Trial Statistical Analysis Plan

T-09-1043-02

BI Trial No.:	1230.1
Title:	An open phase I single dose escalation study of BI 6727 administered intravenously in patients with advanced solid tumours with repeated administration in patients with clinical benefit
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[redacted]

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2. LIST OF ABBREVIATIONS

Term	Definition / description
ADS	Analysis Data Set
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ALKP	Alkaline phosphatase
BI	Boehringer Ingelheim
BMI	Body mass index
bpm	Beats per minute
[redacted]	[redacted]
[redacted]	[redacted]
°C	Degree centigrade
CPK	Creatinine phosphokinase
CR	Complete response
CT	Concomitant therapies
CTR	Clinical trial report
CTCAE	Common terminology criteria for adverse events Version 3.0
CTP	Clinical trial protocol
DLT	Dose limiting toxicity
DQRM	Data quality review meeting
eCRF	Electronic case report form
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
GGT	γ-Glutamyl transpeptidase

Term	Definition / description
HR	Heart rate [bpm]
ICH	International Conference on Harmonization
INR	International normalized ratio of prothrombin time
max	Maximum
MedDRA	Medical dictionary for drug regulatory activities
min	Minimum
MTD	Maximum tolerated dose
N	Number of non missing observations
n. a.	Not applicable
NEV	Non-evaluable
NEVCNPD	Non-evaluable but clinically not progressive disease
NEVCPD	Non-evaluable but clinically progressive disease
O*C	Oracle clinical database
PD	Progressive disease
PFS	Progression free survival
PK	Pharmacokinetic
PR	Partial response
PT	Preferred term
PTT	Partial thromboplastin time
PV	Protocol violation
QTcF	QT interval, corrected according to Fridericias formula [ms]
[redacted]	[redacted]
RECIST	Response evaluation criteria in solid tumours
REML	Restricted maximum likelihood

Term	Definition / description
[redacted]	[redacted]
SAE	Serious adverse event
SD	Stable disease
SD	Standard deviation
SOC	System organ class
SOP	Standard operating procedure
[redacted]	[redacted]
WBC	White blood cell count

3. INTRODUCTION

This Trial Statistical Analysis Plan (TSAP) provides further details on the statistical analyses described in the Clinical Trial Protocol (CTP) dated 3rd October 2005, and subsequent amendments (3) up to 26th June 2008.

[redacted]

3.1 CLINICAL OBJECTIVES

The primary objective of this trial is to determine the Maximum Tolerated Dose (MTD) of BI 6727 therapy in terms of drug-related adverse events.

Secondary objectives are the collection of overall safety and anti-tumour efficacy data and the determination of the pharmacokinetic profile of BI 6727.

3.2 STATISTICAL DESIGN / MODEL

This phase I trial was performed according to an uncontrolled, open label, accelerated dose titration design to determine the MTD of BI 6727 in patients with advanced solid tumours.

The design is that of a 3+3 fixed dose escalation design (R01-0028) using a toxicity guided approach.

Patients with advanced solid tumours were eligible for this trial. BI 6727 was given as a short infusion over 60 minutes on day 1 of each three week treatment course during the escalation phase. The additional patients treated at the phase II recommended dose of 300 mg to investigate QTc changes, were assigned to one of two infusion time schedules: BI 6727-1h-infusion in course 1 and BI 6727-2h-infusion in course 2 or BI 6727-2h-infusion in course 1 and BI 6727-1h-infusion in course 2. The infusion schedule in courses 3 and higher was always the one hour infusion time.

Patients were not randomized, instead they were selected by the investigators and assigned to the cohort being filled at the time the patient was ready to enter the trial. Thus, the analyses will focus on the exploratory description of the results of each cohort, rather than comparing cohorts.

3.3 NULL AND ALTERNATIVE HYPOTHESES

All analyses in this trial are descriptive and exploratory by nature. Any statistical tests are performed only to provide a statistical framework from which to view the results and plan further studies. No formal statistical inferences are foreseen.

3.4 STATISTICAL SOFTWARE

A trial database within the Oracle Clinical™ (O*C) database system was used to store the study data.

The evaluation of the clinical and the PK data and the statistical analyses will be performed within the validated working environment CARE (Clinical data Analysis and Reporting Environment), including SAS® (current version 8.2, by [redacted]

The calculation of the pharmacokinetic parameters will be performed with WinNonlin® (Professional Network version 5 .0.1, [redacted]

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

Some newly created endpoints regarding tumour response are created and explained within the TSAP.

[redacted]

Following Amendment 3, a more extensive analysis of electrocardiograms (ECG) is planned on the additional cohort of 14 patients. The main aim of this cohort was to investigate QTc changes in parallel with PK sampling during and after intravenous infusion of BI 6727 300 mg dose over 1 hour and over 2 hours. For this set of 12 patients a different analysis of ECG data is planned (see Section 7.7.4.1).

5. ENDPOINTS

5.1 PRIMARY ENDPOINTS

The primary objective (to find the MTD) is determined from the primary endpoint, DLT.

Maximum tolerated dose (MTD):

MTD is defined as the highest dose studied for which the incidence of DLT in an individual dose cohort is at most 33% during the first course.

Additionally, all information, including DLT from later treatment courses, will be considered in the final determination of the dose recommended for Phase II.

