Investigational Product(s):	BI 860585
Responsible trial statistician(s):	[redacted] Phone: [redacted] Fax: [redacted]
Date of statistical analysis plan:	17 AUG 2016 SIGNED
Version:	"Revised"

1. TABLE OF CONTENTS

LIST OF TABLES

2. LIST OF ABBREVIATIONS

Include a list of all abbreviations used in the TSAP

Term	Definition / description
AE	Adverse Event
AESI	Adverse Event of Special Interest
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
BMI	Body Mass Index
BRPM	Blinded Report Planning Meeting
BSA	Body Surface Area
CR	Complete Response
CT	Concomitant Therapy
CTC	Common Terminology Criteria
CTP	Clinical Trial Protocol
DBLM	Database Lock Meeting
DILI	Drug Induced Liver Injury
DLT	Dose Limiting Toxicity
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EOT	End of Active Treatment
EoT	End of Text
ES	Enrolled Set
ICH	International Conference on Harmonisation
IPV	Important Protocol Violation
[redacted]	[redacted]
LLT	Lowest Level Term
LVSI	Laboratory Values of Special Interest
MTD	Maximum Tolerated Dose
MedDRA	Medical Dictionary for Regulatory Activities

Term	Definition / description
MQRM	Medical Quality Review Meeting
O*C	Oracle Clinical
PK	Pharmacokinetics
PKS	Pharmacokinetic Set
PR	Partial Response
PT	Preferred Term
PV	Protocol Violation
RECIST	Response Evaluation Criteria in Solid Tumours
REP	Residual Effect Period
RPM	Report Planning Meeting
SCR	Screened Set
SD	Stable Disease
SDL	Subject Data Listing
StD	Standard Deviation
SOC	System Organ Class
TCM	Trial Clinical Monitor
TES	Treated and Evaluable Set
TOC	Table of Contents
TMW	Trial Medical Writer
TS	Treated Set
TSAP	Trial Statistical Analysis Plan
[redacted]	[redacted]
[redacted]	[redacted]

3. INTRODUCTION

As per International Conference on Harmonisation (ICH) E9, 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.

The TSAP describes the analyses of this dose finding study.

In the following, study medication refers to BI 860585 in Arm A, to BI 860585 or exemestane in Arm B, and to BI 860585 or paclitaxel in Arm C.

SAS® Version 9.4 (or higher) will be used for all analyses.

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

Due to stopping the project, the initially planned expansion cohorts are for the moment not planned to be recruited. Therefore, analyses for the expansion cohorts as stated in the CTP will not be described in this TSAP. All analyses on the dose finding part will be performed as planned, besides the derivation corrected in the following paragraph.

Duration of disease control (CR/PR/SD) has been defined in the CTP as time from first clinical benefit to progression or death (CTP Section 5). However, the correct derivation is different. In the analysis of this study, duration of disease control is defined from first treatment administration until the earliest of disease progression or death, amongst patients with disease control.

5. ENDPOINT(S)

All endpoints are comprehensively defined in CTP Section 5.

5.1 PRIMARY ENDPOINT(S)

The primary objective of the trial is the determination of the maximum tolerated dose (MTD) of BI 860585 monotherapy and in combination with either exemestane or paclitaxel based on the number of patients with dose limiting toxicities (DLTs) during the MTD evaluation period.

MTD is defined as the highest dose studied for which the incidence of DLT is none out of three or less than 2 out of 6 patients. The MTD will be derived separately for patients in each treatment arm. For the definition of DLT, see Section 5.2.1 of the CTP.

The MTD will be defined on the basis of DLT observed during the first 28 (28+1) in case the last visit of the first cycle is done on the same day as the first visit of the second cycle) days of treatment only excluding patients who were replaced during the MTD evaluation period. The MTD evaluation period starts after the run-in phase (in case of combination arms) and with the first administration of study medication and ends after the first treatment cycle (28 days).

Primary endpoints:

- MTD in each treatment arm (based on number of DLTs in first course (28 days) of each treatment arm).
- Number of patients with DLTs in first course of each treatment arm.

5.2 SECONDARY ENDPOINT(S)

5.2.1 Key secondary endpoint(s)

Not applicable.

5.2.2 Secondary endpoint(s)

- Objective response rate (complete response (CR), partial response (PR) per RECIST criteria version 1.1): Objective response is defined as best overall response of CR or PR, where best overall response is determined according to RECIST1.1 recorded from date of first treatment administration until the earliest of disease progression, death, or last adequate tumour assessment before new anti-cancer therapy. Objective response rate is defined as the proportion of patients with CR or PR.

