Trial Statistical Analysis Plan

T10-1036-02

BI Trial No.:	1230.4
Title:	An open phase I/IIa trial to investigate the maximum tolerated dose, safety, pharmacokinetics, and efficacy of intraveneous BI 6727 as monotherapy or in combination with subcutaneous cytarabine in patients with acute myeloid leukaemia
Responsible trial statistician:	[redacted] Phone: [redacted] Fax:
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2. LIST OF ABBREVIATIONS

Term	Definition / description
AE	Adverse Event
ALKP	Alkaline Phosphatase
ALT	Alanine Amino Transferase
AML	Acute Myeloid Leukemia
APTT	Activated Partial Thromboplastin Time
ASR	Annual Safety Report
AST	Aspartate Amino Transferase
AUC	Area under the concentration-time curve
BI	Boehringer Ingelheim
BRPM	Blinded Report Planning Meeting
CMAX	Concentration at Maximum
CR	Complete Remission
CRi	Complete Remission With Incomplete Blood Recovery
CTCAE	Common Terminology Criteria For Adverse Events
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
eCRF	Electronic Case Report Form
DLT	Dose Limiting Toxicity
DM&SM	Data Management and Statistics Manual
DQRM	Data quality review meeting
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EFS	Event Free Survival
EMEA	European Medicines Agency
FACS	Fluorescence Activated Cell Sorting
HGB	Hemoglobin
IB	Investigator Brochure
ICH E3	International Conference on Harmonisation - Efficacy 3
IDEA	International Document Management and Electronic Archiving
INR	International Normalized Ratio

Term	Definition / description
LD-Ara-C	Low Dose Ara-C
MedDRA	The Medical Dictionary For Regulatory Activities
MQRM	Medical Quality Review Meeting
MTD	Maximum Tolerated Dose
NC	No Change
O*C	Oracle Clinical
PD	Progressive Disease
PK	Pharmacokinetic
PR	Partial Remission
PT	Preferred Term
PV	Protocol Violation
QTc	(Frequency) Corrected QT-Time
SD	Standard Deviation
SOC	System Organ Class
TAH	Therapeutic Area Head
TCM	Trial Clinical Monitor
TMM	Team Member Medicine
TMW	Team Medical Writer
TPONT	Troponin
TSAP	Trial Statistical Analysis Plan
TSTAT	Trial Statistician
URPM	Unblinded Report Planning Meeting
WBC	White Blood Cell Count

3. INTRODUCTION

This TSAP will describe both the analyses for the final CTR as well as the analyses made for the safety update after phase I (see section 9.5).

3.1 CLINICAL OBJECTIVES

See section 2.1 of the CTP.

3.2 STATISTICAL DESIGN / MODEL

The trial will be performed as an open label study. In phase I patients will be assigned to the two treatment schedules (BI 6727 monotherapy and BI 6727 in combination with LD-Ara-C, respectively). In phase II patients will be randomly allocated to one of the two different treatment schedules BI 6727 in combination with LD-Ara-C and to a monotherapy schedule with LD-Ara-C only, respectively. To determine the two separate MTDs in the phase I part, cohorts of patients will be entered sequentially into escalating dose tiers using the 3+3 design with dose de-escalation.

3.3 NULL AND ALTERNATIVE HYPOTHESES

All analyses in this study are descriptive and exploratory by nature. Any statistical tests are performed only to provide a statistical framework from which to view the results and providing aid for planning further studies. No formal statistical tests are foreseen.

3.4 STATISTICAL SOFTWARE

[redacted] or higher will be used for all analyses.

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

- An additional comparison of objective response rates based on a Bayesian approach has been added.

- Blood products uses have been added as another endpoint in order to reflect supportive care requirements.

- The definition of relapse-free survival and remission duration has been changed. The definition now includes patients who have best response of CR or CRi and not only patients with CR in order to correct a misprint in the CTP.

- Genetic groups have been defined and the analysis of overall response, event-free survival and overall survival in these subgroups has been added.

5. ENDPOINTS

5.1 PRIMARY ENDPOINTS

This study has two separate primary endpoints for the phase I part and the phase II part. The primary endpoint for the phase I part is the determination of the two separate MTDs (mono and combi) as reflected by the dose limiting toxicities (DLT) events in course 1. The primary endpoint for the phase II part is objective response.

5.1.1 Primary endpoint related to safety

The primary objective related to safety (phase I part) of this trial is to determine the MTDs of BI 6727 mono and BI 6727 in combination with LD-Ara-C. This will be done in the phase I part of the trial. Two separate MTDs for the two schedules will be determined.

Maximum tolerated dose (MTD):

The MTD for BI 6727 monotherapy is defined as the dose of BI 6727 (without LD-Ara-C), which is one dose tier below the lowest dose at which two or more out of six patients experienced DLT. The MTD for the combination schedule of BI 6727 and LD-Ara-C is defined analogously.

5.1.2 Primary endpoint related to efficacy

The primary endpoint for efficacy (phase II part) in this study is objective response. This primary endpoint will be determined in the phase II part of the study. For the phase I part this endpoint will also be determined but will be considered as secondary only.

In order to evaluate the objective response, the investigator's assessment as given in the eCRF will be taken into account (no central review and no check vs. bone marrow measurement is planned). Both investigator assessments (clinical progression as well as response assessment) will be taken into account for the determination of objective response. In particular this means that a patient is considered as ‘progressive disease’ if any of the assessments indicates a progression of the disease.

No confirmation of a response / stable disease is necessary, i.e. in the following only unconfirmed responses are considered.

Evaluation of objective response:

The different categories possible for overall response (at a specific timepoint) are provided in section 9.6. In order to derive objective response the secondary endpoint best overall response will be derived first.

The best overall response is the best overall response recorded during the time period from the start of the treatment until end of treatment period, progression or death whichever is earlier. Possible categories for best overall response are complete remission (CR), complete remission with incomplete blood recovery (CRi), partial remission (PR), no change (NC),

progressive disease (PD) and no assessment. Patients dying before any assessment will be summarized under PD regarding best overall response.