5.2 SECONDARY ENDPOINTS

5.2.1 Tumour response

For solid tumours, evaluation of tumour response will be assessed according to the Response Evaluation Criteria in Solid Tumours (RECIST) definition. The overall response of target and non-target lesions together with or without the appearance of new lesions as reported by the investigator is assessed on a four point categorical scale as complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD) according to the RECIST criteria (R01-0754). However, for the analyses within this TSAP, a modified version of the RECIST criteria will be used, in order to best handle measurements that are non-evaluable (NEV). [redacted] Basically, an algorithm is used to determine the outcome, depending on whether the NEV measurement is for target / non-target lesions. If it is still not possible to determine the outcome based upon the algorithm, then a clinical assessment will be used.

Tumour responses will be analysed based on the 'Overall response' question that is asked directly from the Electronic Case Report Form (eCRF). Additionally, clinical progression will be taken into account. It will not be checked whether the answer of the overall response assessment was based on RECIST only or already incorporates clinical progression, i.e. no differentiation will be made between NEVCPD or PD.

Using the RECIST criteria combined with the presence or absence of clinical progression, several endpoints will be analysed and created. Whilst some are at each tumour assessment (unconfirmed), others are summary measures over time (confirmed / best).

Note that for the case of non-target responses, level=2 refers to 'Incomplete response / Stable disease / Partial response'.

The main endpoints with their corresponding definitions are as defined below:

Unconfirmed Overall Response: [redacted] As noted above, for some patients the overall response as reported by the investigator also includes information about clinical progression and is

assigned to progressive disease as soon as a patient experiences clinical progression. For that reason this endpoint is referred to Unconfirmed Overall Response and not to Unconfirmed RECIST Overall Response. Analogous to RECIST, the endpoint Unconfirmed Overall Response will be made up of 6 potential outcomes with 5 ordered levels:

Unconfirmed Overall Response	Abbreviation	Level
Complete response	CR	1
Partial response	PR	2
Stable disease	SD	3
Non-evaluable but clinically non progressive disease	NEVCNPD	4
Progressive disease or Non-evaluable but clinically progressive disease	PD or NEVCPD	5

Unconfirmed Best Overall Response**:** This is the best of the individual 'Unconfirmed Overall Responses', recorded from the start of the treatment until PD.

Unconfirmed Best Objective Response: If the 'Unconfirmed Best Overall Response' is either CR or PR, then this Unconfirmed Best Objective Response is Yes. Otherwise it is No.

Additional supportive endpoints are:

Clinical Benefit: Clinical benefit is defined as the absence of disease progression (no PD or NEVCPD) during a course.

Confirmed objective response: To confirm an objective status here, changes in tumour measurements must be confirmed by at least one later assessment that must be performed ≥ 28 days after the criteria for CR or PR are first met without having an assessment of PD or NEVCPD.

5.2.2 Time-to-Event

Both, formal and informal summary analyses on time-to-event endpoints will be performed. That is to say, Kaplan-Meier analyses will be performed, and summary statistics will be calculated. [redacted]

Progressive disease: Progressive disease (PD or NEVCPD) is level=5 as outlined in the endpoint 'Unconfirmed Overall Response' in Section 5.2.1 above.

Date of progressive disease is the earliest of:

1) date of progression (progdt) recorded on course in e-CRF corresponding to first recurrence of progressive disease

2) date of progression recorded (progdt) on end of trial in e-CRF if first recurrence of progressive disease was at end of trial

3) date of progressive disease recorded on post-study follow-up of eCRF

4) death date (in the case of none of 1-3 being available)

Patients administered a new additional other anti-cancer therapy recorded in the e-CRF but not presenting with progressive disease before the start of this new anti-cancer therapy will be censored at the date of last radiological imaging before the new anti-cancer therapy has started.

Patients not administered another anti-cancer therapy and not presenting with progressive disease or death during the trial will be censored at the date of the last imaging during which the patient was evaluable and did not have the event. Alternatively, if there is an investigators assessment after this, then the date of the NEVCNPD will be used.

Progression-free survival (PFS) [in days] is therefore the time from first administration of trial medication to the earlier of progressive disease or death. (Date of PD as above – date of first administration of trial medication + 1).

Progression-free survival (PFS) censored [in days] is therefore the time from first administration of trial medication to the date of last imaging (or NEVCNPD as above). (Date of last imaging – date of first administration of trial medication + 1, or Date of NEVCNPD – date of first administration of trial medication + 1).

5.2.3 Eastern Cooperative Oncology Group (ECOG) Performance Score

ECOG score: The scale of ECOG score is defined as a six point categorical scale as described in (R01-0787) ranging from 0 (asymptomatic) to 5 (death). Calculation was to be carried out for each patient, for each first visit of each treatment course, each last visit of each treatment course, the end of treatment and the follow up visit.

ECOG score change from baseline to end of treatment will be calculated, and defined as

= ECOG score at end of treatment – ECOG score at baseline.

Scale of ECOG score change: The ECOG score changes from baseline score will be categorized on a three point categorical scale: deteriorated, unchanged, and improved. Improvement or deterioration of performance status will require a decrease or an increase from baseline, respectively, of at least one point on the ECOG scale.

5.2.4 Adverse events

Adverse events (AEs) are defined as the same preferred term (PT) after collapsing of two events less than 24 hours apart.