- Disease control rate/clinical benefit rate (CR/PR/stable disease (SD), per RECIST criteria version 1.1): Disease control is defined as best overall response of CR or PR or SD, where best overall response is defined according to RECIST 1.1 recorded from date of first treatment administration until the earliest of disease progression, death or last adequate tumour assessment before new anti-cancer therapy. Disease control rate is defined as the proportion of patients with CR, PR, or SD.

- Duration of objective response (CR/PR per RECIST) is derived for patients with objective response, defined as time from first objective response to the time of progression or death, whatever occurs first.

  Derivation of duration of objective response:

  For patients with objective response and with disease progression or death:

  - Duration of objective response [days] = date of outcome – date of first assessment indicating objective response + 1.

  For patients with objective response and without disease progression or death:

  - Duration of objective response (censored) [days] = date of outcome – date of first assessment indicating objective response + 1.

  Only radiological assessments after first assessment indicating objective response should be taken into consideration. For patients without disease progression or death, duration of OR will be censored on the date of the last radiological assessment before the data cut-off. In case patients initiated other anti-cancer therapies, the duration of OR will be censored on the date of the last radiological assessment before the start date of the other anti-cancer therapy.

- Duration of disease control (CR/PR/SD), defined as time from first treatment administration until the earliest of disease progression or death, amongst patients with disease control.

  Derivation of duration of disease control:

  For patients with disease progression or death:

  - Duration of disease control [days] = date of outcome – date of first treatment administration + 1.

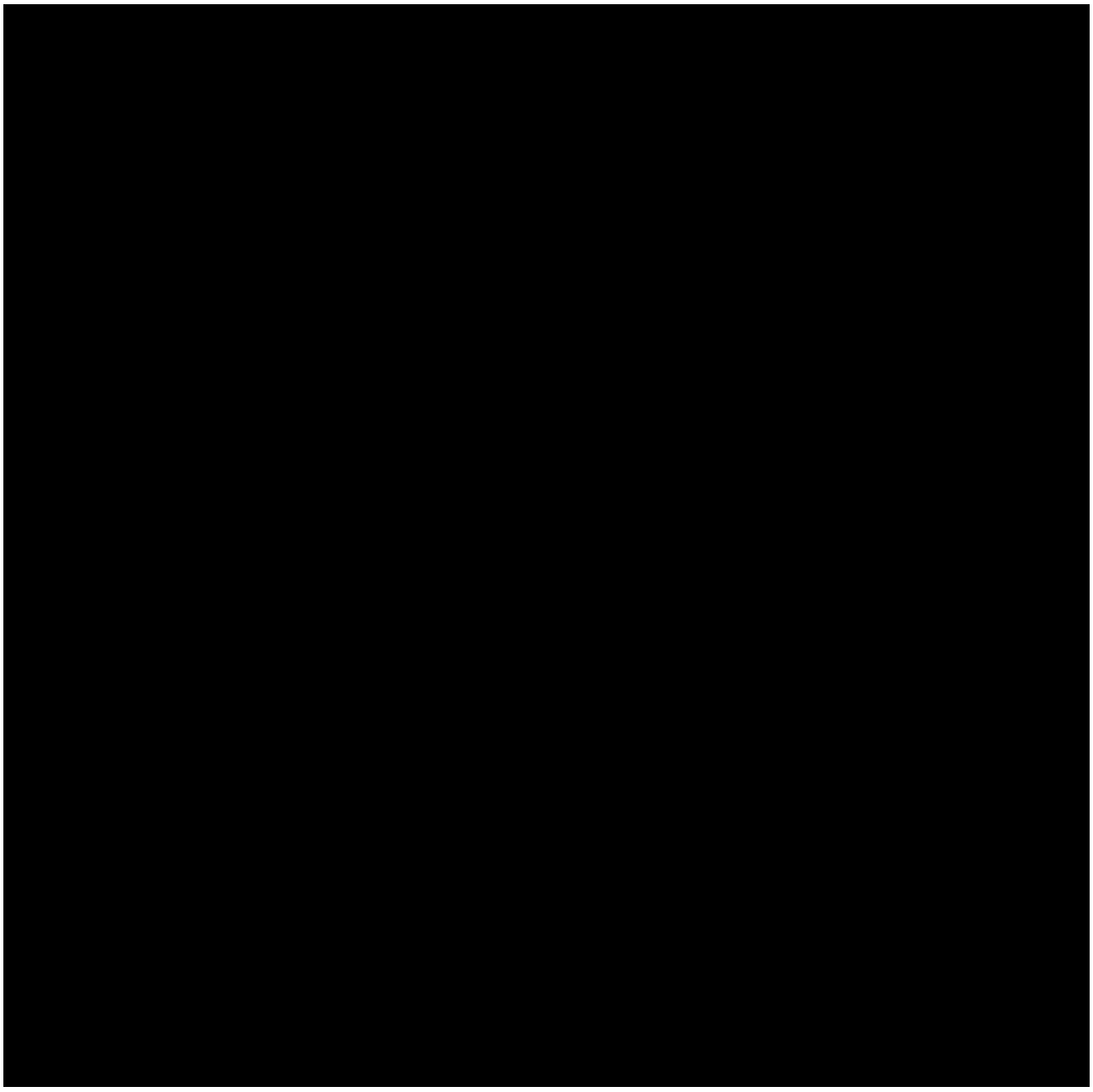
  For patients without disease progression or death:

