Boehringer Ingelheim

Clinical Trial Protocol Revision J
(Including Amendments No. 1, 2, 3, 4, 5, 6 7, 8, and 9)

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c02446030-03

EudraCT No.:	2008-003617-27
BI Trial No.:	1230.4 Including Amendments No. 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10
Investigational Product:	Volasertib (BI 6727)
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
Clinical Phase:	I / IIa
Trial Clinical Monitor:	[redacted] Telephone: Fax: E-mail:
Co-ordinating Investigator:	[redacted] Telephone: Fax:
Status, Version, and Date of Protocol:	**Original:** 16 July 2008 **Revision A:** 13 November 2008 **Revision B:** 29 October 2009 **Revision C:** 13 January 2010 **Revision D**: 13 December 2010 **Revision E**: 06 June 2011 **Revision F**: 05 July 2012 **Revision G:** 23July 2013 **Revision H:** 29 October 2014 **Revision I:** 16January 2017 **Revision J: 19** February 2019
Planned Dates of Trial:	September 2008 - May 2010

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CLINICAL TRIAL PROTOCOL REVISION PAGE

I herewith certify that this Clinical Trial Protocol Revision (Revision J) gives an accurate and complete revision of the protocol, including Amendment*(s)* No. 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10.

Clinical Trial Leader _____ _____
Date

[redacted]

The official documents are the original protocol and applicable amendments. This unofficial copy of the protocol does not require signature, and therefore, the signature pages remain blank.

CLINICAL TRIAL PROTOCOL SYNOPSIS

Name of company: Boehringer Ingelheim		**Tabulated Trial Protocol**	
Name of finished product:			
Name of active ingredient: Volasertib (BI 6727)			
Protocol date 16 July 2008	**Trial number** 1230.4	**Planned trial period** September 2008 to May 2010	

Title of trial:	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
Co-ordinating Investigator:	[redacted] Telephone: [redacted] Fax:
Trial sites:	Multicentre
Clinical phase:	I /IIa
Objectives:	To investigate the maximum tolerated dose, safety, pharmacokinetics and efficacy of BI 6727 monotherapy and BI 6727 in combination with cytarabine in patients with acute myeloid leukaemia (AML)
Methodology:	Open label, randomised, controlled, dose escalation
No. of patients:	
total:	177 enrolled ~~about 143~~
each treatment:	Treatment schedule A (BI 6727 day 1 + 15 in combination with cytarabine): 32 ~~about 21~~ patients (phase I part) + 44 ~~43~~ patients (phase IIa part) Treatment schedule B (BI 6727 day 1 + 15 monotherapy): 56 ~~about 21~~ patients (phase I part) ~~+~~ including extension cohort ~~up to 15 patients~~ Treatment schedule C (cytarabine control group): 45 ~~43~~ patients (only phase IIa part)
Diagnosis and main criteria for inclusion:	Phase I part: Adult patients with relapsed/refractory AML that are not eligible for intensive treatment Phase IIa part: Adult patients with previously untreated acute myeloid leukaemia that are not eligible for intensive treatment
Test products:	BI 6727 as monotherapy and BI 6727 in combination with cytarabine

Name of company: Boehringer Ingelheim		**Tabulated Trial Protocol**	
Name of finished product:			
Name of active ingredient: Volasertib (BI 6727)			
Protocol date 16 July 2008	**Trial number** 1230.4	**Planned trial period** September 2008 to May 2010	

dose:	The starting dose for BI 6727 will be 150 mg.	
	Treatment schedule A:	BI 6727 on day 1 + 15 in combination with cytarabine 2 x 20 mg/d on day 1-10 (28-day cycle)
	Treatment schedule B:	BI 6727 monotherapy on day 1 + 15 (28-day cycle)
mode of admin. :	BI 6727:	intravenous infusion (1 hour)
	Cytarabine:	subcutaneous injection
Reference therapy:	Treatment schedule C:	cytarabine
dose:	2 x 20 mg/d on day 1-10 (28-day cycle)	
mode of admin. :	subcutaneous injection	
Duration of treatment:	Minimum of one 28-day treatment cycle. Patients are eligible for repeated cycles until progression of disease and as long as neither patient nor investigator requests treatment discontinuation.	
Criteria for efficacy, pharmacokinetics and pharmacodynamics:	Response, event free survival, relapse free survival, remission duration, overall survival, pharmacokinetics of trial drugs, pharmacodynamic monitoring (biomarker analysis for target inhibition, i.e. FACS analysis for cell cycle arrest, immunocytochemistry).	
Criteria for safety:	Maximum tolerated dose, incidence and intensity of adverse events graded according to the common terminology criteria for adverse events (CTCAE, version 3.0), incidence of dose limiting toxicity, laboratory parameters.	
Statistical methods:	Exploratory data analyses, conditional power evaluation	

FLOW CHART FOR TREATMENT SCHEDULE A
BI 6727 + CYTARABINE (PHASE I AND IIA PART OF THE TRIAL)

Trial Periods	Screen	Treatment							EoT	FU
Cycle *		**! 1**								
Visit	**Screen**	**1**	**2**	**3**	**4**	**5**	**6**	**7****		
Days	**-14 to -1**	**1**	**5** ∀1	**10** ∀2	**15**	**19** ∀2	**23** ∀2	**28** +3		
Informed consent	x									
Demographics	x									
Medical history	x									
Review of in-/exclusion criteria	x	x[a]								
Document ineligibility for intensive treatment	x									
12 lead-ECG (digital, triplicate)	x	x[b]			x[c]				x	
Blood for pharmacogenetics	x[d]									
Physical examination	x							x	x	
ECOG score, weight	x	x						x	x	x
Height	x									
Vital signs	x	x[e]	x	x	x[e]	x	x	x		
Assignment / Randomisation	x[f]									
Adverse events		x	x	x	x	x	x	x	x	x
Concomitant therapy	x	x	x	x	x	x	x	x		
Administration of BI 6727		x			x					
Administration of cytarabine [g]		x	x	x						
Cytarabine compliance check			x	x	x					
Safety laboratory, incl. urinalysis	x[h]	x[h]	x	x	x[h]	x	x	x[h]		
Serum pregnancy test [i]	x							x		
Blood for pharmacokinetics [k]		x	x	x	x			x		
Disease assessment (blood, clinical)	x	x	x	x	x	x	x	x		
Bone marrow aspiration	x[m]	x[n]						x[p]		
Eligibility for further cycle								x		
Outcome (remission, progression, death)									x	x
Other anti-leukaemia therapy										x
Conclusion of patient participation									x	

EoT end of treatment
FU follow-up
* the visit number follows the cycle number, i.e. visit 2 cycle 1 will read C1_V2 and visit 2 cycle 2 will read C2_V2 and so forth
** can be the same day as visit one of the next cycle. Can be up to 3 days later, but must not be earlier than day 28

a on day one of the very first cycle only

b ECGs are performed at time points specified in 5.2.7 and 6.2.2.1. In the first and second cycle ECGs are performed in triplicate at the related PK sampling time points. Furthermore triplicate ECGs are performed before and at the end of every subsequent BI 6727 infusion.

c ECGs are performed at time points specified in 5.2.7 and 6.2.2.4. In the first and second cycle ECGs are performed in triplicate at the related PK sampling time points. Furthermore triplicate ECGs are performed before and at the end of every subsequent BI 6727 infusion.

d optional, only after separate informed consent

e pre-infusion, and at minutes 30 (∀5), 60 (∀10) and 120 (∀10) after start of BI 6727 infusion

f before the first administration of the trial drug and after informed consent and review of in- and exclusion criteria

g subcutaneous cytarabine is administered twice daily on day one until ten

h including coagulation parameters (see section 5.2.5)

i for women with childbearing potential at screening and after every other cycle

k sampling at the time points as specified in table 1 in section 10.1.2. In cycle 2 only at -0.05 and 1 hour after dose.

m within 14 days before first treatment. Cytogenetics and molecular genetics (see 5.3.4). Pharmacodynamic analysis, i.e. FACS and cytospins (see 5.6)

n only in the first cycle on day 2, i.e. 24 hours after the end of the first BI 6727 administration: Pharmacodynamic analysis (see section 5.6)

p initial response assessment after the first treatment cycle, this analysis may be performed up to 3 days earlier to allow for a timely continuation of the treatment. Pharmacodynamic analysis (FACS and cytospins, see section 5.6) at the end of the first cycle.
Bone marrow aspiration after repeated cycles according to 5.1.1. Additional bone marrow aspiration as necessary for confirmation of haematologic DLT (see section 5.2.3) or progressive disease.