Objective response (yes/no) is yes if the best overall response is either CR or CRi, otherwise it is no.

Objective response including PR (yes/no) is yes if the best overall response is either CR, CRi, or PR otherwise it is no.

5.2 SECONDARY ENDPOINTS

5.2.1 Event free survival

Event-free survival (EFS) [days] is the shortest duration of the following:-

- dates of assessment indicating 'progressive disease' on RESPONSE page of eCRF – date of randomisation + 1day,

- dates of assessment indicating 'clinical progressive disease' on DISEASS or RESPONSE-page of eCRF– date of randomisation + 1day,

- dates of assessment indicating 'progressive disease' on PAT_STATUS of eCRF – date of randomisation +1 day (for patients who have not been censored before, see below)

- death date – date of randomisation +1day.

Date of assessment refers here to the progdt as given in the eCRF. If progdt is missing then the corresponding examdt will be taken instead if available. Progression events are only taken into account if the corresponding date is before the start date of a new anti-leukemia therapy (see below for censored patients).

Patients not being assessed 'progressive disease', clinical progressive disease' or death during the trial will be censored as described below. These patients must be **reviewed on a case by case basis** by the trial statistician (TSTAT) and trial clinical monitor (TCM).

Right censoring rule for event-free survival (EFS):

Patients getting a new additional other anti-leukemia therapy recorded at the eCRF (follow-up) but not being assessed 'progressive disease', clinical progressive disease' or death before the new anti-leukemia therapy was started will be censored at the date of last disease assessment before the new anti-leukemia therapy was started (excluding follow-up).

Event-free survival censored [in days] is the time from randomisation to the date of last visit (Date of last visit (including follow-up) – date of randomisation + 1 day) for all other patients not being assessed 'progressive disease', clinical progressive disease' or death at the time of data base lock. Date of last visit does not include visit dates from follow-up where 'lost to follow-up' = yes.

EFS will be reported in days.

Patients without any response assessment (best overall response = no assessment) and without death will be censored with an EFS of 0. Otherwise the death date will be used.

5.2.2 Overall survival

Overall survival [in days] = (date of death - date of randomisation + 1 day), for patients with known date of death.

Overall survival (Censored) [in days] = (date of last trial visit (or follow-up) - date of randomisation + 1 day), for patients who are still alive at time of data base lock. Date of last visit does not include visit dates from follow-up where 'lost to follow-up' = yes.

Overall survival will be reported in days.

5.2.3 Relapse-free survival, remission duration and time to remission

Relapse-free survival / Remission duration is defined only for patients with a best overall response of CR or CRi.

Relapse-free survival [in days] = (date of first recurrence of disease or death after entering the trial – date of first occurrence of CR or CRi after entering the trial+ 1 day) for patients with a recurrence (this value should be positive).

Relapse-free survival (censored) [in days] = (date of last trial visit (or follow-up) - date of first occurrence of CR or CRi after entering the trial + 1 day) for patients who did not yet experience recurrence of disease or death at the time of analysis.

Remission duration is defined analogously with the exception of censoring patients that die before recurrence.

Time to remission [in days] = (date of first occurrence of CR or CRi after entering the trial – date of randomisation + 1 day) for patients with an objective response (this value should be positive).

Date of first recurrence of disease is given by the first date of being assessed as either 'progressive disease', 'clinical progressive disease' or death after the first occurrence of CR or CRi after entering the trial. If a patient has either no date of being assessed as either 'progressive disease', 'clinical progressive disease' or death or no occurrence of CR or CRi after entering the trial this date is missing and will also not be imputed.

5.2.4 Eastern Cooperative Oncology Group (ECOG) performance score

ECOG score: as given on the eCRF.

ECOG score change from baseline to last visit of last course = ECOG score at last visit of the last course – ECOG score at baseline. See also section 6.4 for missing ECOG scores.

Categorical ECOG score change: The ECOG score changes from baseline score will be categorized on a three point categorical scale: deteriorated (-1), unchanged (0), and improved (1). 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.

5.2.5 ECG/QTc

The following endpoints will be regarded for the ECG analysis.

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

- Absolute QTcF intervals at each time point.

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

- Categories of QTcF values at baseline and maximum post baseline:
  QTcF ≤ 450 ms, 450 ms < QTcF ≤ 470 ms, 470 ms < QTcF ≤ 500 ms, and QTcF > 500 ms (notable prolongation)

- Categories of QT values at baseline and maximum post baseline:
  QT ≤ 500 ms and QT > 500 ms (notable prolongation)

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

All endpoints derived for the QTcF interval will also be derived for the QTcB interval.

5.2.6 Adverse events

According to the BI standards, multiple recordings of AEs will be collapsed to episodes on the lowest level term and for each patient, all episodes with the same PT(SOC) will be condensed to one AE record using a worst case approach for all AE attributes including CTCAE grading. This AE record per PT (SOC) forms the basis for all standard AE analysis on the patient level. CTCAE grade will be displayed in AE listings. MedDRA levels for condensing will be SOC and PT. AE listings will in general display records. A listing of episodes and occurrences will be provided.

AEs with action taken 'discontinued' or 'reduced' will be considered as marked on the eCRF irrespective of seriousness. Hence this includes the non-serious AEs considered as 'other significant' by ICH E3. No type of AE has been predefined as 'significant' in the CTP.

Dose limiting toxicities (DLT) events will be identified by the relevant question on the eCRF.

5.2.7 Laboratory parameters

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

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

Differentials: Neutrophils (-) and Lymphocytes (-)

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

Enzymes: AST (+), ALT (+), Alkaline Phosphatase (ALKP) (+), Troponin (TPONT) (+)

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

Coagulation: International Normalised Ratio of prothromin time (INR) (+) and Partial thromboplastin time (APTT) (+)

The signs + (-) means the above (below) the reference ranges.

It is important to note that these above described values are the only parameters that can be graded according to CTCAE criteria. The other parameters reported cannot be graded according to CTCAE criteria.