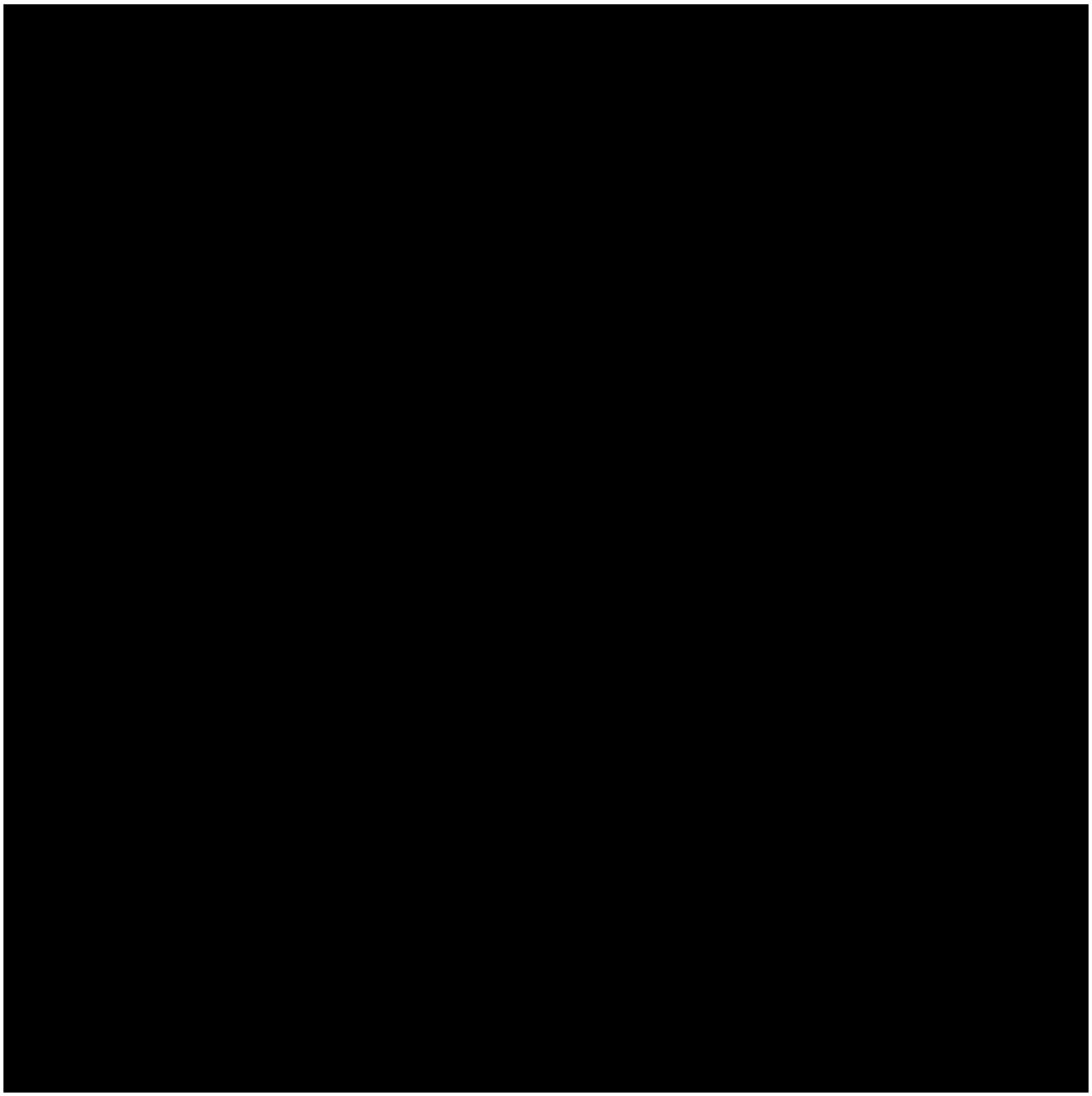
  - Duration of disease control (censored) [days] = date of outcome – date of first treatment administration + 1.

For patients without disease progression or death, duration of disease control will be censored on the date of the last radiological assessment before the data cut-off. In case patients initiated other anti-cancer therapies, the duration of DC will be censored on the date of the last radiological assessment before the start date of the other anti-cancer therapy.