FLOW CHART FOR TREATMENT SCHEDULE B
BI 6727 MONOTHERAPY (ONLY PHASE I PART OF THE TRIAL)

Trial Periods	Screen	Treatment							EoT	FU[s]
Cycle *		**! 1**								
Visit	**Screen**	**1**	**2[t]**	**3[t]**	**4**	**5[t]**	**6[t]**	**7[**]**		
Days	**-14 to -1**	**1**	**5** ∀1	**10** ∀2	**15**	**19** ∀2	**23** ∀2	**28** +3		
Informed consent	x									
Demographics	x									
Medical history	x									
Review of in-/exclusion criteria	x	x[a]								
Document ineligibility for intensive treatment	x									
12 lead-ECG ~~(digital, triplicate)~~	x	x[b]			x[c]				x	
Blood for pharmacogenetics	x[d]									
Physical examination[q]	x							x	x	
ECOG score, weight[q]	x	x						x	x	x
Height	x									
Vital signs[q]	x	x[e]	x	x	x[e]	x	x	x		
Assignment / Randomisation	x[f]									
Adverse events		x	x	x	x	x	x	x	x	x
Concomitant therapy	x	x	x	x	x	x	x	x		
Administration of BI 6727		x			x					
Safety laboratory, incl. urinalysis[q]	x[h]	x[h]	x	x	x[h]	x	x	x[h]		
Serum pregnancy test [i]	x							x		
Blood for pharmacokinetics [k]		x	x	x	x			x		
Disease assessment (blood, clinical)[r]	x	x	x	x	x	x	x	x		
Bone marrow aspiration[r]	x[m]		x[n]					x[p]		
Eligibility for further cycle								x		
Outcome (remission, progression, death)									x	x
Other anti-leukaemia therapy										x
Conclusion of patient participation									x	

EoT end of treatment
FU follow-up
* the visit number follows the cycle number, i.e. visit 2 cycle 1 will read C1_V2 and visit 2 cycle 2 will read C2_V2 and so forth
** can be the same day as visit one of the next cycle. Can be up to 3 days later, but must not be earlier than day 28

a on day one of the very first cycle only

b ECGs are performed at time points specified in 5.2.7 and 6.2.2.1. In the first and second cycle ECGs are performed in triplicate at the related PK sampling time points. Furthermore triplicate ECGs are performed before and at the end of every subsequent BI 6727 infusion. After approval of Protocol Revision I, ECG should be performed prior to and at the end of volasertib infusions as single reads using a local ECG machine.

c ECGs are performed at time points specified in 5.2.7 and 6.2.2.4. In the first and second cycle ECGs are performed in triplicate at the related PK sampling time points. Furthermore triplicate ECGs are performed before and at the end of every subsequent BI 6727 infusion. After approval of Protocol Revision I, ECG should be performed prior to and at the end of volasertib infusions as single reads using a local ECG machine.

d optional, only after separate informed consent

e pre-infusion, and at minutes 30 (∀ 5), 60 (∀ 10) and 120 (∀ 10) after start of BI 6727 infusion

f before the first administration of the trial drug and after informed consent and review of in- and exclusion criteria

h including coagulation parameters (see section 5.2.5)

i for women with childbearing potential at screening and after every other cycle

k sampling at the time points as specified in table 2 in section 10.1.2. In cycle 2 only at -0.05 and 1 hour after dose.

m within 14 days before first treatment. Cytogenetics and molecular genetics (see 5.3.4). Pharmacodynamic analysis, i.e. FACS and cytospins (see 5.6)

n only in the first cycle at visit 2, i.e. 5±1 days after the end of the first BI 6727 administration: Pharmacodynamic analysis (see section 5.6)

p initial response assessment after the first treatment cycle, this analysis may be performed up to 3 days earlier to allow for a timely continuation of the treatment. Pharmacodynamic analysis (FACS and cytospins, see section 5.6) at the end of the first cycle.
Bone marrow aspiration after repeated cycles according to 5.1.1. Additional bone marrow aspiration as necessary for confirmation of haematologic DLT (see section 5.2.3) or progressive disease.

q After approval of Protocol Revision I, physical examination, vital signs, weight, ECOG score, and safety laboratory incl. urine analysis should be done as medically indicated at discretion of the investigator. The results should be recorded in the source data only; documentation in the eCRF is not required.

r After approval of Protocol Revision I, disease assessments and bone marrow aspirations only have to be performed per local standard of practice to support the decision on further treatment with volasertib. The results should be recorded in the source data only; documentation in the eCRF is not required.

s After approval of Protocol Revision I, FU is completed 21 days after discontinuation of study drug.

t After approval of Protocol Revision I, Visits 2, 3, 5, and 6 are optional.

FLOW CHART FOR TREATMENT SCHEDULE C
CYTARABINE MONOTHERAPY (ONLY PHASE IIA PART OF THE TRIAL)

Trial Periods	Screen	Treatment							EoT	FU
Cycle *		**! 1**								
Visit	**Screen**	**1**	**2**	**3**	**4**	**5**	**6**	**7****		
Days	**-14 to -1**	**1**	**5** ∀1	**10** ∀2	**15**	**19** ∀2	**23** ∀2	**28** +3		
Informed consent	x									
Demographics	x									
Medical history	x									
Review of in-/exclusion criteria	x	x[a]								
Document ineligibility for intensive treatment	x									
12 lead-ECG	x								x	
Blood for pharmacogenetics	x[d]									
Physical examination	x							x	x	
ECOG score, weight	x	x						x	x	x
Height	x									
Vital signs	x	x	x	x	x	x	x	x		
Assignment / Randomisation	x[f]									
Adverse events		x	x	x	x	x	x	x	x	x
Concomitant therapy	x	x	x	x	x	x	x	x		
Administration of cytarabine [g]		x	x	x						
Cytarabine compliance check			x	x	x					
Safety laboratory, incl. urinalysis	x[h]	x[h]	x	x	x[h]	x	x	x[h]		
Serum pregnancy test [i]	x							x		
Blood for pharmacokinetics [k]		x								
Disease assessment (blood, clinical)	x	x	x	x	x	x	x	x		
Bone marrow aspiration	x[m]							x[p]		
Eligibility for further cycle								x		
Outcome (remission, progression, death)									x	x
Other anti-leukaemia therapy										x
Conclusion of patient participation									x	

EoT end of treatment
FU follow-up
* the visit number follows the cycle number, i.e. visit 2 cycle 1 will read C1_V2 and visit 2 cycle 2 will read C2_V2 and so forth
** can be the same day as visit one of the next cycle. Can be up to 3 days later, but must not be earlier than day 28

a	on day one of the very first cycle only
d	optional, only after separate informed consent
f	before the first administration of the trial drug and after informed consent and review of in- and exclusion criteria
g	subcutaneous cytarabine is administered twice daily on day one until ten
h	including coagulation parameters (see section 5.2.5)
i	for women with childbearing potential at screening and after every other cycle
k	sampling at the time points as specified in table 3 in section 10.1.2
m	within 14 days before first treatment. Cytogenetics and molecular genetics (see 5.3.4). Pharmacodynamic analysis, i.e. FACS and cytospins (see 5.6)
p	initial response assessment after the first treatment cycle, this analysis may be performed up to 3 days earlier to allow for a timely continuation of the treatment. Pharmacodynamic analysis (FACS and cytospins, see section 5.6) at the end of the first cycle. Bone marrow aspiration after repeated cycles according to 5.1.1. Additional bone marrow aspiration as necessary for confirmation of haematologic DLT (see section 5.2.3) or progressive disease.