The change of the laboratory value will be calculated for all laboratory parameters from the baseline to the end of the treatment for the whole treatment duration. No post-study laboratory values will be considered.

Worst lab value and its CTCAE grade (highest CTCAE grade) over all courses will be calculated for each laboratory parameter specified above.

The last lab value on treatment is the lab value of the last visit of the last course of each patient.

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

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

Note: For calculating the change in CTCAE grade from baseline/ pre-dose level, patients with a CTCAE grade of -9 at baseline will be reviewed on a case-by-case basis. If there is no evidence 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 (grade 3) or not (grade 1). A listing of the laboratory values with an assigned grade of -1 will be provided together with the re-assigned grade.

5.3 OTHER ENDPOINTS

5.3.1 Demographics and baseline characteristics

Number of previous systemic anti-leukemia therapies: Derived from PSYSTETHER page in the eCRF

Number of previous anti-leukemia radiotherapies: Derived from PRADIOTHER page in the eCRF

Previous systemic anti-leukemia therapies that have the same start date and end date will be counted as a single anti-leukemia therapy. Previous therapies with the same compound but different start dates or end dates will be counted separately. These rules apply even in case of overlapping or time-adjacent dates.

With respect to previous radiotherapies the same rules apply as for systemic anti-leukemia therapies.

Time since last systemic anti-leukemia therapy [months]: = (date of informed consent - end date of the last systemic anti-leukemia therapy + 1 day) [days] / 30.

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

Age at the first Cytological diagnosis [years] = (date of first cytological diagnosis – birth date+1)[days] / 365.25)

Secondary AML: Secondary AML is yes if the respective answer on the eCRF page is given. Otherwise Secondary AML is no and the patient is considered to have de novo AML.

Karyotype is considered ‘complex’ if cytogenetics are available (cytogenetics = yes on the eCRF) and the corresponding specification equals 2. It is considered ‘normal’ if cytogenetics are available and specification equals 1. It is considered ‘neither’ if cytogenetics are available and specification equals 2. Otherwise it is considered missing or not evaluable.

Findings for molecular genetics (e.g. t(8,21), inv16 and NRAS gene mutation) and the WHO classification of AML and related neoplasms will all be taken directly from the corresponding question on the eCRF page.

5.3.2 Extent of exposure

Number of days of administration BI6727 [N]: Cumulative number of days with an administration of BI 6727.

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

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

Cumulative total dose BI6727 [mg] = Sum of doses (administered dose of BI 6727) calculated across all courses

Total dose BI 6727 [mg] within a course = Sum of doses (administered dose of BI 6727) calculated per treatment course

Similar variables (cumulative total dose) will also be derived for LD-Ara-C.

Total exposure time to the trial drug [days] = date of first administration to MINIMUM (date of last trial drug administration of the last course + 21 days, death date if death occurs earlier than 21 days) + 1 day

Total observation time [days] = (last visit date (including follow-up) - date of randomisation + 1 day). Date of last visit does not include visit dates from follow-up where 'lost to follow-up' = yes.

The following two characteristic apply to BI 6727 only:

Number of patients with at least one dose escalation will be counted. A patient is considered to have at least one dose escalation if a dose escalation occurred at least once with BI 6727.

Number of patients with at least one dose reduction will be counted. A patient is considered to have at least one dose reduction if a dose reduction occurred at least once with BI 6727.

5.3.3 Other relevant observation related to safety

Vital signs will be recorded at baseline (including body weight), at each visit of each course and end of trial for each patient. Change from baseline to the end of the trial will be derived for each patient. Vital signs will be recorded also during infusion. If there are multiple measurements at a specific time point for vital signs, the last value will be taken.

Changes from baseline to the end of the trial = Parameter at end of the trial – parameter at baseline.

Percent change from baseline at the end of the trial = 100*(parameter at the end of the trial – baseline parameter) / baseline parameter.

6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENTS

6.1.1 Treatment regimens / study intervals

The following study phases with short label, sort order and start date/time will be included in the treatment set-up in O*C.

Table 6.1.1: 1 Treatment regimens / study intervals

Short label (REGSHNM in E_REG) unblinded	**Sort order** (SORTREG in E_REG)	**Start date** (CRF)	**Start time** (CRF/ derived)
Screening	A	Date of informed consent If date of informed consent = date of administration then the start date for "Screening" will be derived as date of informed consent – 1 day	0:00:00
150mg 1+15	BA	Date of administration of BI 6727 150 mg d1 + 15	Start time of administration of BI 6727 150 mg d1 + 15
200mg 1+15	BC	Date of administration of BI 6727 200 mg d1 + 15	Start time of administration of BI 6727 200 mg d1 + 15
250mg 1+15	BE	Date of administration of BI 6727 250 mg d1 + 15	Start time of administration of BI 6727 250 mg d1 + 15

Short label (REGSHNM in E_REG) unblinded	**Sort order** (SORTREG in E_REG)	**Start date** (CRF)	**Start time** (CRF/ derived)
300mg 1+15	BG	Date of administration of BI 6727 300 mg d1 + 15	Start time of administration of BI 6727 300 mg d1 + 15
350mg 1+15	BI	Date of administration of BI 6727 350 mg d1 + 15	Start time of administration of BI 6727 350 mg d1 + 15
400mg 1+15	BK	Date of administration of BI 6727 400 mg d1 + 15	Start time of administration of BI 6727 400 mg d1 + 15
450mg 1+15	BL	Date of administration of BI 6727 450 mg d1 + 15	Start time of administration of BI 6727 450 mg d1 + 15
500mg 1+15	BM	Date of administration of BI 6727 500 mg d1 + 15	Start time of administration of BI 6727 500 mg d1 + 15
550mg 1+15	BN	Date of administration of BI 6727 550 mg d1 + 15	Start time of administration of BI 6727 550 mg d1 + 15
150+Cy20	AA	Date of first administration of either BI 6727 150 mg d1 + 15 or Cytarabine 20 mg d1-10	Time of first administration of either BI 6727 150 mg d1 + 15 or Cytarabine 20 mg d1-10