- $AUC_{0\text{-}24(ss)}$, $AUC_{0\text{-}\infty}$, $t_{1/2(ss)}$, $t_{max(ss)}$ and $C_{max(ss)}$ of BI 860585 administered as single agent and with combination agents.

SD refers to confirmed SD, which means that the response evaluation should record SD twice after baseline. Non-CR/Non-PD for patients that only have non-target lesions at baseline will be merged to SD in the CTR.





6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENT(S)

Treatments are not randomised. Data will be displayed by patient for each arm separately, and summarized by initial assigned dose level and arm. Additionally totals by arms will be shown. To justify the MTD determination, DLTs occurring during the MTD evaluation period will be presented separately from those occurring during the complete on-treatment period.

The three treatment arms will follow separate fixed dose-escalation designs with dose de-escalation steps:

- Arm A will be a 3+3 dose-escalation design (multiple ascending doses of BI 860585 administered continuously in a 28-day cycle) in patients with unselected solid tumours who progressed before inclusion.

- Arm B will be a 3+3 dose-escalation design with BI 860585 being administered in multiple ascending doses in combination with fixed dose exemestane in patients with progressed metastatic disease and in whom the administration of exemestane may be considered as appropriate. This arm will only start recruiting once the combination starting dose of BI 860585 has been fixed (see CTP Section 3.1).

- Arm C will be a 3+3 dose-escalation design with BI 860585 being administered in multiple ascending doses in combination with fixed dose paclitaxel at initial 75% of standard dose followed by standard combination dose, in patients with progressed metastatic disease in whom the administration of paclitaxel may be considered as appropriate. This arm will start recruiting only once the combination starting dose of BI 860585 has been fixed (same as Arm B).

The on-treatment period is defined from the first administration of any trial medication until the end of the residual effect period (REP, 28 days).

The screening period ranges from the date of informed consent until the date of initial administration of any study medication.

Follow-Up period starts with the end of the REP (date of last administration of trial medication +28 days + 1 day) and ends with the last per-protocol contact.

For the on-treatment period and the MTD evaluation period, the initial trial medication assigned at the beginning of the first treatment cycle will be used as the label of the analysing treatment.

6.2 IMPORTANT PROTOCOL VIOLATIONS

Due to the fact that this is a Phase I study, no per protocol population is defined, however important protocol violations (IPVs) should be identified for patients in the treated set (any protocol violation which may affect safety or efficacy evaluation).

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

Each protocol deviation must be assessed to determine whether it is an important protocol violation. 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 measure(s) for the respective patients in a way that is neither negligible nor in accordance with the study objectives. This last category of important PV forms the basis for the decision of whether a patient does or does not belong to a specific analysis set. PVs that do not influence the patient's rights and safety or the evaluability of the patients for the main study objectives are called non-important PVs. These are only considered when checking the trial quality in general.

If any manual important PVs are identified, they are to be summarised into categories and will be captured in the MQRM/RPM minutes via an accompanying Excel spreadsheet 001-MCS-50-413_RD-02 (7). The following table (Table 6.2: 1) contains the categories which are considered to be possible important protocol violations in this trial.

Table 6.2: 1 Description of PVs

Category/ Code		Description	Comment/Example	Excluded from
A		**Inclusion/Exclusion Criteria**		
	A1	**Criteria related to safety**		
	A1.1[1]	Patient has condition that may cause additional risk from study medication	EX 21 and 22	None
	A1.2[1]	Patient has laboratory assessments that may cause additional risk.	EX 6-10	None
	A1.3[1]	Patient is unable to comply with the protocol	EX 13	None
	A1.4[1]	Patient has condition that may interfere with evaluation of safety (and/or efficacy)	EX 1-3, EX 15, EX 18-20	None
	A2	**Criteria related to efficacy**		

Category/ Code		Description	Comment/Example	Excluded from
	A2.1[1]	Patient does not have trial diagnosis or is not part of the target population	IN 1-4, IN 6, EX 1	None
B		**Legal criteria**		
	B1[1]	Informed consent not available/not done	IN 5	All
	B2[1]	Informed consent after visit 1	IN 5	None
	B3[1]	Men or women who are sexually active and not using adequate contraception.	EX 12	None
	B4[1]	Pregnant or nursing female patient	EX 11	None
	B5[1]	Patient's age < 18	IN 3	None
C		**Administration of trial medication not in accordance with the protocol**		
	C1[2]	Administration of trial medication not in accordance with the protocol	Create listing, decision at MQRM/RPM	None
	C2[2]	Dose reduction scheme not according to protocol (Section 4.1.4)	Include two situations: no adjustment when required and adjustment when not required. A listing will be created and decision made at MQRM/RPM.	None
	C3[2]	Unjustified intra-patient dose-escalation	Create listing, decision at MQRM/RPM, see CTP Section 4.1.4	None
	C4[2]	Withdrawal of patient not performed according to CTP	Create listing, decision at MQRM/RPM, see CTP Section 3.3.4	None
	C5[2]	Discontinuation of trial drug not performed according to CTP	Create listing, decision at MQRM/RPM, see CTP Section 3.3.4	None
	C6[2]	Overdose of BI 860585	Create listing, decision at MQRM/RPM	None
	C7[2]	Overdose of either exemestane or paclitaxel	Create listing, decision at MQRM/RPM	None
D		**Restrictions**		
	D1[2]	Prohibited medication use during the on-treatment period.	Create listing, decision at MQRM/RPM	None