Intensity of adverse events is scaled according to Common Terminology Criteria of Adverse Event (CTCAE version 3.0, R06-1666).

A separate listing for all patients who developed the following events will be generated.

- AEs with CTCAE grade ≥ 3,
- DLT,
- serious AEs, or,
- significant AEs as defined in Section 7.7.1.2

5.2.5 Laboratory parameters

In this trial the original laboratory values will be converted into standard units and CTCAE grades for parameters which have a CTCAE criteria (For definition of CTCAE grade for laboratory values, [redacted]). For this study, the laboratory parameters and their functional groups [redacted] together with the direction of concern, which were to be recorded and which have a CTCAE criteria are:-

Haematology: Haemoglobin (-), white blood cell (WBC) (-) and Platelets (-)

Differentials: Neutrophils (-) and Lymphocytes (-)

Coagulation: International normalized natio of prothrombin time (INR) (+) and Partial thromboplastin time (PTT) (+)

Electrolytes: Sodium (+ and -), Potassium (+ and -) and Calcium (+ and -)

Enzymes: Aspartate aminotransferase (AST) (+), Alanine aminotransferase (ALT) (+) and Alkaline phosphatase (ALKP) (+)

Substrates: Total bilirubin (+),Glucose (+ and -), Creatinine (+), Albumin (-) and Creatinine Phosphokinase (CPK) (+)

+ (-) means the higher (lower) the value the worse the toxicity. (+ and -) means the parameter can be considered as hyper or hypo.

It is important to note that these are only the parameters that have a CTCAE criteria, and that other parameters were recorded which have no CTCAE criteria.

Laboratory parameters were to be recorded for each patient on days 0-3, 5, 8, 15 and 22 of first treatment course, and all except days 3 and 5 at subsequent treatment courses. Recording of standard laboratory parameters was optional at follow-up. Changes from baseline will be calculated for each day of the first treatment course where measured, the last visit of each treatment course and the end of the trial. For the CTCAE grades, some changes from other time-points will also be calculated.

The baseline, last value on treatment and corresponding change from baseline will be presented using N, median and interquartile range. This will be done for all continuous laboratory parameters using the Boehringer Ingellheim (BI) normalised values, except, however, in the case of WBC differentials (Neutrophils and Lymphocytes) which have been

recorded in percentage. These have been re-derived to normalised values in such a way that the accuracy of decimal places is maintained for longer. [redacted]

Patients with clinically relevant laboratory abnormalities, [redacted] will be summarised.

Note: For calculating the change in CTCAE grade from baseline/ pre-dose level, patients with a CTCAE grade of -9 will be reviewed on a case-by-case basis. If there is no suggestion that the corresponding laboratory value is of clinical significance, these values will be changed to -7 and treated as a CTCAE grade of 0 for analyses. All other values with CTCAE grade -9 will be regarded as CTCAE grade -8. Values with a CTCAE grade of -8 will either be removed from analyses concerning determination of baseline and worst CTCAE grade or if needed the category "not covered by CTC criteria" will be included. Values with CTCAE grades of -7 and -8 will be displayed in two separate listings.

In a similar manner, patients with a CTCAE grade of -1 will be reviewed on a case-by-case basis. For uric acid, values with CTCAE grade -1 will be regarded as either CTCAE grade 3 or CTCAE grade 1, depending on whether accompanied with physiological consequences or not.

The worst post baseline laboratory value and its CTCAE grade over all treatment courses will be calculated for each laboratory parameter specified above.

The time to worst CTCAE value [in days] will be defined as the time from first administration of trial medication to the first occurrence of the worst CTCAE grade. (Date of first occurrence of worst CTCAE grade – date of first administration of trial medication + 1).

The last value on treatment will be determined using a similar algorithm to the adverse events, and presented descriptively.

The change of the CTCAE grade of the lab value will be calculated

- from baseline to the last laboratory value on treatment
- from baseline to the worst value on treatment

5.2.6 Tumour markers

Selected tumour markers will be recorded at baseline and visit 8, and again at visit 5 of repeated courses. These parameters are outlined in Section 5.2.5 of the CTP. However, specific attention will be paid to the markers CA-125, CA 19-9 etc. These will be presented in listings.

5.3 OTHER ENDPOINTS

5.3.1 Demographics

Only derived endpoints are defined here. Standard demographic and baseline characteristics (sex, age, race, etc.) are used as recorded in the eCRF.

Body Mass Index (BMI)

$$BMI\left[kg/m^2\right] = \frac{weight\,[kg]}{(height\,[m])^2}$$

Time from first histological diagnosis [years] is the time between the date of first histological diagnosis and the date of informed consent:

Time [years] = (informed consent - date of first histological diagnosis + 1)[days] / 365.25

Age at the first Histological diagnosis [years]:

Age [years] = INT(date of first histological diagnosis – birthday)[days] / 365.25,

where the INT function truncates the decimal portion of the value of the argument.

[redacted]

5.3.3 Extent of exposure

Number of days of administration [N]: Cumulative number of days with an administration of treatment.

Number of courses initiated [N]: course initiated means that the patients received at least one administration of BI 6727 in the initiated course.

Number of courses completed [N]: A course is considered completed if one of the following is true:

- Another course was initiated.

- The patient was observed in the trial until at least 21 days after the last administration of trial medication of the respective course or stopped the trial due to DLT or PD.