Short label (REGSHNM in E_REG) unblinded	**Sort order** (SORTREG in E_REG)	**Start date** (CRF)	**Start time** (CRF/ derived)
200+Cy20	AC	Date of first administration of either BI 6727 200 mg d1 + 15 or Cytarabine 20 mg d1-10	Time of first administration of either BI 6727 200 mg d1 + 15 or Cytarabine 20 mg d1-10
250+Cy20	AE	Date of first administration of either BI 6727 250 mg d1 + 15 or Cytarabine 20 mg d1-10	Time of first administration of either BI 6727 250 mg d1 + 15 or Cytarabine 20 mg d1-10
300+Cy20	AG	Date of first administration of either BI 6727 300 mg d1 + 15 or Cytarabine 20 mg d1-10	Time of first administration of either BI 6727 300 mg d1 + 15 or Cytarabine 20 mg d1-10
350+Cy20	AI	Date of first administration of either BI 6727 350 mg d1 + 15 or Cytarabine 20 mg d1-10	Time of first administration of either BI 6727 350 mg d1 + 15 or Cytarabine 20 mg d1-10
400+Cy20	AK	Date of first administration of either BI 6727 400 mg d1 + 15 or Cytarabine 20 mg d1-10	Time of first administration of either BI 6727 400 mg d1 + 15 or Cytarabine 20 mg d1-10
Cy20	W	Date of first injection of Cytarabine 20 mg d1-d10	Time of first injection of Cytarabine 20 mg d1-d10

Short label (REGSHNM in E_REG) unblinded	**Sort order** (SORTREG in E_REG)	**Start date** (CRF)	**Start time** (CRF/ derived)
Post-trt	X	For BI 6727 monotherapy: Date of last administration	For BI 6727 monotherapy: Stop time of last administration + 1min.
		For BI 6727 combi with Cytarabine or Cytarabine mono: Date of last administration of BI 6727 or Cytarabine whichever is later	For BI 6727 combi with Cytarabine or Cytarabine mono: Time of last administration + 1min.
Post-study	Y	Date of last administration of trial medication (last treatment course) + 21 days.	0:00:00

6.1.2 Randomised treatment

Table 6.1.2: 1 Randomised treatment

Code unblinded (TPATT in E_TPATT)	**Decode unblinded** (NAME in E_TPATT)	**Short decode unblinded** (NAME in ADS.TPATT)	**Sort order** (L_CODE in E_TPATT)
A	Cytarabine, 20 mg bid (d1-d10)	Cy 20	01
C	BI 6727, 150 mg (d1+d15)	150mg1+15	08
E	BI 6727, 200 mg (d1+d15)	200mg1+15	09
K	BI 6727, 350 mg (d1+d15)	350mg1+15	12
L	BI 6727, 400 mg (d1+d15)	400mg1+15	13
M	BI 6727, 450 mg (d1+d15)	450mg1+15	14
N	BI 6727, 500 mg (d1+d15)	500mg1+15	15
O	BI 6727, 550 mg (d1+d15)	550mg1+15	16
AD	Cytarabine, 20 mg bid (d1-d10) + BI 6727, 150 mg (d1+d15)	150mg1+15+Cy	02
AE	Cytarabine, 20 mg bid (d1-d10) + BI 6727, 200 mg (d1+d15)	200mg1+15+Cy	03
AG	Cytarabine, 20 mg bid (d1-d10) + BI 6727, 250 mg (d1+d15)	250mg1+15+Cy	04
AI	Cytarabine, 20 mg bid (d1-d10) + BI 6727, 300 mg (d1+d15)	300mg1+15+Cy	05
AK	Cytarabine, 20 mg bid (d1-d10) + BI 6727, 350 mg (d1+d15)	350mg1+15+Cy	06
AM	Cytarabine, 20 mg bid (d1-d10) + BI 6727, 400 mg (d1+d15)	400mg1+15+Cy	07

6.1.3 Specification of treatments for analyses

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

Label of the "ATP" (ANALLBL)	**Analysis number (ANALNO)**	**Label for the columns displayed in the tables (NWTRCD)**	***Start date***	***End date***
Screening	5	Actual treatment (atrcd) [2]	Date of informed consent	Start date of first treatment in course 1
Course 1 analysis	4	Initial treatment schedule[1]	Start date of first treatment in course 1	Start date of first treatment in course 2 or start date of the actual treatment "post-study"
Course 1 analysis	4	Total	Start date of first treatment in course 1	Start date of first treatment in course 2 or start date of the actual treatment "post-study"
All course analysis	3	Initial treatment schedule[1]	Start date of first treatment in course 1	Start date of actual treatment "post-study"
All course analysis	3	Total	Start date of first treatment in course 1	Start date of actual treatment "post-study"
Post-study	7	Initial treatment schedule [1]	Start date of actual treatment "post-study"	Date of Data Base Lock + 1 day

[1]- use treatment specification of the initial treatment schedule defined in Table 6.1.2: 1 and column 'Format for TPATT'
[2]- use treatment specification of the actual treatment defined in Table 6.1.1: 1

Note that death or lost to follow-up automatically ends the currently ongoing analysing treatment period for a patient.