ABBREVIATIONS

µL	Mikrolitre
µmol	Mikromol
AE	Adverse Event
ALT	Alanine amino transferase
AML	Acute myeloid leukaemia
APL	Acute promyelocytic leukaemia
aPTT	Activated partial thromboplastin time
Ara-C	Cytarabine
Ara-CTP	Cytosine arabinoside triphosphate
AST	Aspartate amino transferase
AUC	Area under the concentration-time curve
BI	Boehringer Ingelheim
BLQ	Below the limit of quantification
C	Celsius
CA	Competent (Regulatory) Authority
CFR	Code of Federal Regulations
CL	Total clearance
cm	Centimetre
C_{max}	Maximum measured concentration
CML	Clinical Monitor Local
CPK	Creatine phosphokinase
CR	Complete remission
CRA	Clinical Research Associate
CRF/eCRF	Case Report Form / electronic Case Report Form
CRi	Complete remission with incomplete blood count recovery
CRO	Contract research organisation
CTCAE	Common terminology criteria for adverse events
CTMF	Clinical Trial Master File
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
d	Day
DLT	Dose limiting toxicity
DMPK	Drug Metabolism and Pharmacokinetics
DNA	Deoxyribonucleic acid
DOC	Documentation of Change
EC/IEC	Ethics Committee / Independent Ethics Committee
EC50	Half maximal effective concentration
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic Data Capture
EFS	Event free survival
EOT	End of treatment
EU	European union
FAB	French-American-British

FACS	Fluorescence activated cell sorting
FDA	Food and Drug Administration
FU	Follow up
GCP	Good Clinical Practice
G-CSF	Granulocyte colony stimulating factor
GLP	Good laboratory practice
GmbH	Gesellschaft mit beschränkter Haftung (german for limited liability company)
gMean	geometric mean
h	Hour
i.v.	intravenous
IB	Investigator´s brochure
IC_{50}	half maximal inhibitory concentration
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
INN	International Nonproprietary Name
INR	International normalized ratio
ISF	Investigator Site File
KG	Kommanditgesellschaft
kg	Kilogramm
L	Litre
LD-Ara-C	Low dose Ara-C
MedDRA	Medical dictionary for regulatory activities
mg	Milligramm
min	Minute
mL	Millilitre
MRT	Mean residence time
MTD	Maximum tolerated dose
NC	Not calculated
No.	Number
NOA	Not analyzed
NOP	No peak detectable
NOR	No valid result
NOS	No sample
NSCLC	Non small cell lung cancer
OS	Overall survival
PD	Progressive disease
pH	Potentia hydrogenii
PK	Pharmacokinetic
Plk	Polo like kinase
PR	Partial remission
PT	Prothrombin time
RBC	Red blood cell count
s.c.	Subcutaneous
SAE	Serious Adverse Event
SDV	Source data verification

SOP	Standard Operating Procedure
SPC	Summary of product characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
$t_{1/2}$	Terminal half-life
TDMAP	Trial data management and analysis plan
t_{max}	Time from dosing to maximum measured concentration
ULN	Upper level of normal
V_{ss}	Apparent volume of distribution at steady state
V_z	Apparent volume of distribution during the terminal phase
WBC	White blood cell count
WHO	World health organisation

1. INTRODUCTION

1.1 MEDICAL BACKGROUND

Acute myeloid leukaemia (AML) is a heterogeneous clonal disorder of haematopoietic progenitor cells and represents the most common malignant myeloid disorder in adults. AML predominantly affects older adults with median age at diagnosis of about 70 years. Without therapeutic intervention the disease progresses and leads to death within months after initial diagnosis (R07-2768).

Genetic alterations in leukaemic cells constitute the most important factor for the prognosis of AML (R07-2768, R07-2770, R07-2774). AML patients are classified in groups of favourable, intermediate, and unfavourable risk. Other factors with impact on prognosis are age, performance score, white blood cell count, blood chemistry disturbances and de-novo versus secondary AML.

Intensive treatment approaches for AML with curative intention include two phases. The first, remission induction treatment, most commonly consists of cytarabine and an anthracycline and is followed by the second phase of post-remission treatment aiming at the consolidation of remission. AML patients under the age of 60 years achieve complete remission (CR) with intensive treatment regimens in up to 75%, while AML patients over 60 years of age (referred to as elderly patients) have a 40 - 60 % chance of CR when receiving intensive remission induction treatment (R07-2767).

However, while the majority of younger AML patients receives intensive treatment, a substantial number of elderly patients is considered ineligible for this treatment approach (R07-2773, R07-2854). Therefore the CR rates up to 60% reported in elderly previously untreated AML patients receiving intensive treatment are by no means representative for the entire group of elderly AML patients. For AML patients considered ineligible to receive intensive treatment investigational treatment is widely regarded as the preferred therapeutic option (R07-2769, R07-2772). For most patients with relapsed AML or AML refractory to induction treatment no satisfactory therapy exists. Currently, major efforts focus on the improvement of the therapy in these subgroups of patients with unfavourable prognosis.

Although patients that are considered as ineligible for intensive treatment constitute a generally accepted subgroup of AML patients, no validated criteria are defined to judge a patient's eligibility for intensive treatment (R07-2771). The assessment of eligibility for intensive treatment is regularly done for every single patient based on the specialised physician's clinical experience and the comprehensive review of factors like patient age, performance score, organ dysfunctions and co-morbidities, as well as the patient's informed decision.

1.2 DRUG PROFILE

1.2.1 BI 6727

BI 6727 is a highly selective and potent small molecule Polo-like kinase 1 (Plk-1) inhibitor. The pharmacological profile of BI 6727 was evaluated in vitro in enzymatic assays, cellular cytotoxicity assays and assays examining cell cycle progression. In vivo efficacy of BI 6727 was determined in human tumour xenografts in nude mice.

In an enzymatic assay using human recombinant Plk-1 the molecular potency of BI 6727 was in the low nanomolar range. More than 45 kinases tested in parallel with Plk-1 were not inhibited, demonstrating the high molecular specificity of the compound. The compound was also tested for its cellular activity on a panel of tumour cell lines. Cytotoxicity in vitro and inhibition of Plk-1 in enzymatic assays was achieved at comparable concentrations. Activity was not dependent on cellular origin or molecular phenotype. Cell biological profiling revealed that BI 6727 induced a typical Plk-1 mitotic arrest phenotype (G2/M arrest, abnormal mitotic figures) at similar concentrations. When comparing the activity in parental cell lines to the activity in the respective chemo-resistant counterparts activity of BI 6727 was much better conserved than the activity of conventional chemotherapeutics such as taxanes or vincristine.

Efficacy of BI 6727 was shown in various xenograft models. Tumour regression up to complete cures of animals was demonstrated. Tumour regression was also shown in models of larger tumours. Doses shown to be effective were well tolerated and were administered to nude mice 1-2 times per week intravenously.

The non-clinical safety profile of BI 6727 is considered favourable regarding the oncological indication and the antiproliferative principle. In 3-cycle toxicity studies in dogs and rats mechanism-related side effects were observed in organs with high turnover as expected. Main target organs were the gastrointestinal tract (mucosal lesions), bone marrow and lymphatic system. Complete reversibility even of severe lesions at higher doses was observed. Moreover, no evidence for unspecific toxicity affecting other organs such as kidney or liver was found. However, an exploratory investigation on the cardiovascular system in pigs, given at very high doses of up to 30 mg/kg BI 6727, showed that BI 6727 induced QT prolongation starting at a plasma level of 3700 nmol/L and slight QTcSE prolongation in chronically treated dogs starting at 36 mg/m^2 at plasma levels of about 880 – 1090 nmol/L. The hERG channel was inhibited with an IC_{50} value of 2.4 µmol/L while the action potential in guinea pig papillary muscle was not affected up to 10 µmol/L. Based on these results, QT-monitoring is continued in the clinical phase II trials with BI 6727. More detailed information is provided in the Investigator's Brochure (IB; c01694302-14).