Total observation time [in days] = (Date of last observation from the eCRF – first administration of trial medication date in course 1 + 1).

Cumulative total dose [mg] = Sum of doses (administered dose of BI 6727) calculated across all courses.

Total exposure time to the trial drug [days] = duration of "on treatment period" = MINIMUM (date of last trial drug administration of the last course + 21 days, death if occurring earlier than 21 days after the last administration) – date of first administration in the first course + 1 day.

[redacted]

5.3.5 ECG

- QTcF changes from baseline at each point in time: the QTcF post baseline measurement obtained at time t minus baseline QTcF measurement at time t.

The above endpoint will also be computed for the uncorrected QT interval and for the heart rate (HR). The heart rate (HR) will be derived from RR intervals.

- New*) onset of QT/QTcF > 500 ms (notable prolongation)

- New*) onset of QTcF > 470 ms

- New*) onset of QTcF > 450 ms

*): "New" means not present at any time pre-dose

- Categories of the QTcF increase from baseline to the maximum value:
  intervals for a given patient as QTcF ≤ 30 ms, 30 ms < QTcF ≤ 60 ms, QTcF > 60 ms,
  (the latter increase reflects a notable change)

- Categories of the QT increase from baseline to the maximum value:
  intervals for a given patient as QT > 60 ms (the latter increase reflects a notable change)

- PR and QRS changes from baseline at each point in time

- PR, QRS and HR percentage changes from baseline at each point in time

[redacted]

5.3.5.1 ECG - Assessment for patients of the extension cohort for additional QT/QTc analysis

Three consecutive ECGs were recorded

at screening, and

- prior to the start of the infusion (baseline)
- 5 minutes before the end of the infusion,
  (i.e. around 1 hour, if infusion duration is 1 hour or around 2 hours, if infusion duration is 2 hours, respectively)
- 1 hour after the end of the infusion,
  (i.e. around 2 hour, if infusion duration is 1 hour or around 3 hours, if infusion duration is 2 hours, respectively)
- 4 hours
- 24 hours

  after the end of infusion of Courses 1 and 2

5.3.5.2 ECG - All other patients

Resting ECG was recorded prior to the start of the infusion (baseline) of treatment courses 1 and 3, directly after the end of the infusion, and again at the end of the treatment course. A series of three consecutive ECGs using dedicated equipment were recorded.

6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENTS

6.1.1 Treatment regimens / study intervals

The treatment regimens/study phases with short label, sort order and start date/time included in the treatment set-up in O*C (actual treatment set-up) [redacted]

6.1.2 Randomised treatment

Codes, decodes and sort order for initial treatment labels [redacted]

6.1.3 Specification of treatments for analyses

"Analysing treatment" will be used for reporting of treatment emergent AEs and to differentiate between screening, on-treatment and post-study safety data. The inequalities start date (in Table 6.1.3: 1 below) ≤ onset date of AE < end date will determine whether the AE will be assigned to the "analysing treatment" or not.

The labels of the analysing treatment, analysing numbers (analno), the labels used for displays in the tables as well as start date and end date to be used for reporting of AEs and laboratory values in the CTR, are seen in the table below.

Table 6.1.3: 1 Definition of the label of the analysing treatment, analysis numbers, the labels using for displaying in the tables, start date and end date

Label of the analysing treatment (ANALLBL)	**Analysis number (ANALNO)**	**Label for the columns displayed in the tables**	***Start date***	***End date***
Screening	5		Date of informed consent If date of informed consent = date of administration then the start date for "Screening"-period will be derived as date of informed consent – 1 day	Start date of treatment course 1

Table 6.1.3: 1 Definition of the label of the analysing treatment, analysis numbers, the labels using for displaying in the tables, start date and end date - continued

Label of the analysing treatment (ANALLBL)	**Analysis number (ANALNO)**	**Label for the columns displayed in the tables**	***Start date***	***End date***
Treatment course 1 analysis	4	- use treatment specification of the initial treatment [redacted] and column 'NAME in E_TPATT'	Date of first administration of BI 6727 within the treatment course 1	Date of first administration of BI 6727 within the treatment course 2, Or, Start date of actual treatment post-study.
Treatment course 1 analysis	4	Total	Date of first administration of BI 6727 within the treatment course 1	Date of first administration of BI 6727 within the treatment course 2, Or, Start date of actual treatment post-study.
All course analysis	3	- use the treatment specification of the initial treatment [redacted] and column 'NAME in E_TPATT'	Date of first administration of BI 6727 within treatment course 1	Start date of post-study interval [redacted]
All course analysis	3	Total	Date of first administration of BI 6727 within the treatment course 1	Start date of post-study interval [redacted]

Table 6.1.3: 1 Definition of the label of the analysing treatment, analysis numbers, the labels using for displaying in the tables, start date and end date - continued

Label of the analysing treatment (ANALLBL)	**Analysis number (ANALNO)**	**Label for the columns displayed in the tables**	***Start date***	***End date***
Post-study	6	- use the treatment specification of the initial treatment [redacted] and column 'NAME in E_TPATT'	Start day of post-study-interval	Date of Data Base lock+1day

6.2 IMPORTANT PROTOCOL VIOLATIONS

Due to the fact that this is a phase I study, no per protocol population is needed, however important protocol violations (PV) should be identified for patients in the treated set (see Section 6.3). Any PV which may affect safety, efficacy or the patient's rights will be determined.