[1] IPV will be derived automatically

[2] IPV will be identified via individual review at MQRM/RPM/DBL

6.3 PATIENT SETS ANALYSED

Treated set (TS):

The treated set includes all patients who were administered at least one dose of any study medication (BI 860585, exemestane, or paclitaxel). This set will be used for all planned safety and efficacy analyses but not for the MTD determination according to the 3+3 algorithm.

Pharmacokinetic set (PKS):

This patient set includes all evaluable patients in the TS which provide at least one observation for at least one PK endpoint without important PVs relevant to the evaluation of PK. It is used for the statistical PK analysis.

Treated and evaluable set (TES):

The treated and evaluable set includes all patients who were administered at least one dose of trial medication and who are evaluable with respect to DLT in the MTD evaluation period. This patient set will be used for the MTD determination according to the 3+3 algorithm.

Enrolled set (ES):

ES includes all patients who signed informed consent form and will be used to summarize patient disposition over all treatment arms.

[redacted]

[redacted]

No per protocol population will be used for analyses. However protocol violations will be described in the final report.

Patients who were treated, but replaced within the MTD evaluation period will be excluded from the determination of the MTD and will not be in the TES. Replacement of patients is not captured in the eCRF. The final list of replaced patients is supplied by the trial clinical monitor (TCM) no later than the last report planning meeting (RPM) before the data base lock.

[redacted]

6.5 POOLING OF CENTRES

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

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") (2)

Missing data and outliers of PK data are handled according to 001-MCS-36-472_RD-01 (3).

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

1) Partial or missing start date of subsequent anti-cancer therapy

If the day of the start date of subsequent anti-cancer therapy is missing, then the 15th of the month will be imputed. If both, the day and the month of the start date of a subsequent anti-cancer therapy are missing, then July 1st will be imputed. If the imputed start date is equal to or later than the date of death or the last contact date, then the earlier of date of death minus 1 day and the date of last contact minus 1 day will be used.

2) Definition of on-treatment period and actual treatment

Date of permanent discontinuation of last study medication: All reasonable efforts should be undertaken during the study to obtain the dates of permanent discontinuation of last study medication. However, if the date of the very last intake of study medication is missing, this will be imputed with the date of first BI 860585 intake in the last course +28 days. If the imputed date leads to a date that is later than the death date (date patient is last known to be alive), then the imputed date will be the date of death (date patient last known to be alive). If the imputed date leads to a date that is later than the snapshot date, then the imputed date will be the snapshot date.

3) Partial death dates

If a partial (year and month) death date is reported the date will be imputed with the end of the month for the analysis of duration of disease control and duration of objective response.

[redacted]

[redacted]

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

In general baseline is defined as the last time point immediately before the very first administration of trial medication. If there is no measurement before the very first administration of trial medication, no baseline will be derived. For ECOG performance status, body weight, vital signs and some safety lab parameters, baseline measurement could be on the same date as the very first administration of trial medication. If the time of the measurement is not collected or missing and the baseline measurement is done on the same day as the first administration of trial medication, it is assumed that the baseline measurement

was done before the administration. Baseline tumour assessments will be based on imaging performed no more than 28 days prior to the very first administration of trial medication.

7. PLANNED ANALYSIS

In general, the display templates for End-of-Text (EoT) tables and figures should follow BI internal reference (6) as closely as possible and only a minimum number of custom-designed table shells will be specified if necessary.

For EoT tables, the set of summary statistics for continuous variable is: N/Mean/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 time-to-event analysis tables, the set of statistics is: number of patients [N(%)], Number of patients with event [N(%)], <Time to event> [months] followed by P25 (25^{th} percentile), median, P75 (75^{th} percentile), Number of patients censored [N(%)]. If not specified otherwise, the duration as well as the time to event will be displayed in months and a final decision will be made at the last RPM.

Tabulations of frequencies for categorical data will include all possible categories (even if with no count and also the missing category if there is missing data) and will display the number of observations in a category as well as the percentage (%) relative to the number of treated patients in the respective treatment group (all patients in the respective treatment group 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. The denominator of the main categories is defined by the number of patients in the used patient set. The main categories define the denominators of the subcategories. Subcategories should be indented and ”[N (%)]” will be displayed only for the main category.