6.2 IMPORTANT PROTOCOL VIOLATIONS

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

Table 6.2: 1 Description of PVs

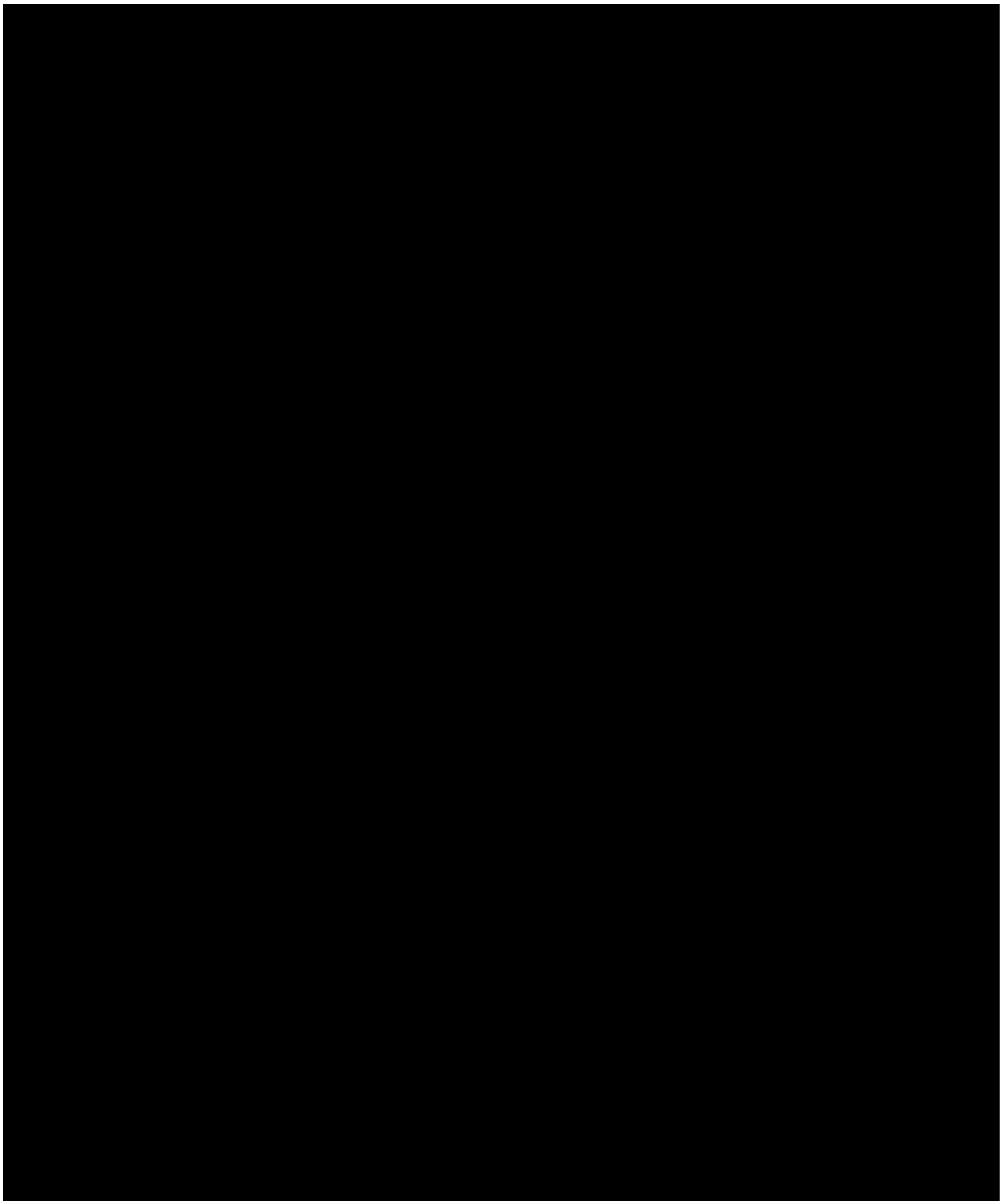
Category/ Code		**Description**	**Comment/Example**	**Efficacy (E) / Safety (S) / Patients right (R)**
A		**Inclusion/Exclusion Criteria**		
	A1	**Criteria related to safety**		
	A1.1	Patient has condition that may cause additional risk from study medication	IN 4, Ex 4, 6, 7, 15	S
	A1.2	Patient has laboratory assessments that may cause additional risk.	Ex 8-11	S
	A1.3	Patient is unable to comply with the protocol	IN 5, Ex 13. Ex 18	S
	A1.4	Patient has condition that may interfere with evaluation of safety (and/or efficacy)	Ex 5, Ex 12, Ex 14	S
	A2	**Criteria related to efficacy**		
	A2.1	Patient does not have trial diagnosis or is not part of the target population	IN1-3, 6, Ex 1-3	E
B		**Legal criteria**		
	B1	Informed consent not given or after visit 1	IN7	R
	B2	Men or women who are sexually active and not using adequate contraception.	Ex 16	R
	B3	Pregnant or nursing female patient	Ex 17	R
C		**Administration of trial medication not in accordance with the protocol**		
	C1	Administration of trial medication not in accordance with the protocol	As marked on the eCRF	
	C2	Continuation of treatment although criteria for re-treatment are not met	Create listing, decision at DQRM/RPM, see CTP section 4.1.4	
	C3	Unjustified intra-patient dose-escalation	Create listing, decision at DQRM/RPM, see CTP section 4.1.4	

Category/ Code		Description	Comment/Example	Efficacy (E) / Safety (S) / Patients right (R)
	C4	Withdrawal of patient not performed according to CTP	Create listing, decision at DQRM/RPM, see CTP section 6.3	
	C5	Discontinuation of trial drug not performed according to CTP	Create listing, decision at DQRM/RPM, see CTP section 6.3	
D		**Restrictions**		
	D1	Additional experimental anti-cancer, chemo-, immuno-, hormone - or radiotherapy during the study or too shortly before the study.	Create listing, decision at DQRM/RPM	E
E		**Missing data**		
	E1	Baseline bone marrow assessment not within 14 days prior to first treatment	Create listing, decision at DQRM/BPRM	E
	E2	Missing disease assessment at a time point where disease assessment was required	Create listing, decision at DQRM/BPRM	E

6.3 PATIENT SETS ANALYSED

Two analysis populations are defined according to the different trial phases for both the efficacy and safety analyses. For the phase I part the treated set (phase I) is defined, in analogy to the intention to treat population as the treated set with respect to phase I; i.e. all patients of phase I who have received at least one single dose of either BI 6727 or cytarabine will be considered, including the patients who have been replaced for any reason.

For the phase II part the treated set (phase II) is defined, in analogy to the intention to treat population as the treated set with respect to phase II; i.e. all patients of phase II who have received at least one single dose of either BI 6727 or cytarabine will be considered, No per protocol population will be used for analyses. However protocol violations will be described.