PVs are summarised into categories and are coded in O*C. [redacted]

Table 6.2: 1 Listing of protocol violations

Category/ Code		**Description**	**Comment/Example**	**Efficacy (E), Safety (S) or Right (R)**
A		**Inclusion/Exclusion Criteria**		
	A1	**Criteria related to safety**		
	A1.1	Patient has condition that may cause additional risk from study medication	IN 2, 5 EX 1, 3-5, 11, 13	S

Table 6.2: 1 Listing of protocol violations – continued

Category/ Code		Description	Comment/Example	Efficacy (E), Safety (S) or Right (R)
	A1.2	Patient has laboratory assessments that may cause additional risk	EX 6-10	S
	A1.3	Patient is unable to comply with the protocol	EX 15	S
	A2	**Criteria related to efficacy**		
	A2.1	Patient does not have trial diagnosis	IN 1	E
	A2.2	Patient does not have ECOG score ≤ 2	IN 4	
	A2.3	Chemo-, radio-, or immunotherapy within the past four weeks before start of therapy or concomitant with this trial. This does not apply to steroids and biphosphonates.	EX 14	E
	A2.4	Patient does not have any measurable tumour deposits (RECIST), only for additional patients recruited at the MTD.	IN 6	E
	A3	**Any other criteria not met that are considered relevant at DQRM/BPRM**	n.a.	E/S
B		**Legal criteria**		
	B1	Informed consent not given	IN 3	R
	B2	Informed consent after visit 1		R
	B3	Patient < 18 years old	IN 2	R
	B4	Men or women who are sexually active and unwilling to use a method of contraception, women who are pregnant or breastfeeding	EX 2, 12	R
C		**Administration of trial medication not in accordance with the protocol**		
	C1	BI 6727 taken before PK sampling at visit 2 (treatment course1)	As entered in e-CRF. Create listing, decision at DQRM/BPRM.	E
	C2	**Criteria for repeated treatment eligibility**		
	C2.1	Patient continuing on study medication despite experiencing progressive disease and/or clinical progression.	Create listing, decision at DQRM/BPRM.	S

Table 6.2: 1 Listing of protocol violations – continued

Category/ Code		Description	Comment/Example	Efficacy (E), Safety (S) or Right (R)
	C2.2	Patient continuing on study medication after experiencing drug-related clinically relevant AE and/or DLT without following recovery.	Create listing, decision at DQRM/BPRM.	S
	C2.3	Patient continuing on study medication after delaying a treatment course for more than 6 weeks.	Create listing, decision at DQRM/BPRM.	S
D		**Concomitant medication**		
	D1	Any other chemotherapy, immunotherapy or radiotherapy during the trial	Create listing, decision at DQRM/BRPM.	S, E
E		**Missing data**		
	E1	**Missing PK and administration data**		
	E1.1	Missing PK sampling date and/or time	Create listing, decision at DQRM/BRPM.	E
	E1.2	Missing BI 6727 administration date and/or time	Create listing, decision at DQRM/BRPM.	E
	E2	**Missing response data**		
	E2.1	Baseline scan of tumour measurement not within four weeks prior to treatment.	Create listing, decision at DQRM/BRPM.	E
	E2.2	Different imaging techniques were used for lesion measurement(s) during trial.	Create listing, decision at DQRM/BRPM.	E
	E2.3	Missing image(s) at one or more time points.	Create listing, decision at DQRM/BRPM.	E

6.3 PATIENT SETS ANALYSED

Only one analysis population (Treated Set) will be considered for efficacy and safety (except ECG).

The Treated Set consists of all patients who received at least one application of the BI drug BI 6727.

Trial medication is defined as BI 6727.

First administration of trial medication is defined as date of first administration of BI 6727.

ECG

Per protocol set (PPS):

This is a subset of the Treated Set, restricted to patients, who have an ECG assessment in both courses (e.g. patients, who were replaced will be excluded).

[redacted]

6.5 POOLING OF CENTRES

There are only two centres in this trial. In general centres will be pooled. Due to the fact that a centre effect can not be excluded, specific analyses might be performed by centre additionally. Apart from that, centre effects will be described descriptively.

6.6 HANDLING OF MISSING DATA AND OUTLIERS

If not stated otherwise, missing data will not be imputed and remain missing. [redacted].

Adverse Event

Missing or incomplete AE dates are imputed according to BI standards ([redacted]

PK data

Missing data and outliers of PK data is handled according to [redacted]

[redacted]

[redacted]

[redacted]

ECOG Performance Score

In case of non-available values of ECOG score at the time point before first administration the score measured just before administration on day 1 of first course will be considered as

baseline. In case the ECOG score was not determined at the end of treatment visit, the last ECOG score available will be used instead.

[redacted]

Date of progression (progdt)

If progression date (progdt) is missing for the evaluation of progression free survival, the corresponding visit date/examination date (visdt/examdt) is taken instead.

[redacted]

ECG

If one or two of the three consecutive ECG measurements is missing the available data will be used for that point in time.

Assessment of ECG for patients of the extension cohort for additional QT/QTc analysis:

If one baseline measurement is missing, this will be replaced by the other baseline measurement. If both baseline measurements are missing, this will be replaced by the measurement obtained at screening. Otherwise, baseline is missing and the patient is excluded for that endpoint.