If a table presents only categorical data, ”[N (%)]” will be displayed in the column header only.

A “Total” column displaying totals over all arms will not be included in summary tables for post-baseline data. Only totals for each arm separately will be shown.

Abbreviations (e.g., Wors.) or acronyms (e.g., PD) should not be displayed in tables and Subject Data Listings (SDLs) without any explanation. They will be either spelled out or explained in footnotes.

The conversions among days, weeks, months and years should follow:

- Weeks = days ÷ 7
- Months = 12 × days ÷ 365.25
- Years = days ÷ 365.25

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Standard descriptive analysis and summary tables will be presented for all patients in the treated set by treatment group.

Disposition of patients

Standard descriptive analysis of disposition will be provided.
If applicable, the number of patients who will continue treatment after database lock will be reported in the disposition table.

Important protocol violation

A table or listing of patients with important protocol violations will be created.

Demographics and baseline characteristics

Standard descriptive analysis of demographics and baseline characteristics will be provided.

[redacted]

7.4 PRIMARY ENDPOINT(S)

The primary endpoints of this trial are the MTD and the number of patients with DLTs during the MTD evaluation period.

The primary analysis is for the determination of MTD. The purpose of the analysis is to summarize and document the data that led to the selection of MTD.

A summary of the number of patients with DLTs in the MTD evaluation period and overall on the on-treatment-period will be given by initial treatment. Only patients in the TES will be used for MTD determination.

A listing of patients with DLTs by initial treatment will include: Type of DLT (preferred term (PT)), CTCAE grade of AEs, Onset and Duration of DLTs [days], Patients recovered [yes/no], Actual dose of BI 860585 at onset of the AE [mg].

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 CTP.

7.5.2 (Other) Secondary endpoint(s)

Early efficacy signals of BI 860585 as single agent or in combination with exemestane or paclitaxel will be explored as secondary endpoints.

Objective response rate and disease control rate:
Objective response rate and disease control rate according to RECIST criteria version 1.1 will be analysed descriptively for all treated patients.

Duration of Objective Response:
Duration of objective response will be listed for patients achieving objective response (CR or PR according to RECIST). Median duration of objective response will be calculated based on the Kaplan-Meier method.

Duration of disease control:
Duration of disease control will be listed for patients achieving disease control (CR, PR or SD according to RECIST). Median duration of clinical benefit will be calculated based on the Kaplan-Meier method.

Overall response:

As objective response is defined as the best overall response of PR and CR, overall response needs to be determined. This is defined as:

- If the overall response is progressive disease, the earliest date of multiple assessments (target lesion, non-target lesion, new lesion) will be taken,

- If the overall response is CR, PR, SD, no change, or not evaluable, the latest of multiple assessment dates will be taken, i.e. in the case of CR, PR, SD, no change, or not evaluable the latest of multiple dates will be used.

PK Parameters:

Plasma concentrations of BI 860585, exemestane, and paclitaxel will be plotted against time. The calculation of the pharmacokinetic parameters as well as the descriptive analysis of the concentration values and the descriptive and comparative analysis of the pharmacokinetic parameters will be based on the methods outlined in Section 7.3.5 of the CTP as well as in

001-MCS-36-472_RD-01 (3). Tables and figures for concentrations values and PK parameters will be created according to the reference document 'Graphs and Tables for Clinical Pharmacokinetic Noncompartmental Analyses' (001-MCS-36-472_RD-02 (5)).

[redacted]

7.8 SAFETY ANALYSIS

All safety analyses besides the MTD determination according to the 3+3 algorithm will be performed on the treated set.

MTD determination will be performed on the TES. Patients who were replaced within 28 days after first administration of BI 860585 monotherapy or in combination with exemestane or with paclitaxel will be excluded from the TES however they are part of the safety analysis on the treated set. Replaced patients will be listed with the reason for replacement.

7.8.1 Adverse events

The analyses of adverse events (AEs) will be descriptive in nature. All analyses will be based on the number of patients with AEs (not the number of AEs).

According to BI standards, multiple overlapping or adjacent AE occurrences of the same AE are collapsed into one AE event if all AE attributes are identical. These AE attributes are: lowest level term (LLT), intensity, action taken, therapy required, seriousness, reason for seriousness, relationship, outcome, and AE of special interest (AESI).

The analyses will be based on BI standards. Adverse events will be coded with the most recent version of MedDRA. The severity of AEs will be scaled according to CTCAE version 4.03 (R10-4848).