6.5 POOLING OF CENTRES

All centres will be analyzed together, with any centre effects being ignored. Country or region effects will also not be considered. This means that the patient sets analysed will be defined without taking into account the centre a patient comes from.

For the primary endpoint in phase II (objective response) any centre effects will be analysed descriptively if necessary.

6.6 HANDLING OF MISSING DATA AND OUTLIERS

Missing or incomplete AE dates are imputed according to BI standards ([3.])

Missing data and outliers of PK data are handled according to [1.].

If not stated otherwise, missing data will not be imputed and remain missing. Potential outliers will be reported and analysed as observed.

ECOG Performance Score

In case that the very last ECOG score is missing the ECOG score with the latest date available will be used if the latest date is after baseline. Otherwise ECOG remains missing.

Laboratory values, vital signs:

In case of missing data at visit 1 (before very first administration of BI 6727), the data of preceding visits will be used if not obtained longer than seven days before treatment course 1.

Missing of dates:

Dates that must have taken place before informed consent (e.g time of first cytological diagnosis)

> If (only) the day is missing then day 15 will be imputed except if day 15 is later than the informed consent day, then the date of informed consent will be imputed.
>
> If the month is missing (additionally to the day) then July 1st will be imputed except if July 1st is later than the informed consent month, then the month of informed consent will be imputed.

Other dates

> For other dates, if the day is missing then day 15 will be imputed. If the month is missing then July 1st will be imputed.

Missing PHYSDT:

In general if a physdt is missing (e.g. for ECOG or weight) the corresponding visdt will be used. Since visdt will not be cleaned such imputations need to be examined for appearing impossible results.

Missing of infusion time:

If the time of infusion is missing, then the start time of the infusion will be imputed as "0:00" and the stop time will be imputed as “1:00”.

Missing administration times LD-Ara-C:

If the start time of the first injection is missing, then the start time of the injection will be imputed as "0:00" If the stop time of the last injection is missing the new stop time is 23:59.

Start and end dates of concomitant therapies:

The dates will be imputed such that the extent of exposure to concomitant therapy is maximal, i.e. the first day (month) of the month (year) for incomplete start dates and the last day (month) of the month (year) for incomplete end dates.

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

Study days and visits will be labelled according to the flow chart of the CTP.

Unless otherwise specified, baseline is defined as the latest time-point before the very first treatment administration (≤ 7 days before first administration). If this criterion is not fulfilled then no baseline will be derived.

For height baseline is defined as the latest time point before the very first treatment administration (no 7-day-rule).

ECOG:

Baseline is defined as value at the day of first administration. If there is no value available at the day of first admin, the latest value before the first admin will be used.

Laboratory values/ other safety measurements:

Baseline is defined as value at time point closest to but prior to first administration of trial medication of the first course. (i.e. Time of laboratory value on day of first administration <= time of first administration, then lab value on day of first administration = lab value at baseline. If time of lab value on day of first administration > time of first administration then closest non-missing lab value before time of first admin = lab at baseline)

If any of these times are missing and date of lab = date of first admin, then lab at first admin = lab at baseline.

ECG

Baseline ECG is available from three time points (prior infusion at course 1 visit 1, course 1 visit 4 and course 2 visit 1). 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 at each time point, i.e. each time point has its own baseline.

2. Combined baseline is defined as the mean of the (three) triplicates at the time points closest to but prior to the start of the infusion at the three time points, i.e. a common baseline is used.

Day 1 will be the day of randomisation, so time to event will be taken from Day 1.

6.8 GENERAL CALCULATION RULES

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

In the case of having multiple values at one visit, for example, laboratory data or vital signs, then the worst case will be used, for post baseline values. Note that pre-treatment values are handled under 'baseline'. To determine worst case, in the case of laboratory data, section 5.2.2 indicates the worst case. In the case of vital signs, the minimum value will be used for weight and the maximum value for ECOG.

7. PLANNED ANALYSIS

For in-text tables, the set of summary statistics is: N (number of patients with non-missing values), mean, standard deviation (SD).

For end-of-text tables, the set of summary statistics is: N / Mean / SD / Min / Median / Max.

For appendix 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. Percentages will be rounded to one decimal place. The category missing will be displayed if and only if there are actually missing values. Percentages will be based on all patients in the respective patient set whether they have non-missing values or not.

In general all analyses will be performed for the treated set (phase I) and the treated set (phase II) separately. No pooling across these two treated sets will be performed unless noted otherwise.

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Standard descriptive analysis and summary tables will be presented for all patients of the treated set by treatment group. At the report planning meeting it will be decided which additional variables will be tabulated in chapter 15 or the interim section of the CTR.

Disposition of patients

Standard descriptive analysis of the disposition will be provided.

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

Additionally, patients with discontinuations of the trial medication due to DLT will be listed by treatment and the reasons will be given. Listing of all patients with dose changes will be provided.

Important protocol violation

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

Demographics and baseline characteristics

Standard descriptive analysis of the disposition will be provided.

7.2 CONCOMITANT DISEASES AND MEDICATION

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

A summary of the most frequently concomitant medication (drug classes and generic Name for patients with medication at generic Name) during the treatment and before starting of treatment will be reported. Separate listings/tables will be provided for therapy starting before therapy and those therapies starting after first administration of the trial drug. A summary of the most frequently concomitant diseases (system organ class (SOC) and PT) will be reported. A summary of concomitant therapy will be given.

Listings of the data will present the concomitant therapy PT and verbatim text as well as the verbatim text of the indication. In addition the listings will include study day for start and stop dates and duration of therapy. Patients with no concomitant therapy will not be included in the listing. The number of these patients will be presented by a footnote.

7.3 TREATMENT COMPLIANCE

Only descriptive statistics of the variable "all administration according to the protocol" are planned for this section of the report. "all administration according to the protocol" equals 'no' if any of the entries for 'Administration according to protocol' equals 'no'. Otherwise it is 'yes'. The variable will be derived separately for BI 6727 and cytarabine if applicable.