To date 50 patients with a variety of tumour types have been treated in a phase I trial with BI 6727. Thirty-one patients were treated at doses at or above 300 mg, with the maximum tolerated dose (MTD) at 400 mg. The results demonstrated that BI 6727 had good tolerability with reversible haematotoxicity (neutropenia, thrombocytopenia) constituting the dose limiting toxicity. No relevant unspecific toxicity has been observed as yet. Encouraging signs of efficacy were seen in two patients with confirmed partial regressions of urothelial and

ovarian tumours, respectively. In addition long term disease stabilizations were observed in several patients. More than 20 courses of treatment were given without signs of persisting or cumulative toxicity.
In the electrocardiogram (ECG) monitoring BI 6727 dose dependant QtcF prolongations at the time of C_{max} have been observed in patients, but no associated clinical events were reported.

By virtue of a different therapeutic principle, new classes of drug substances may be promising either as monotherapy or in combination with already available drugs. In this trial, the safety and efficacy of BI 6727 will be tested in combination with and in comparison to low-dose cytarabine, the most widely established treatment for patients considered ineligible for intensive treatment (R07-2771); furthermore, in patients with relapsed/refractory AML BI 6727 monotherapy will be investigated.

1.2.2 Cytarabine

Cytarabine (1-beta-D-Arabinofuranosylcytosin) is indicated alone or in combination with other antineoplastic agents for induction of remission and/or maintenance treatment in patients with AML.
Cytarabine (Ara-C) is metabolised *in vivo* to Ara-CTP (arabinoside cytosine triphosphate) phosphorylated compound, which competitively inhibits DNA polymerase and may also inhibit certain acid kinases. Primarily the drug acts as a false nucleoside and competes for enzymes involved in the conversion of cytidine nucleotide to deoxycytidine nucleotide and also incorporation into the DNA. Cytarabine is a cell cycle specific antineoplastic drug and has no effect on non-proliferating cells nor on proliferating cells unless in the S phase.

The major adverse effect of cytarabine is haematological toxicity. Furthermore, gastrointestinal toxicity may also occur. Other reported adverse effects of cytarabine include fever, rash, alopecia, skin ulceration, conjunctivitis, chest pain, urinary retention, dizziness, neuritis, neurotoxicity or neural toxicity and pain, cellulitis and thrombophlebitis (including irritation or sepsis) at the site of injection. Cytarabine has also been associated with renal dysfunction, hepatic dysfunction and jaundice in some patients. It has also been associated with freckling, skin and mucosal bleeding, joint pain. Very rare cases of pericarditis have been reported. Cases of pancreatitis have also been reported.
A cytarabine reaction is characterised by fever, myalgia, bone pain, occasionally chest pain, maculopapular rash, conjunctivitis and malaise. It usually occurs 6-12 hours after administration.
Cytarabine is teratogenic in some animal species. It should not be used in pregnant women. It should not be used in women who may become pregnant, unless a medically acceptable method of contraception is used during the trial. It is not known if cytarabine or its metabolite is distributed into breast milk, therefore it should not be used in breastfeeding women.

For more detailed information please refer to the Summary of Product Characteristics (SPC) provided by the manufacturer.

1.3 RATIONALE FOR PERFORMING THE TRIAL

New therapeutic strategies are needed to significantly improve the prognosis of AML patients assessed ineligible for intensive treatment at initial diagnosis as well as for patients with relapsed/refractory AML. Recent successful developments of signal transduction inhibitors or antibodies targeting specific molecules that are deemed important for the malignant cell biology have spurred the search for other targets and respective inhibitory molecules.

The Plk-1 is a key enzyme regulating the processes during the metaphase of mitosis and BI 6727 specifically inhibits Plk-1. Although not specific for acute leukaemia, molecules targeted to disturb cellular division and to induce apoptosis are especially promising in rapidly proliferative malignancies such as AML.

To maximize the chance of significant therapeutic improvement BI 6727 will be combined with and compared to low-dose Cytarabine (LD-Ara-C). LD-Ara-C was investigated in a randomized trial in AML patients ineligible for intensive treatment, since then LD-Ara-C has been widely used in this patient group (R07-2771).

After implementation of Protocol Revision I, based on BI's decision to discontinue the development of volasertib, one ongoing patient with clinical benefit from volasertib based on investigator´s assessment will stay in this trial to continue treatment with volasertib until disease progression or withdrawal from treatment and safety follow-up measures are completed. No documentation of volasertib effects in the eCRF will take place other than safety monitoring. Assessment of benefit from treatment will be performed per local standard of practice to support the decision on further treatment with volasertib. The results should be recorded in the source data only; documentation of efficacy results in the eCRF is no longer required.

1.4 BENEFIT - RISK ASSESSMENT

Patients with AML that are considered ineligible for intensive treatment at initial diagnosis as well as patients with relapsed/refractory AML have an overall adverse prognosis with very limited treatment options. LD-Ara-C is an established treatment for these patients, but outcome results are not satisfactory; in previously untreated patients considered ineligible for intensive treatment complete remissions up to 18% (R07-2771) were reported with LD-Ara-C treatment.

As no objective criteria are established to assess a patient's eligibility for intensive treatment the decision which treatment to adopt is based on the specialised investigators medical experience. To allow continuous monitoring and periodic reporting of the reasons why patients are assessed ineligible for intensive treatment the rationale for decision-making will be documented by the investigator for every single patient entered in the trial.

The most relevant side effect of BI 6727 administration is expected to be a transient inhibition of proliferation of normal dividing cells in bone marrow and mucosal tissue. Thymic atrophy seen in toxicological studies is not deemed relevant in the target population of adult cancer patients. Inhibition of mucosal proliferation may lead to gastrointestinal symptoms such as nausea or diarrhoea. The side effects on bone marrow stem cells may lead

to a temporary decrease of blood cells and platelets. These side effects are frequently seen in cancer patients treated with conventional cytotoxics or targeted therapies and can easily be monitored. Supportive treatment for these effects is available. In contrast to many established antiproliferative agents no unspecific toxic effects have been identified for BI 6727 in preclinical studies. AML patients often present with disease-related cytopenias, which without effective therapy will aggravate as the disease progresses. For most anti-leukaemia therapeutics, a drug-related transient worsening of cytopenias is common and inevitable. As described above, transient cytopenias are expected to occur with BI 6727. Cytarabine treatment is known to cause toxicities that overlap with BI 6727. Therefore, the CTCAE (common terminology criteria for adverse events) grade and duration of cytopenias and gastrointestinal toxicity will be important safety criteria to limit the risk of the treatment with the trial drugs (see section 5.2).
QT-monitoring will be performed in this trial, although the QT-prolongation observed at high doses in an animal model are not expected to impair clinical development of the compound.

In summary, the adverse event profile of BI 6727 as monotherapy as well as in combination with cytarabine is expected to be acceptable in the treatment of AML patients ineligible for intensive treatment, as these patients have an adverse prognosis, the effect of other therapies (e.g. LD-Ara-C) is limited, and the risk of fatal outcome within one year of diagnosis is high. For these AML patients the potential benefit of the investigational treatments may outweigh the risks associated with the therapy.

2. TRIAL OBJECTIVES

2.1 GENERAL AIM - OBJECTIVES

The trial will be performed in two parts, a phase I part and a phase IIa part.

In the phase I part of the trial, BI 6727 will be investigated as monotherapy and in combination with low dose cytarabine (LD-Ara-C) in patients with relapsed/refractory AML that are not eligible for intensive treatment. First the dose of BI 6727 will be escalated to determine the maximum tolerated dose (MTD) of BI 6727 in combination with LD-Ara-C (treatment schedule A) in AML patients. A safety analysis and conclusion on the MTD based on a database snapshot will be performed after the primary endpoint (MTD) of the phase I part was reached in treatment schedule A. The selection of the recommended dose for the phase II part of the trial will be based on the MTD and will furthermore account for the safety observed during treatment beyond the 1st cycle. The risk-benefit assessment will be updated if necessary (see section 7.3.4). After determination of the MTD in schedule A, patients will be recruited to schedule B (BI 6727 monotherapy); starting from the BI 6727 dose determined as MTD in schedule A the dose of BI 6727 will be further escalated to determine the MTD of BI 6727 monotherapy in AML patients.

In the phase IIa part, the combination of BI 6727 either at MTD or at another recommended dose for phase II with LD-Ara-C and LD-Ara-C monotherapy will be investigated to explore the efficacy of the combination schedule in comparison to LD-Ara-C monotherapy in previously untreated AML patients that are not eligible for intensive treatment.