Assessment of ECG for all other patients:

If one baseline measurement is missing, this will be replaced by the other baseline measurement. If both measurements are missing, the baseline is missing and the patient is excluded for that endpoint.

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

Study days and visits will be labelled according to the flow chart on page 6-8 of the CTP.

Unless otherwise specified, baseline is defined as the time-point closest to but prior to first administration of trial medication in the first treatment phase, where the first administration of trial medication is defined in Section 6.3 above.

However, in the case of laboratory data, if the time is missing but the date of lab assessment is equal to the first medication date, [redacted]. This will then become the baseline value.

[redacted]

ECG

Baseline ECG is available from two courses. To account for possible variations between the study days, two different baseline definitions will be used:

1. Individual baseline is defined as the mean of the triplicate at the time-point closest to but prior to the start of the infusion of each treatment course, i.e. each treatment course has its own baseline.

2. Combined baseline is defined as the mean of the (two) triplicates at the time-point closest to but prior to the start of the infusion of both treatment courses, i.e. a common baseline is used for both treatment courses.

6.8 GENERAL CALCULATION RULES

Months = days / 30, Years = days / 365.25 = months / 12

[redacted]

7. PLANNED ANALYSIS

For the production of summary tables, standard programs [redacted] will be used if available.

The following standard descriptive statistical parameters will be the basis for displays in summary tables of continuous variables. [redacted]

N	Number of non-missing values
Min	Minimum value
Q1	Lower quartile (25% percentile)
Median	Median value
Q3	Upper quartile (75% percentile)
Max	Maximum value

[redacted]

The following standard descriptive statistical parameters will be displayed in frequency tables of categorical or categorised variables:

N	number of non-missing observations
%	percentage

[redacted]

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

7.1.1 Disposition of patients

For patient disposition the standard descriptive table will be populated. Additionally, patients with discontinuations by initial treatment and the reasons will be listed.

7.1.2 Important protocol violations

A listing with the number of patients with protocol violations by initial treatment will be created in Section 15 of the CTR.

7.1.3 Demographic and other baseline

Standard descriptive analysis and summary tables for all patients treated by initial treatment will be created for demography, smoking/alcohol status, physical examination, ECOG, tumour information and oncology history.

7.4 PRIMARY ENDPOINTS

The primary objective is to find the MTD. Refer to Section 7.7.1 for a description of the analysis of safety and tolerability, the primary objectives of this trial.

7.5 SECONDARY ENDPOINTS

The following endpoints relating to tumour response will be summarised descriptively in tables, by initial treatment:

- Unconfirmed Overall Response at all timepoints
- Unconfirmed Best Overall Response

- Unconfirmed Best Objective Response
- Clinical Benefit
- Confirmed Best Objective Response

Progression Free Survival: If applicable, for PFS a Kaplan-Meier analyses will be performed on the MTD dose group and other cohorts of interest, depending on the final DLT results. Additionally, this information will be listed, including whether or not the endpoint has been censored.

For the ECOG score, the following endpoints will be summarised in tables:

- ECOG score changes at the end of treatment
- Scale of ECOG score changes at the end of treatment.

The analysis of PK parameters is performed [redacted] and will be reported separately by the PK department within BI.

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 is based on the [redacted] reference document.

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'.

7.6 EXTENT OF EXPOSURE

Standard descriptive analyses over all treatment courses will be performed. This will include a summary of the variables already described in Section 5. This descriptive analysis will comprise a mixture of frequency and percentages, as well as summary statistics.

[redacted].

7.7 SAFETY ANALYSIS

The primary analysis is for determination of MTD. No statistical model is foreseen allowing assessment of MTD, descriptive analysis is confined to a listing by dose group. The purpose of these tables is to summarize and document the data that led to the selection of MTD.

7.7.1 Adverse events

7.7.1.1 Maximum tolerated dose and dose limiting toxicity

A summary of the number of patients with DLT in treatment course 1 will be given by initial treatment.

7.7.1.2 Adverse events

AE analysis will be performed for all treatment periods and for the first treatment course.

The analyses of AEs will be descriptive in nature and will follow the standard procedure laid down in the DM & SM (including all required tables and listings) (current guideline 001-MCG-156 'Handling and Summarization of AE Data for CTR and Integrated Summaries'). AEs will be coded with the most recent version of Medical Dictionary for Regulatory Activities (MedDRA version 10.0). The version number will be displayed as a footnote in the respective tables and listings. The system organ classes will be sorted according to the standard sort order specified by EMEA, preferred terms will be sorted alphabetically (within system organ class).

Each patient can be observed during the trial under several doses. Analysing the AE of all treatment courses will be carried out under the initial treatment. No formal statistical analysis is planned for the safety comparison.

The analysis of AEs will be based on the concept of treatment emergent AEs. AEs will be distinguished for the treatment course in which the subjects are on-treatment as well as for screening, and post-study [redacted] The actual

dosage of BI 6727 administered on the day each AE starts will also be derived and will be included in the listing. Listings of screening events will not be sorted by initial treatment (Table 6.1.3: 1). But post-study listings will be sorted by initial treatment.