For patients with "all administration according to the protocol" equals 'no' a listing will be presented.

7.4 PRIMARY ENDPOINTS

One primary objective for this study is the tolerability and safety of the BI 6727 in each treatment schedule as reflected by the MTD (phase I part). Refer to section 7.7 for a description of the analysis of safety and tolerability.

The primary endpoint for efficacy in the phase II part is objective response derived from the data of all courses. The primary analysis of efficacy will be done for all patients of the treated set (phase II) for both treatment schedules separately. Patients with objective response will be listed (both phase I and phase II).

7.4.1 Statistical Group Comparisons

All statistical group comparisons will be performed with respect to the treated set (phase II) The comparison of the treatment schedule to the control schedule will be based on the conditional power approach and on a stopping for futility check [7.,8.]. The conditional power for showing superiority of a treatment schedule with respect to the control schedule at a later time point will be evaluated assuming that the final analysis is the interim analysis of a larger trial. These calculations will be based on an O'Brien-Fleming design with interim analysis to stop for futility. The assumptions are an information fraction of 60% of patients, an overall type I error of 5% (one-sided), 15% objective response rate in the control vs. 30% objective response rate in experimental arm and a power of 65% as described in the CTP. The

conditional power will be computed under the current trend hypothesis [8.] using the standardized logarithm of the odd's ratio of proportions as a test statistic (approximately N(0,1) distributed). [redacted] will be used for these computations. Additionally, similar computations will be performed for other scenarios with a planned sample size of approximately 86 patients at the assumed interim analysis (25% information fraction, alpha=0.025 and power 90%, 33% information fraction, alpha=0.025 and power 80% as well as 40% information fraction, alpha=0.05 and power 80%).

The conditional power will be evaluated in addition under the null hypothesis of no treatment effect and under the assumption that the true treatment effect (measured as the log odds ratio) captures only 50% of the observed treatment effect in order to check the robustness of the result.

Odds ratios, confidence intervals, and Fisher's exact test will be used to compare treatments in an exploratory manner if appropriate.

Additionally, objective response rates will be evaluated by a Bayesian approach with a non-informative prior (9.) given by a beta(1,1) distribution. Denoting the total number of patients per arm by n and the number of responders per arm by r this leads to a beta(1+r,1+n-r) distribution for the posterior (per arm separately).

Based on this approach the following posterior probabilities will be evaluated: Probability that the treatment arm is at least as good as the control arm, probability that the treatment arm is at least 5% better than the control arm, probability that the treatment arm is at least 10% better than the control arm. Evaluation is performed based on simulating the posterior distribution for each arm m=1000000 times and by evaluating the respective characteristics.

The exploratory nature of these analyses will be considered when interpreting the significance levels. P-values derived from statistical tests smaller than 5% will only be reported as nominally significant regarding the small sample size in each treatment schedule.

For the genetic subgroups defined in Section 6.4 frequency tables of best overall response will be presented.

7.5 SECONDARY ENDPOINTS

Event-free survival (EFS)

EFS will be analyzed with the Kaplan-Meier method for each of the treatment arms as well as overall treatments. An exploratory (non-stratified) logrank test will be used to compare the different treatment arms. For phase II Kaplan-Meier curves for EFS in the genetic subgroups defined in Section 6.4 will be presented separately.

The percentage of patients who are event free will be displayed at monthly or greater time intervals as appropriate.

Patients for whom no leukemia assessment is available within 42 days prior to discontinuation from treatment will be examined on **a case by case basis**. A listing will be provided.

Overall survival

Overall survival will be analyzed in a manner similar to that of event-free survival.

Remission duration

Remission duration will be summarized by treatment group. Kaplan-Meier plots of the relapse-free survival will be displayed without displaying hazard rates, associated confidence intervals and p-values. Expected duration of response will be calculated based on an exponential model if appropriate.

Note that for remission duration no formal comparison between different treatment arms will be done since remission duration is based on a non-randomised set and therefore possibly biased.

ECOG performance score

The proportion of patients with improved (decreased), and with unchanged, ECOG at end of treatment with respect to baseline will be tabulated.

BI 6727 plasma concentration

See section 7.7.5

Incidence and intensity of adverse events graded according to CTCAE

See section 7.7

Pharmacodynamic monitoring

Analysis of pharmacodynamics will be performed separately and will not be contained in the CTR.

Pharmacogenetics

Analysis of pharmacogenetics will be performed separately and will not be included in the CTR.

7.6 EXTENT OF EXPOSURE

Standard descriptive analysis is planned for overall courses/visits by treatment groups.

7.7 SAFETY ANALYSIS

All safety analyses will be performed on the treated sets (separately for phase I and phase II).

7.7.1 Adverse events

The analyses of adverse events will be descriptive in nature and will be based on BI standards (see [3.]). Adverse events will be coded with the most recent version of MedDRA. According to the BI standards, multiple occurrences of adverse events are collapsed to episodes if time overlapping or adjacent (maximal one day) on the MedDRA lowest level term and multiple episodes will be condensed to records on the preferred term and SOC level.

AEs as well as DLTs will be evaluated both for all courses as well as for first course only (in the phase I part).

The analysis of adverse events will be based on the concept of treatment emergent adverse events. Adverse events will be distinguished for the period in which the subjects are under study drug (on-treatment) as well as for screening, and post-study (For details on the analysing treatment period, see section 6.1.3). If applicable, the actual dosage of BI 6727 administered on the day each adverse event starts will also be derived and will be included in the listing. The system organ classes will be sorted according to the standard sort order specified by EMEA, PTs will be sorted alphabetically (within SOC).

All patients will be reported in the summary tables under the initial treatment group (randomised treatment) including the initial treatment schedule.

AEs with onset date at Screening- and Post-study-period (as defined in Table 6.1.1: 1) will be displayed in two separate listings. Listings of screening events will not be sorted by initial treatment (Table 6.1.2: 1). But post-study listings will be sorted by initial treatment.

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.

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 not be reported under that category.