2.2 PRIMARY ENDPOINTS

1.) Phase I part: MTD of BI 6727 monotherapy and BI 6727 in combination with LD-Ara-C

2.) Phase IIa part: Efficacy (complete remission, CR; complete remission with incomplete blood count recovery, CRi)

2.3 SECONDARY ENDPOINTS

1.) Incidence and intensity of adverse events graded according to CTCAE (version 3.0)

2.) Incidence of dose limiting toxicity (DLT)

3.) Pharmacokinetics of BI 6727 when given alone and in combination with cytarabine

4.) Pharmacokinetics of cytarabine after a single dose when given alone and in combination with BI 6727

5.) Pharmacodynamic monitoring: drug effect on leukaemia cells (see section 5.6)

6.) Partial remission (PR)

7.) Event free survival (EFS) (see section 5.1.2)

8.) Relapse free survival

9.) Remission duration

10.) Overall survival (OS)

11.) QTc changes during and after intravenous infusion of BI 6727

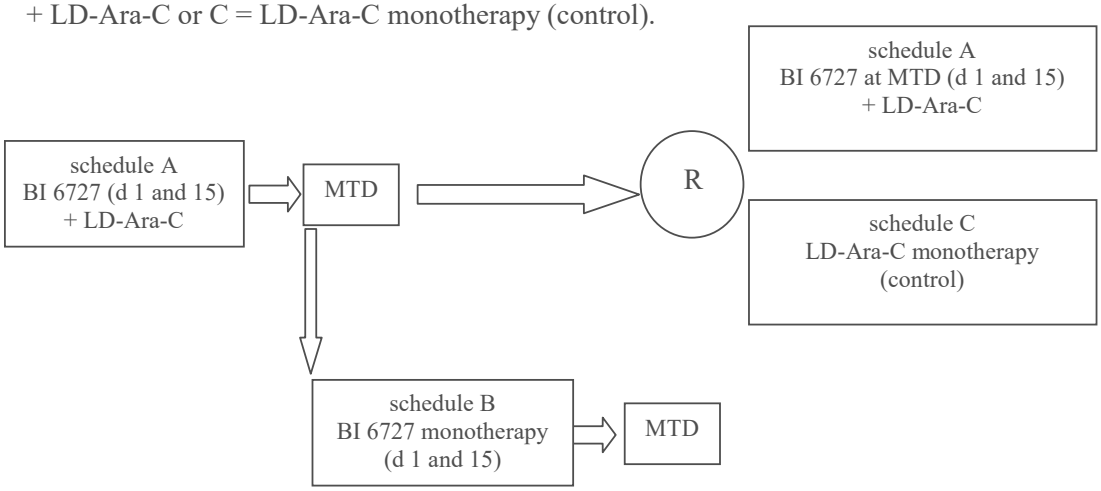
12.) Supportive care requirements (blood products, antibiotic usage, hospitalisation)

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN - DESCRIPTION

The trial is performed according to an open randomised design. The data obtained from this trial shall allow the definition of an MTD for two treatment schedules, one consisting of BI 6727 in combination with LD-Ara-C and one consisting of BI 6727 monotherapy. Furthermore, this trial shall allow an explorative analysis whether BI 6727 in combination with LD-Ara-C is effective compared to the established LD-Ara-C monotherapy. The results of the trial should help to decide on the further development programme of the BI 6727 in this indication.

Adult patients with relapsed/refractory AML who are considered ineligible for intensive treatment will be eligible for treatment in the phase I part of the trial. AML Patients with previously untreated AML will be eligible for the phase IIa part of the trial if they are considered ineligible for intensive treatment. After review of the inclusion and exclusion criteria, patients will be randomised / assigned to one treatment schedule. In the phase I part of the trial, patients will be assigned to schedules A and B. Schedule A patients will receive BI 6727 on days one and fifteen (1 hours i.v.) combined with LD-Ara-C (2 x 20 mg/d s.c.) on days 1-10 of a 4-week treatment cycle while schedule B patients will receive BI 6727 on days one and fifteen as monotherapy. The starting dose of BI 6727 in schedule A will be 150 mg/administration. After determination of the MTD for schedule A, patients will be recruited for dose escalation in schedule B (BI 6727 monotherapy), starting from the BI 6727 dose determined as MTD in schedule A. After determination of the MTD for schedule A and after review of the phase I safety analysis by the Clinical Monitor and the Coordinating Investigator, and if appropriate an updated risk-benefit assessment (see section 7.3.4), the phase IIa part of the trial will be opened. The safety analysis together with the conclusion on the recommended dose for the phase IIa part will be distributed to all involved competent authorities, ethics committees, and participating investigators prior to the initiation of the phase IIa part of the trial. Patients will be recruited to the phase II part of the trial only if a favourable risk-benefit assessment persists after the phase I safety analysis. In the phase IIa part of the trial patients will be randomised into one of the two schedules: A = BI 6727 d 1/15 + LD-Ara-C or C = LD-Ara-C monotherapy (control).



After the MTD has been determined in treatment schedule B, up to 15 additional patients with relapsed/refractory AML will be recruited to treatment schedule B to receive BI 6727 monotherapy.

To determine the MTD, dose escalation will be conducted for each treatment schedule following the 3+3 design as described in 4.1.3 (R04-0569). Briefly, cohorts of three patients will be treated per dose tier. The dose for BI 6727 will be escalated by up to 50 mg per administration until the highest dose has been found at which no more than one out of six patients experience a DLT. After definition of the MTD in schedule A and the phase I safety analysis (see section 7.3.4) the phase IIa part of the trial will start. In the phase IIa part 43 patients will be treated at the defined MTD of BI 6727 in combination with LD-Ara-C, and another 43 patients will be entered to the control group receiving standard LD-Ara-C monotherapy.

In the phase I part of the trial intrapatient dose escalation of BI 6727 will be allowed in patients who continue therapy beyond the first cycle as described in section 4.1.4.

During treatment, the investigator will determine the safety laboratory parameters, record the adverse events, and perform additional investigations as outlined in the flow charts. Assessment of response will be performed at the investigator site and will be sufficient for the decision whether the patient will continue treatment. After implementation of Protocol Revision I, assessment of response will only have to be done per local standard of practice to support the investigator´s decision on treatment continuation/discontinuation. Safety laboratory parameters and additional investigations as outlined in the flow chart will be done as medically indicated at discretion of the investigator.

The duration of one treatment cycle will be four weeks, including the days of treatment administration, unless haematologic toxicities necessitate an additional observation period of up to three weeks (for details see 4.1.4). At the end of each cycle, the decision will be made about continuation of treatment or withdrawal according to the criteria specified (sections 4.1.4 and 6.3).

The trial will be performed by investigators experienced and specialised in the treatment of AML. These investigators are trained to assess a patient's eligibility for intensive treatment - based on their special medical experience. The criteria impacting the decision to assess a patient ineligible for intensive treatment will be documented to allow continuous monitoring and to enable periodic reporting of the rationale to enter patients into the study.

The safety laboratory investigations will be performed at the investigator site and no central laboratory will be used except for pharmacokinetic, pharmacodynamic (immunocytochemistry), cytogenetic/molecular genetic and pharmacogenetic analyses. A vendor will be used for centralised ECG analysis. After implementation of Protocol Revision I, ECG readings prior to volasertib infusion and at the end of infusion will continue to ensure patient safety, but centralised ECG analysis will be discontinued.

The trial drugs will be forwarded by Boehringer Ingelheim to the investigators' pharmacies where they will be stored according to the storing condition requirements. Upon request of

the investigator the trial drugs will be prepared by the investigator's pharmacy for an individual patient and forwarded to the investigator.

All trial relevant documentation will be stored in BI's clinical trial master file (CTMF). Trial relevant documentation which has to be at the trial site will be filed in the investigator site file (ISF) at the investigator site.

The co-ordinating investigator who finally shall sign the clinical trial report of this trial has been elected by Boehringer Ingelheim. The co-ordinating investigator is one of the investigators participating in the trial and has experience in this type of trials and investigations.