The analyses of adverse events will be based on the concept of treatment-emergent adverse events, where a treatment emergent AE has an onset in the analyzing treatment period. Adverse events will be distinguished for the period in which the patients are under study drug (on-treatment) as well as for screening, and post-study. Adverse events will be displayed by the initial dose of BI 860585 monotherapy or in combination with exemestane or with paclitaxel administered on the first day of treatment with study medication. In addition, a listing will be provided, detailing the actual dose of BI 860585 monotherapy or in combination with exemestane or with paclitaxel administered on the day when the adverse event starts.

Sorting order: In tables presenting PTs only, PTs will be sorted by descending frequency in the respective arm. In tables presenting system organ classes (SOCs) and PTs, SOCs will be sorted alphabetically and PTs (within SOC) by descending frequency of the respective arm.

Reporting of CTCAE grades in tables: AEs with a given CTCAE definition will be displayed in tables showing AEs by worst CTCAE grade. AEs with missing CTCAE grade will be in the category "All grades".

Displaying of CTCAE grades in AE tables (Section 15) will be "All grades", "Grade 1/2" and "Grade 3/4/5". A separate table will show AEs leading to death. In the appendix (Section 16), the categorization "All grades", "Grade 1", "Grade 2", "Grade 3", "Grade 4" and "Grade 5" will be used.

Listings of adverse events will be displayed by patients. Adverse events will be reported with start and end date (calendar date) rather than with start day and end day as calculated from the first day of treatment with study medication.

Incidence and severity of adverse events
The incidence of AEs overall (irrespective of relatedness to study medication), related AEs, and of serious AEs (SAE) will be reported by severity according to CTCAE grades.

Other significant adverse events
Other significant AEs are defined as serious and non-serious AEs that lead to dose reduction or permanent discontinuation of study medication (BI 860585, exemestane, or paclitaxel). Their incidence will be reported by severity according to CTCAE grades.
A listing of patients who developed 'other significant' AEs will be provided and a flag for serious and non-serious will be included.

Drug-related adverse events
The frequency of patients with drug-related AEs will be tabulated.

Adverse events leading to dose reduction
AEs leading to dose reduction of BI 860585 and AEs leading to dose reduction of paclitaxel will be tabulated. This includes patients with AEs leading to dose reduction of BI 860585 after increasing the dose.

Adverse events leading to discontinuation of study medication
AEs leading to discontinuation of any study medication will be reported.
AEs leading to discontinuation of BI 860585, AEs leading to discontinuation of exemestane, and AEs leading to discontinuation of paclitaxel will be reported separately for the respective arms.

Serious adverse events
The frequency of patients with SAEs will be tabulated.

Adverse events leading to death
AEs leading to death during the on-treatment period will be tabulated. Reported fatal AEs that occurred in the post-study phase will be displayed.

Adverse events of special interest (AESI)
Adverse events of special interest (AESI) as defined in the protocol and collected on the eCRF will be analysed.

Dose-limiting toxicities (DLTs)
A summary of the number of patients with DLTs within the MTD evaluation period and in the whole on-treatment period will be given.

7.8.2 Laboratory data

The analyses of laboratory data will be descriptive in nature and will be based on BI standards (4). The same on-treatment periods as considered for the analysis of adverse events will be applied for laboratory values. Patients having at least one post-baseline laboratory value will be displayed in the descriptive analyses.

Descriptive statistics, including change from baseline and frequency of patients with transitions relative to the reference range, will be provided. CTCAE grades for applicable laboratory parameters will be calculated according to CTCAE v4.03. The following outputs will be presented:

Worst CTCAE grade experienced during the on-treatment phase.

Transitions of CTCAE grade from baseline to worst laboratory value and from worst to last laboratory value during the on-treatment phase.

Patients with missing CTCAE grade at baseline or no baseline value but post baseline values will be displayed in the category "Missing CTCAE grade at baseline".

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 has been defined, BI standard definition will be used to determine possible clinical significance. Frequency of patients with possible clinically significant abnormal laboratory values will be provided whenever applicable. If no baseline value is available but the patient has a post-baseline laboratory value of CTCAE Grade ≥ 2 an increase from baseline will be assumed, i.e. the laboratory value considered as possible clinically significant.

Generally, in case only one direction of worsening (high or low laboratory values) is specified in the CTCAE document, there is no need to examine the other direction. Therefore for calculating the change in CTCAE grade from baseline / pre-dose level, patients with a CTCAE grade of "-9" (no CTCAE grade defined) will be treated as a CTCAE grade 0 for all analyses. In laboratory listings, the CTCAE grade will be displayed as "-9".

For Uric Acid, Glomerular filtration rate (GFR) and Hypokalemia, the CTCAE grade cannot always be assigned by the laboratory parameter itself as two different CTCAE grades have the same laboratory constellation, but are distinguished by additional clinical parameter. In this case a CTCAE grade of "-1" will be assigned initially. Patients with a CTCAE grade of "-1" will be treated as

- Grade 1 for Uric Acid
- Grade 3 for GFR
- Grade 1 for Hypokalemia

for all analyses. In laboratory listings, the CTCAE grade will be displayed as "-1".