The number of patients with DLT will be listed per treatment group with the respective events fulfilling the criteria for DLT.

A separate listing for all patients who developed AEs with CTCAE grade >= 3, DLT, and serious AEs will be generated.

Incidence and intensity of adverse events

The overall incidence and intensity of adverse events, as well as relatedness of adverse events to treatment with BI 6727 will be reported for all treatment schedule arms.

Serious adverse events will be tabulated. In addition, Events leading to dose reduction or treatment discontinuation will be examined, but may not be reported as individual tables, depending upon the extent of overlap with the occurrence of DLT.

For the phase I part only, the dose-toxicity relationship will be examined descriptively and inferentially, using DLTs in treatment course 1 and DLTs up to the end of the on treatment phase, in separate analyses. Further, the time to first DLT will be explored descriptively in all dose groups, and Kaplan-Meier plots based upon the MTD group will be presented.

As a first step, for each time period, the number of DLTs that a patient has will be summarised. If the majority of the patients have either 0 or 1 DLT, then a simple logistic regression will be calculated. If however, there are quite a few patients with >1 DLT, then a proportional odds model will be used.

With this logistic regression, a model including only the BI 6727 dose (and intercept) will be used. Hence, by back-transformation of the logit model, the probability (and 95% confidence interval) of a DLT in this time period will be presented on a graph together with the dose. The dose corresponding to a 25% probability of a DLT in the time period will be indicated and the p-values for the intercept and slope of this model will also be included in the footnote. Additionally the expected toxicity level for the dose chosen in phase II will be provided.

Finally, the time on treatment prior to the first DLT will be presented graphically together with the dose. Different symbols will be used for patients with (filled dot) and without (unfilled dot) a DLT. Using the MTD group, the Kaplan Meier plot estimating the probability of an event over time will be presented.

7.7.2 Laboratory data

The analyses of laboratory data will be descriptive in nature and will be based on BI standards (see [5]) The CTCAE grade will be calculated for each lab value (see section 9.2).

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 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. This is documented in section 9.2.

Patients with clinically relevant laboratory abnormalities, as defined in section 9.1 will be summarised. Project-specific rules for flagging possible clinically significant abnormal laboratory values will be applied.

Patients will be counted under the initial treatment group. Separate listings for patients treated under different doses will be created. Thereby the data will be reported under course regimen. The analysis of lab data will use the same analyzing treatment periods as described for the AEs.

Single time courses by treatment regimen will be used to display laboratory values over time. The graphs may be truncated if no sufficient data is available. These graphs will be produced for absolute neutrophile count, platelets, Creatinine phospokinase, haemoglobin, and for other laboratory parameters *(if considered important in this trial, decision will be given in URPM of the final analysis)*.

7.7.3 Vital signs

Descriptive statistics of absolute values (and change from baseline) of vital signs (including body weight at baseline) will be provided by treatment group, for actual time and visit over all courses. Vital signs during infusion will be analysed descriptively.

7.7.4 ECG / QTc

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

7.7.4.1 Derivation of ECG endpoints

Three replicate digital ECG recordings will be collected at each time-point. Each of the three recorded single ECGs will then be evaluated for cardiac intervals, which comprise the RR, PR, QT interval and QRS duration. Measurements of these intervals will be made on four (possibly consecutive) waveforms from the lead chosen (usually lead II). The measurements of the waveforms will be stored in the database, i.e. twelve values per time-point. The four waveforms will be averaged prior to the calculation of the heart rate and heart rate corrected QT intervals. Further aggregation of the three replicate QT/QTc intervals and heart rates at each scheduled time-point will be performed using arithmetic means. These values will be used for the derivation of the ECG endpoints as they are specified in Section 5.3.5.

The heart rate will be derived from the RR interval as

HR [bpm] = 60000/RR [ms]

For each QT interval, the RR interval preceding the QT interval will be used for frequency correction.

Heart rate corrected QT intervals (generally denoted as QTc) will be calculated using Fridericia's (QTcF) and Bazett's formulas (QTcB):

$$\mathrm{QTcF}\,[\mathrm{ms}] = \left(\frac{1000}{\mathrm{RR}}\right)^{1/3} * \mathrm{QT}\,[\mathrm{ms}],$$

and

$$\mathrm{QTcB}\,[\mathrm{ms}] = \left(\frac{1000}{\mathrm{RR}}\right)^{1/2} * \mathrm{QT}\,[\mathrm{ms}]$$

7.7.4.2 ECG Analysis

Absolute values and change from baseline in QTcF, QTcB, QT, PR intervals, HR, and QRS duration will be summarised descriptively by course for the MTD groups (including patients treated at the MTD in Phase II) using the Treated Set.

Frequencies of the increases in QTcF/QTcB/QT intervals above thresholds such as 450 ms, 470 ms and 500 ms between baseline and on-treatment will be displayed in two-way shift-tables by initial dose for the Treated set.

Frequencies of patients with increases from baseline in QTcF, QTcB and QT intervals above the defined thresholds and notable findings will be displayed, as well.

Frequency tables by overall clinical interpretation and findings possibly impacting interval measurement, and a new onset (not present at baseline) of an abnormal finding will be generated.

7.7.5 Pharmacokinetics

The analysis of standard PK parameters is performed according to [2.].

The distribution of BI 6727 plasma concentrations will be graphically inspected and summarised by time point in the CTR.

If felt necessary based on the clinical outcome, BI 6727 pharmacokinetic parameters (Cmax, exposure, eg AUC) will be correlated with the observed neutropenia, leukopenia and leukemic myeloblasts.

7.7.6 Others

If considered necessary, the number of patients who died, and the number of patients who are lost to follow-up will be listed by treatment regimen at follow-up-visits.

Blood products used will be listed by patient.

8. REFERENCES

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2. DCG-103 'Noncompartmental Pharmacokinetic Analysis Using WinNonlin', current version; BI Intranet

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4. DM&SM: 'Handling of missing and incomplete AE dates', current version, BI Intranet

5. DM&SM: 'Display and Analysis of Laboratory Data', current version; BI Intranet

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