3.2 DISCUSSION OF TRIAL DESIGN, INCLUDING THE CHOICE OF CONTROL GROUP

In the phase I part of the trial the investigational drug BI 6727 will be administered either as monotherapy or in combination with LD-Ara-C to patients with relapsed/refractory AML ineligible for intensive treatment. To determine the MTD (for definition see 5.2.4), dose escalation for BI 6727 will be conducted following the "3 + 3 design with de-escalation" (for details see section 4.1.3). A phase I safety analysis will be performed before start of the phase IIa part (see section 7.3.4). Patients will be recruited to the phase IIa part of the trial only if a favourable risk-benefit assessment persists after the phase I safety analysis.

In phase IIa of the trial, patients with previously untreated AML considered ineligible for intensive treatment will be randomised to receive BI 6727 at MTD in combination with LD-Ara-C or LD-Ara-C monotherapy. LD-Ara-C is considered an established treatment for patients with AML who are ineligible for intensive treatment (R07-2771).
This trial will be performed according to an open design, because placebo-infusions / injections, which would be necessary for blinding, are considered dispensable in this phase I/IIa exploratory trial (see section 4.1.5).

The primary objectives of the trial are to establish separately the MTD for BI 6727 monotherapy and BI 6727 in combination with LD-Ara-C in AML patients (phase I part), and to obtain a signal whether BI 6727 in combination with LD-Ara-C is effective in the treatment of AML as compared to the established LD-Ara-C monotherapy (phase IIa part).

Adult AML patients who have relapsed or failed prior chemotherapy and are considered ineligible for an intensive treatment were selected for inclusion in the phase I part of this trial, because these patients constitute a group with unfavourable prognosis for whom currently no satisfactory standard treatment exists.

Adult patients with previously untreated AML who are considered ineligible for intensive treatment were selected for inclusion in the phase IIa part this trial. LD-Ara-C is an established treatment for this group of patients, but outcome results are not satisfactory.

At the screening visit and before a patient is enrolled in the trial the investigator will document comprehensively the reasons why the patient is considered ineligible for intensive treatment (section 5.3.3).

The trial shall allow the investigation of BI 6727 and BI 6727 + LD-Ara-C in AML with regard to safety and efficacy for the future clinical development programme in this disease and possibly other malignancies.

The likelihood of any monotherapy to improve on the outcome of AML patients is considered low at this time. Therefore BI 6727 will be tested in combination with the established compound cytarabine in the phase II part of the trial. Still BI 6727 monotherapy will be evaluated in the phase I part of the trial to generate safety, pharmacokinetic and pharmacodynamic data for BI 6727 in this indication. If warranted by efficacy data of BI 6727 monotherapy phase II development of BI 6727 monotherapy may be considered in addition.

To avoid potential bias at inclusion, in the phase II part the patients will be randomly allocated to the treatment schedules. The trial will be performed in an open-label manner (see also section 4.1.5).

3.3 SELECTION OF TRIAL POPULATION

A total of about 175 evaluable patients are planned. As in the phase I part of the trial (dose escalation) at most 6 patients per month can be recruited, this part of the trial will be performed at up to eight trial sites. The phase IIa part of the trial will be performed at least at twenty trial sites. Each site is expected to recruit about one patient every month. A log of all patients screened will be maintained in the ISF at the investigational site.

3.3.1 Inclusion criteria

- Male or female adult with relapsed/refractory AML ineligible for intensive treatment. **(phase I part only)**
- Male or female adult with previously untreated (except hydroxyurea, see section 4.2.2) AML ineligible for intensive treatment **(phase IIa part only)**
- Confirmed diagnosis of AML according to the WHO definition (except for acute promyelocytic leukaemia, APL)
- Patient is eligible for LD-Ara-C treatment
- Life expectancy ≥ 3 months
- Eastern co-operative oncology group (ECOG, R01-0787) performance score ∀2 at screening
- Signed written informed consent consistent with international conference on harmonisation – good clinical practice (ICH-GCP) and local legislation

3.3.2 Exclusion criteria

- Previously untreated AML **(phase I part only)**

- Relapsed or treatment refractory AML **(phase IIa part only)**
- Patient with APL (AML subtype M3 according to the French-American-British (FAB) classification)
- Hypersensitivity to one of the trial drugs or the excipients
- Other malignancy requiring treatment
- Symptomatic central nervous system involvement
- Clinically relevant QT prolongation (e.g. long QT syndrome, QTcF > 470 ms)
- Aspartate amino transferase (AST) or alanine amino transferase (ALT) greater than 2.5 times the upper limit of normal (ULN), or AST or ALT greater than 5 times the ULN in case of known leukaemia liver involvement
- Prothrombin time (PT) > 1.5 x ULN for subjects not on therapeutic vitamin K antagonists (phenprocoumon, warfarin)
- Bilirubin greater than 1.5 mg/dl (> 26 #mol/L)
- Serum creatinine greater than 2.0 mg/dl
- Concomitant intercurrent illness, which would compromise the evaluation of efficacy or safety of the trial drug, e.g. active severe infection, unstable angina pectoris, cardiac arrhythmia, or severe heart failure/cardiac insufficiency
- Psychiatric illness or social situation that would limit compliance with trial requirements
- Concomitant therapy, which is considered relevant for the evaluation of the efficacy or safety of the trial drug (see section 4.2.2)
- Contraindications for cytarabine treatment according to the SPC
- Female patients of childbearing potential who are sexually active and unwilling to use a medically acceptable method of contraception during the trial, i.e. combination of two forms of effective contraception (hormonal contraception, intrauterine device, condom with spermicide, etc.). Male patients with partners of childbearing potential who are unwilling to use condoms in combination with a second medically acceptable method of contraception during the trial
- Pregnant or nursing female patients
- Patient unable to comply with the protocol

4. TREATMENTS

4.1 TREATMENTS TO BE ADMINISTERED

BI 6727 will be administered as a strictly intravenous infusion over a period of 1 hour through a secure venous access on days one and fifteen of a 28-day treatment cycle. The duration (actual start and end time) of the infusion needs to be documented in the electronic-case report form (eCRF).

Cytarabine will be administered as a subcutaneous injection at a dose of 20 mg every 12 hours on days one until ten of a 28-day treatment cycle. The injections (date and time) need to be documented in the eCRF.

4.1.1 Identity of investigational products

4.1.1.1 BI 6727

Substance (INN):	BI 6727
Pharmaceutical form:	Solution for infusion after dilution
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Unit strength:	2 mg /mL (vials with 100 mL) OR 2 mg/mL (vials with 175 mL)
Daily dose:	See section 4.1.3
Duration of use:	Single dose on day 1 and 15 of each 28 day cycle
Route of administration:	intravenous
Posology:	Infusion over 60 minutes

4.1.1.2 Cytarabine

Substance (INN)	Cytarabine
Brand names	e.g. [redacted]
Pharmaceutical form	solution for injection
Unit strength	20 mg/mL
Daily dose	2 x 20 mg
Duration of use	days 1-10 in 4-week cycles
Route of administration	subcutaneous
Posology	subcutaneous bolus injection

4.1.2 Method of assigning patients to treatment groups

Patients will be assigned to two treatment schedules (A and B) in the phase I part of the trial (dose escalation phase to determine MTD) as follows: patients will first be entered in treatment schedule A. After determination of the MTD for schedule A, patients will be recruited for dose escalation in schedule B (BI 6727 monotherapy).
In the phase IIa part of the trial (after MTD in schedule A is determined), patients will be randomised to two treatment schedules (A and C).
Random allocation will be performed using randomisation envelopes (for details see section 7.5).

4.1.3 Selection of doses in the trial

Two treatment schedules will be investigated in the phase I part of the trial to determine the MTD. All patients will receive either BI 6727 on days 1 and 15 either as monotherapy or in combination with LD-Ara-C (2 x 20 mg/d on days 1-10) in 28-day cycles. The starting dose of BI 6727 in treatment schedule A is 150 mg and corresponds to 50 % of the recommended Phase II dose of 300mg and 38% of the MTD of 400mg that has been determined in a phase I monotherapy dose escalation trial to be well tolerated.