Laboratory values of special interest (LVSI)

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 with total bilirubin ≥ 2ULN and ALKP < 2ULN. The events can occur in any order, but must occur within 14 days of the previous event, i.e. the second event must occur within 14 days of the first event, and the third event must occur within 14 days of the second event, etc. Patients with missing laboratory values for liver enzymes will be excluded from these analyses, but presented separately.

Tabulations of hepatic enzyme elevations and liver laboratory values will be done according to the FDA Drug Induced Liver Injury (DILI) guidance [P09-12413].

7.8.3 Vital signs

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

7.8.4 ECG

Newly emergent abnormalities will be recorded and analysed as adverse events.

[redacted]

[redacted]

8. REFERENCES

1 *001-MCG-160_RD-01*: "TSAP annotations", current version; IDEA for CON.

2 *001-MCG-156_RD-01*: "Handling of missing and incomplete AE dates", current version; IDEA for CON.

3 *001-MCS-36-472_RD-01*: "Noncompartmental Pharmacokinetic/Pharmacodynamic Analyses of Clinical Studies", current version; IDEA for CON.

4 *001-MCG-157*: "Display and Analysis of Laboratory Data", current version, IDEA for CON.

5 *001-MCS-36-472_RD-02*: “Graphs and Tables for Clinical Pharmacokinetic and Pharmacodynamic Noncompartmental Analyses”, current version; IDEA for CON

6 *001-MCG-159_RD-03*: "Standard table shells for inferential and descriptive End-of-Text tables (EoT-Catalogue)", current version; IDEA for
CON.

7 *001-MCS-50-413_RD-02:* “Important Manual Protocol Violations Spreadsheet”, current version; IDEA for CON

P09-12413 Guidance for industry: drug-induced liver injury: premarketing clinical evaluation U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), 2009.

R10-4848 Common terminology criteria for adverse events (CTCAE): version 4.0 (NIH publication no. 09-5410, published: May 28, 2009 (v4.03: June 14, 2010), revised June 2010, reprinted June 2010). Website evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06 14_QuickReference_8.5x11.pd f (2010)

10. HISTORY TABLE

This is a revised TSAP including the following modifications to the final TSAP:

Table 10: 1 History table

Version	Date (DD-Mmm-YY)	Author	Sections changed	Brief description of change
Final	**03-Feb-14**	[redacted]	None	This is the final TSAP without any modification
Revised	**17-Aug-16**	[redacted]	Title Page	Protocol amendment included Name of trial statistician and phone number adapted
			2	Updated list of abbreviations
			3	SAS Version changed to Version 9.4 Definition of study medication included
			4	Analysis of expansion cohorts cancelled, derivation of duration of disease control adapted
			5	Detailed description of endpoints with censoring rules, MTD evaluation period, and other variables added Statement that DLTs during MTD evaluation period will be presented separately added Changed to reflect CTP Amendment No. 2 Clarification that SD refers to confirmed SD, definition of confirmed SD added Clarification that Non-CR/Non-PD should be merged to SD [redacted]
			6.1	Definition of label of analysing treatment that will be used
			6.2	Adaption of definition of IPVs (C6 and C7 added, footnotes added)
			6.3	Clarification of patient sets, added definition of treated and evaluable set, of enrolled set
			6.6	Added specifications for missing data

Version	Date (DD-Mmm-YY)	Author	Sections changed	Brief description of change
				(partial or missing start dates of subsequent anti-cancer therapy and definition of on-treatment and actual treatment, [redacted] Handling of partial death dates added
			6.7	Statement added that baseline measurement is assumed to be prior to administration if on the same day
			7	Standard about time to event analyses included Clarification of "total" columns in tables
			[redacted]	[redacted] Updated to reflect changes in patient analysis sets
			7.4	Deletion of logistic regression analysis of conditional probabilities of observing a DLT in the MTD evaluation period given the dose
			7.5	Clarification of analysis of duration of disease control, added definition of overall response
			7.8	[redacted] Alignment of patient sets Adaption to reflect current SOPs/Guidelines Version of CTCAE added Handling of AEs with missing CTCAE grade changed Paragraphs on analysis of DLTs, of SAEs, of drug-related AEs, [redacted]

Version	Date (DD-Mmm-YY)	Author	Sections changed	Brief description of change
				[redacted]
				Paragraph on AEs leading to discontinuation and to dose reduction of study medication adapted
				Analysis of AEs leading to dose reduction of paclitaxel added
				Definition of potential Hy's law cases corrected
				Handling of CTCAE -9 and -1 added
				[redacted]
				[redacted]
				[redacted]
			8	Updated list of references
			[redacted]	[redacted]