According to the BI standards, multiple recordings of AEs will be collapsed to episodes on the lowest level term and multiple episodes will be condensed to records on the PT and system organ class (SOC) level. CTCAE grade will be an additional criterion for collapsing and condensing AEs. The maximum CTCAE grade will be assigned to episodes and records. CTCAE grade and DLT information will be displayed in AE listings. MedDRA levels for condensing will be SOC and PT.

According to ICH E3 (International Conference on Harmonisation Efficacy 3), AEs classified as 'other significant' will include those non-serious and non-significant AEs with
(i) 'action taken = discontinuation' or 'action taken = reduced', or
(ii) those identified by the Trial clinical monitor/Investigator at a BRPM.

An overall summary of AEs with additional columns 'CTCAE','DLT (yes/no)' and 'total' will be presented.

AE flags and attributes

An AE flag will be defined for patients who developed an AE that was CTCAE grade ≥ 3, DLT, or serious AE (SAE).

An AE attribute "CTCAE grade 3/4 or 5 combined with drug relation" will be derived to avoid incorrect condensing. Consider, for instance, a patient with coincident drug-related abdominal pain with CTCAE 1, and non-related vomiting with CTCAE 3. Without the new attribute these AEs would be reported as drug-related Grade 3/4 under the SOC Gastrointestinal disorder. With the new AE attribute these AE would be excluded.

An additional AE attribute "Drug relationship combined with seriousness of the AE" is needed similarly to the AE attribute "CTCAE grade 3/4 or 5 combined with drug relation" described above.

Frequency of patients with AEs will be summarised by treatment, primary SOC and PT. Separate tables will be provided for patients with other significant AEs, for patients with significant non-serious AEs and for patients with SAEs. Additionally, there will be a summary table presenting maximum CTCAE grade for each AE, as well as patients who developed AEs with CTCAE grade greater than 3, DLT, SAE, and significant AEs.

AE of special interest (User-defined AE categories): these will be the same as for project 1216.P1 (BI 2536). Frequency tables and listings for these AE categories will be provided.

7.7.2 Laboratory data

The analyses of laboratory data will be descriptive in nature and will follow the standard procedure laid down in the DM & SM (Guideline 'Display and Analysis of Laboratory Data').

Patients will be counted under the initial treatment. Separate listings for patients treated under different doses will be created. The analysis of laboratory data will use the same 'analysing treatments' as described for the AEs.

Single time courses by initial treatment will be used to display laboratory values over time. The graphs may be truncated if sufficient data is not available. These graphs will be displayed in Chapter 16.1.9.2 for the following parameters, using the BI normalised values for Haematology and Differentials, and the multiples of the ULN for Substrates and Enzymes:

Haematology: Haemoglobin, WBC count and Platelets

Differentials: Neutrophils (absolute count)

Substrate: Creatinine, Total Bilirubin and Creatinine Phosphokinase

Enzymes: AST, ALT and γ-Glutamyl transpeptidase (GGT)

In addition, laboratory tests will be analysed within the treatment courses as defined below. Maximum CTCAE grades will be tabulated by treatment course and over the entire trial.

Where applicable, standard CTCAE grading Shift tables from first visit to end of trial will be generated in Appendix 16.1.9.2.

Number of patients treated [N (%)]

Number of patients with maximum change of CTCAE grade [N (%)]

Number of patients with transition of CTCAE grade:

- from baseline to the last value on treatment [N (%)]
- from baseline to the worst grade on treatment [N (%)]
- from worst to the last value on treatment [N (%)]

Clinically relevant abnormalities [redacted]) will also be summarised.

7.7.3 Vital signs

Descriptive statistics of absolute values (and change from baseline) for vital signs (including body weight) will be provided by initial treatment and planned time or visit of the first treatment course and over all treatment courses.

7.7.4 ECG

7.7.4.1 ECG - Assessment for patients of the extension cohort for additional QT/QTc analysis

All analyses described in this section will be performed using the Treated Set.

7.7.4.1.1 Central tendency analysis

The endpoint, QTcF change from individual baseline at each point in time (cf. Section 5.3.1, endpoint 1, cf. section 6.7), will be analysed using a linear mixed-effects model for repeated measures data.

This model will include the following effects 'sequence', 'course', 'treatment' (both infusion types i.e. 1 hour duration and 2 hours duration) and 'time' as fixed, categorical effects, 'patient within sequences' as a random, categorical effect, the interaction effect 'treatment*time' as well as the continuous, fixed covariate of baseline value. The blocking effect specified by the SUBJECT variable within the repeated SAS statement (effect 'time') is patient*course implying that the values of 'time' are correlated within each subject's course. This model will use all observed data available. The variance covariance structure for the main analysis will be ''Compound symmetry'. Should the estimated G matrix be not positive definite, 'patient within sequences' will be included as fixed effect.

The endpoint, QTcF change from combined baseline at each point in time (cf. Section 5.3.1, endpoint 1, cf. section 6.7), will be analysed using the same model as described above, except that 'patient within sequences' will be removed from the model.

The SAS® procedure MIXED will be used involving the restricted maximum likelihood (REML)-estimation and the Kenward and Roger approximation of denominator degrees of freedom. Details of the programming code are described in the Analysis Data Set (ADS) plan, section 3 (Program Modules).