To determine the MTD (for definition see 5.2.4), dose escalation for BI 6727 will be conducted following the "3 + 3 design with de-escalation" (R04-0569). A cohort of three patients will be treated at the starting dose level and observed until the end of the cycle. The dose level will be escalated with each new cohort until at least one out of three patients of a cohort experiences DLT (for definition see section 5.2.3). If one patient experiences a DLT, then three additional patients will be treated at the same dose level; if none of the three additional patients experiences a DLT, then the dose escalation will be continued by treating the next cohort of three patients at the next higher dose level. If at least two out of up to six patients at a dose level experience a DLT, the MTD has been exceeded and the dose will be deescalated until a dose level is reached in which at most one DLT out of six patients is observed (R01-0028). A dose step for escalation shall not exceed 50 mg/administration, a dose step for de-escalation shall not exceed 50 mg/administration.
The starting of BI 6727 for dose escalation in schedule B will be the dose determined as BI 6727 MTD in schedule A.
The dose of the trial drug on days one and fifteen will always remain the same (i.e. simultaneous and equal dose escalation for days one and fifteen). The dose of cytarabine remains always unchanged.
In case two or more cases of DLT are observed at the starting dose of 150 mg either in monotherapy or in combination with LD-Ara-C the dose BI 6727 will be deescalated to a lower dose cohort as outlined above.

After the MTD has been determined in treatment schedule A, a safety analysis based on a database snapshot will be performed (see section 7.3.4). Patients will be recruited to the second phase of the trial only after a favourable assessment in the phase I safety analysis. In this phase IIa part, patients will be randomised to receive either BI 6727 at MTD in combination with LD-Ara-C or LD-Ara-C monotherapy.
After the MTD has been determined in treatment schedule B, up to 15 additional patients

with relapsed/refractory AML will be recruited to treatment schedule B to receive BI 6727 monotherapy.

4.1.4 Selection and timing of doses for each patient

Prior to inclusion of a new patient in the phase I part the investigator has to confirm the actual dose tier of BI 6727 for the patient with the clinical monitor of the sponsor who oversees the dose escalation steps according to the safety data of patients from all trial sites.

BI 6727 will be administered as an intravenous infusion under the supervision of the investigator or designated personnel. Subcutaneous cytarabine injections will be administered according to the SPC.

The trial drugs may be administered at any time during the day. In case the second dose of BI 6727 is missed for administrative reasons the respective dose will be administered on the following two days. In case a dose of cytarabine is missed for administrative reasons the respective dose will not be administered at a later time (any missed cytarabine dose must be documented in the eCRF).

At the end of each treatment cycle, the response to treatment will be assessed. To continue treatment with further cycles, the following criteria must be met:

1.) Absence of disease progression (see section 5.1.1)

2.) Neutrophils ≥ 500 /µL (0.5 x 10^9/L) and platelets ≥ 25,000 /µL (25 x 10^9/L); unless CTCAE grade 4 neutropenia or thrombopenia was preexistent

3.) Acceptable tolerability (in case of DLT, patients may continue therapy only after recovery from DLT to CTCAE levels which allow further therapy and only with a reduced dose), and recovery from drug-related cardiac toxicity.

In case criterion 2 is not fulfilled, the peripheral blood should be re-evaluated for up to three weeks. As soon as criterion 2 is met the treatment should be continued (unless other criteria for discontinuation or withdrawal apply, see section 6.3). A delay of haematopoietic reconstitution (i.e criterion 2 unmet) for more than three weeks after the end of the treatment cycle qualifies for DLT in patients with CRi or PR (see section 5.2.3). Any case of a delay in treatment cycle should be communicated to the clinical monitor of Boehringer Ingelheim. Progressive disease will lead to discontinuation of treatment.

Administration of the trial drugs has to be stopped temporarily in case of a DLT (see section 5.2.3). Patients may continue therapy only after recovery from the DLT to CTCAE levels which allow further therapy and only with a reduced dose of BI 6727, the LD-Ara-C dose will remain unchanged. The new dose of BI 6727 must be finally agreed on between the clinical monitor of Boehringer Ingelheim and the investigator. The reduced dose will be valid for all following treatment cycles in the individual patient. A reduction of the dose will be allowed only once for an individual patient during the whole trial. In case, a patient experiences a second episode of DLT with the reduced BI 6727 dose, the treatment has to be

permanently discontinued. Likewise, treatment has to be discontinued in case the DLT is not reversible.

In this trial, an intrapatient dose escalation of BI 6727 will be allowed in the phase I part of the trial to increase the probability of clinical benefit. In case of a clinical response other than CR or CRi (i.e. PR or no change), the patient may receive a higher dose of BI 6727 provided that the drug is tolerated well (i.e. non-haematological drug related adverse events CTCAE grade ∀2 and haematological drug related adverse events CTCAE grade ∀3 unless preexistent). The BI 6727 dose escalation may be up to 50 mg/administration for both schedules. All decisions on intrapatient dose escalation will be made only in agreement between the investigator and the sponsor. Beginning after the first cycle of treatment, dose escalations may be repeated after every cycle and may in individual patients exceed the MTD found in this trial. A dose escalation must not be performed in patients who have achieved CR or CRi.

All changes of the BI 6727 dose will simultaneously affect both days of BI 6727 administration, i.e. BI 6727 dose will always remain the same on days one and fifteen.

4.1.5 Blinding

This phase I / IIa trial will be performed according to an open design. Although a double-blind double-dummy design would be feasible, this would necessitate additional placebo-infusions/injections which are considered dispensable in this phase I/IIa exploratory trial in these highly compromised patients. Without placebo-infusions/injections, the obvious difference in treatment schedules precludes blinding of both the patient and the investigator. Therefore, no blinding is done. For similar technical reasons, the statistical analyses will be performed in an open fashion.

This open-label trial will also be handled in an open fashion by the sponsor throughout. The eCRF will contain information on randomised treatment.

4.1.6 Packaging, labelling, and re-supply

BI 6727 will be supplied in 100 mL vials containing 200 mg BI 6727 OR in 175 mL vials containing 350 mg BI 6727.
Ara-C will be supplied in vials containing cytarabine at a concentration of 20 mg/ml.

BI 6727 will be labelled with trial number, medication number, quantity of dosage units and strength, identification code, pharmaceutical dosage form, route and mode of administration, term ‘for clinical trial use’ (domestic language), sponsor name and address, storage conditions, use-by-date.

In the phase I part of the trial cytarabine will be dispensed with the commercially available label and an additional label indicating trial number, medication number, term ‘for clinical trial use’ (domestic language) and sponsor name.

In the phase II part of the trial cytarabine will supplied in 2 ml vials containing 40 mg cytarabine. Cytarabine will be labelled with trial number, medication number, quantity of

dosage units and strength, identification code, pharmaceutical dosage form, route and mode of administration, term ‘for clinical trial use’ (domestic language), sponsor name and address, storage conditions, use-by date. The cytarabine dispensed for the phase I part of the trial might be used - if still available - in phase II part as well.

Examples of the labelling of the medication are included in the ISF.

Medications will be delivered to the investigator's pharmacy where the total dose per patient will be prepared upon request from the investigator.

For preparation of the BI 6727 infusion solution, the preconcentrate of BI 6727 will be diluted in 0.9% sodium chloride. The maximum concentration of BI 6727 in the ready-for-use infusion must not fall below 0.02 mg/mL nor exceed 1.0 mg/ml. The content of several vials may be needed for administration of the requested dose. For further details, please refer to the ISF.

Cytarabine will be prepared and handled according to the package insert and the SPC provided by the manufacturer.

Please refer to section 8.2.1 for drug accountability.

4.1.7 Storage conditions

BI 6727 and cytarabine have to be stored in the original packaging in the hospital pharmacy in a limited access area at the temperature indicated on the trial drug label.

For more details on BI 6727, please refer to the IB (c01694302-14) and the ISF. For more details on cytarabine, please refer to the SPC.

4.2 CONCOMITANT THERAPY

4.2.1 Rescue medication and additional treatments

Rescue medication to reverse the action of BI 6727 or cytarabine is not available. Potential side effects of BI 6727 and cytarabine have to be treated symptomatically. Patients should receive supportive care according to local guidelines regarding blood product support, antibiotics, analgesics, skin and mouth care etc. The use of growth factors such as granulocyte colony stimulating factor (G-CSF) will be allowed, but growth factors should be avoided in the first treatment cycle for better assessment of safety and response parameters. Treatment with corticosteroids will be allowed. All treatments have to be recorded in the eCRF with duration.