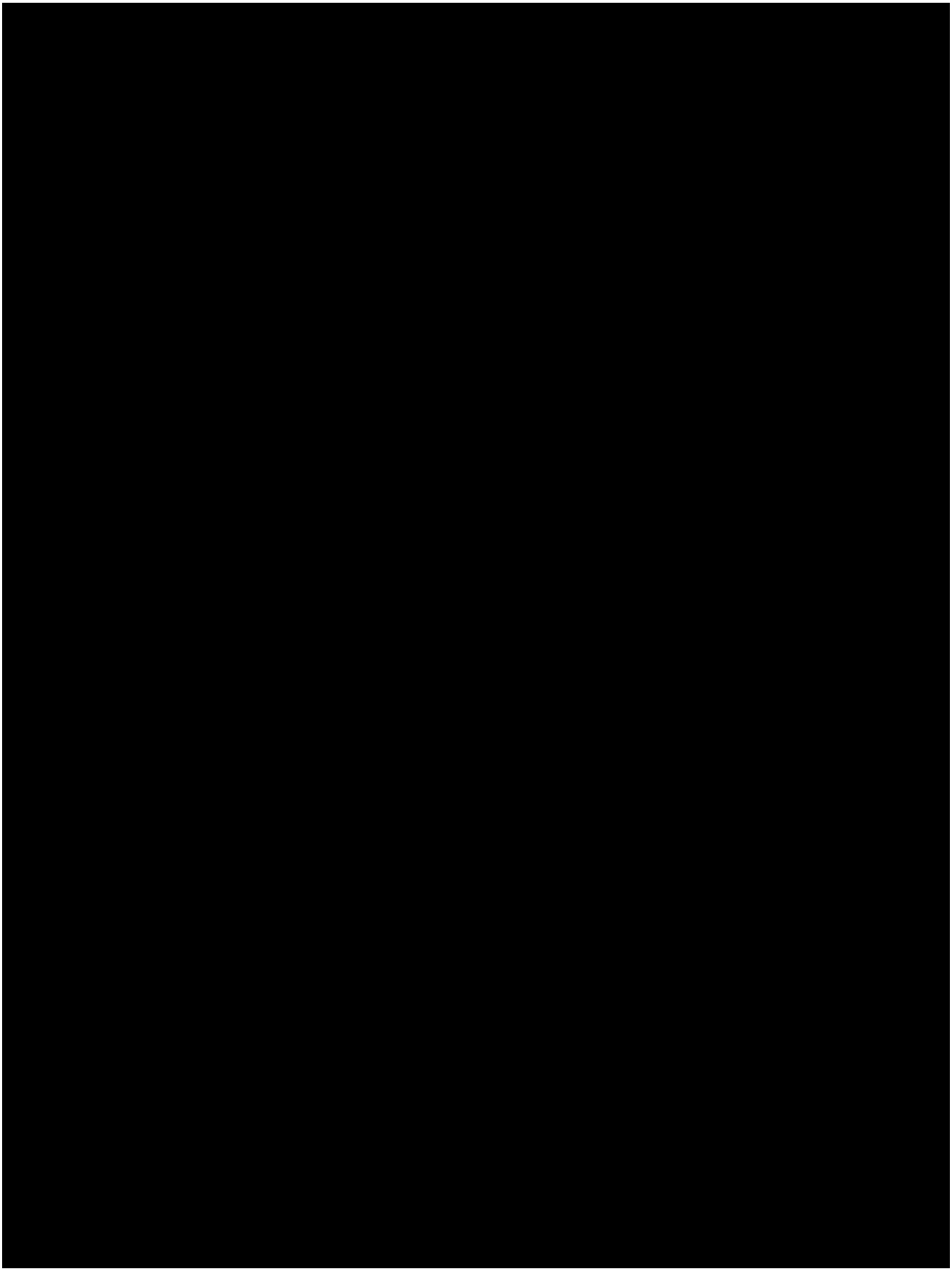
For the pairwise comparisons of the different treatments at each time-point the differences between the expected means for the BI 6727 infusions at each sampling point will be estimated by the difference in the corresponding Least-Squares Means and two-sided 90 % confidence intervals based on the t-distribution will also be computed. The 1-hour infusion is considered as the reference while the 2-hour infusion is considered as the test treatment, i.e. the difference '2-hour infusion - 1-hour infusion' will be computed.

The analysis described above will also be performed for the endpoints QTcF/HR change from baseline at each point in time.

[redacted]

7.7.4.1.2 Categorical endpoints / [redacted]

Frequency tables will be provided for categorical endpoints. [redacted]



[redacted]

[redacted]

[redacted]

[redacted].

7.7.4.2 ECG - Assessment for all other patients

All analyses described in this section will be performed using the Treated Set.

Patient [redacted], who received a dose of 127 mg/kg, will be included in the 125 mg/kg dose group for the analysis.

The quantitative QTcF, QT and HR endpoints will also be summarised descriptively for each treatment using statistical parameters such as N, mean, SD, min, median, max. These analyses will also be performed using PPS.

Endpoints for the PR and QRS intervals ([redacted] will be summarised using standard descriptive statistics.

Frequency tables will be provided for categorical endpoints. [redacted]

Frequencies of patients with threshold increases from baseline in the QT/QTcF intervals (cf. Section 5.3.1, endpoints 5 and 6) will be displayed.

[redacted]

[redacted]

8. REFERENCES

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R01-0787 Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, Carbone PP. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982;5:649-655

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[redacted]