All concomitant non-antileukaemia therapies to provide adequate care may be given as clinically necessary but should be recorded in the eCRF except for vitamins or nutrient supplements.

Trade name, indication and dates of administration of concomitant therapies will be documented. The use of prophylactic antiemetic drugs should be documented. For parenteral

nutrition during the trial, the components need not to be specified in detail. It should just be indicated as 'parenteral nutrition'. If a patient needs anaesthesia, it will be sufficient to indicate 'anaesthesia' without specifying the details.

4.2.2 Restrictions

During the trial, no additional chemo- or immunotherapy will be allowed.

For patients included in the phase I part of the trial (relapsed/refractory AML) prior cytotoxic antileukaemia chemotherapy (except hydroxyurea) or antileukaemia immunotherapy must have been discontinued at least two weeks before the first administration of the trial drug and the patient must have recovered from all clinically relevant reversible toxicities. For any other prior investigational treatment, a time interval of the investigational drug's half-life x5 must have elapsed from the last administration of the other investigational drug to the first administration of BI 6727.

For patients included in the phase IIa part of the trial (previously untreated AML) no prior chemo- or immunotherapy for AML is allowed (except hydroxyurea) before the administration of the trial drugs.

For peripheral blast control, hydroxyurea may be given until one day before the first administration of the trial drug in all patients. The start date, end date, and dose will be recorded in the e-CRF.

Concomitant therapy with other investigational drugs will not be allowed during the trial.

4.3 TREATMENT COMPLIANCE

BI 6727 will be administered as an intravenous infusion under the supervision of the investigator or designated personnel. Subcutaneous cytarabine injections will be administered according to the SPC. The investigator or his/her deputy will check at visits 2, 3 and 4 whether the patient has received the cytarabine medication according to the protocol on the scheduled previous days until day 10. Any discrepancies will be explained in the CRF by the investigator or his/her deputy.
The plasma concentrations of the trial drugs will be determined.

5. OBSERVATIONS

5.1 EFFICACY - PHARMACODYNAMICS

The efficacy endpoints will be assessed at the time points specified in the flow charts. The primary endpoint for efficacy is response. Secondary endpoints for efficacy are event free survival, relapse free survival, remission duration, overall survival.

5.1.1 Assessment of response

Response will be assessed in the peripheral blood and in the bone marrow.
In case of extramedullary manifestations of leukaemia, assessment by imaging will complement the blood and bone marrow assessment of response.

The baseline bone marrow assessment should be done within 2 weeks prior to start of treatment with the trial drugs.

The first response assessment in the bone marrow will be performed at the end of the first treatment cycle. The classification of response is defined below.
Response assessment after further treatment cycles will be performed in a two step fashion to reduce patient stress:

- First, the manifestation of leukaemia will be assessed clinically and in the peripheral blood. In case of persistence of leukaemia cells in the blood no bone marrow aspiration must be performed.
- If leukaemia cells cannot be detected in the peripheral blood and other clinical signs of active leukaemia are absent, a bone marrow aspirate will be obtained before the next treatment cycle.
  If the bone marrow demonstrates CR or CRi, further bone marrow examination will be performed after every other treatment cycle.
  In case of persistence of leukaemia in the bone marrow and continuing absence of leukaemia in the peripheral blood, further bone marrow examination will be performed after each treatment cycle to earlier detect CR or progressive disease.
- A bone marrow examination should be performed as soon as possible when progressive disease or relapse after CR or CRi is suspected.

After approval of Protocol Revision I, bone marrow aspirations and disease assessments only have to be done per local standard of practice to support the decision on further treatment with volasertib. These efficacy data will not be entered in the eCRF; documentation in the source data is sufficient.

5.1.1.1 Definition of response

Response to treatment will be evaluated according to the following criteria (modified from the National Cancer Institute/Cancer and Leukemia Group B criteria, R06-0452):

- Complete remission (CR)
  morphologically leukaemia free state (i.e. bone marrow with < 5% blasts by morphologic criteria and no Auer rods, no evidence of extramedullary leukaemia) and absolute neutrophil count ≥ 1,000/µL and platelets > 100,000/µL.
- Complete remission with incomplete blood count recovery ("incomplete" CR, CRi)
  All of the above criteria for CR must be met, except that neutrophils < 1,000/µL or platelets < 100,000/µL in the blood.
- Partial remission (PR)
  All of the above criteria for CR must be met, except that the bone marrow contains ≥ 5% but less than 25% blasts (or ≤ 50% of initial blast count), or < 5% blasts in the presence of Auer rods or abnormal morphology.
- No change
  Patient survives ≥ 7 days following completion of initial treatment cycle with persistent leukaemia in the last peripheral blood smear or bone marrow (>25% blasts), or with persistent extramedullary disease, but without further clinical deterioration due to leukaemia or increase of blast population in the bone marrow or peripheral blood.
- Progressive disease (PD)
  Patient survives ≥ 7 days following completion of initial treatment cycle with increase of blast population in the bone marrow or peripheral blood or aggravation or new development of extramedullary disease or further deterioration or death due to leukaemia. Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of pd at that time should be classified as having 'symptomatic deterioration'. Every effort should be made to document the objective pd even after discontinuation of treatment.
- Aplasia
  Patient survives ≥ 7 days following completion of initial treatment cycle, then dies while cytopenic, with the last post-treatment bone marrow aplastic or hypoplastic (i.e. <20% cellularity) and without leukaemia blasts.
- Indeterminate
  (a) Patient survives < 7 days after completion of initial treatment cycle; or (b) patient survives ≥ 7 days following completion of initial treatment cycle, then dies with no persistent leukaemia in the peripheral smear but no post-treatment bone marrow examination or (c) patient does not complete the first cycle
- Recurrence (relapse)
  after CR reappearance of leukaemic blasts in the blood or > 5% blasts in the bone marrow not attributable to any other cause.

Patients with the response status "aplasia" or "indeterminate" will be treated as non-responders for primary statistical analyses of efficacy parameters.

5.1.2 Event Free Survival

Event free survival (EFS) is defined for all patients that entered the trial, and measured from the date of randomisation to the date of disease progression (treatment failure), relapse or death from any cause, whichever occurs first (R06-0452).

5.1.3 Relapse-free survival

Relapse free survival is defined only for patients who achieve CR, and is measured from the date of attaining CR until the date of disease recurrence or death from any cause, whichever occurs first.

5.1.4 Remission duration

Remission duration analysis is defined only for patients who achieve CR, and is measured from the date of attaining CR until the date of disease recurrence (relapse). For patients who die without report of relapse, remission duration will be censored on the date of death, regardless of cause.

5.1.5 Overall survival

Overall survival (OS) is defined for all patients that entered the trial, and measured from the date of randomisation until death from any cause.

5.2 SAFETY

5.2.1 Adverse events

Upon inclusion into the trial, the patient's condition is assessed (e.g. documentation of history / concomitant diagnoses and diseases), and all relevant changes from baseline are noted subsequently.

Patients will be required to report spontaneously any adverse events (AEs) as well as the date of onset and end of these events. These include all events that affect the well-being of the patients irrespective of their relatedness to the treatment. Specific questions will be asked whenever required or useful to more precisely describe an AE and to allow a grading according to the CTCAE criteria (version 3, R04-0474).

A carefully written record of all AEs has to be kept by the investigator in charge of the trial. Records of AEs will include data on the date of onset, end date and CTCAE grading of the event as well as any treatment or action required for the event and its outcome.

The events leukopenia, neutropenia, thrombocytopenia are expected after treatment with BI 6727 and will be considered as listed events for regulatory purposes (see IB for details, c01694302-14). The events listed in the SPC are expected after treatment with cytarabine.

AEs with onset within 21 days after the last trial drug administration in the last treatment cycle will be considered as on treatment. All AEs, including those persisting after trial completion must be followed up until they have resolved or have been sufficiently characterised or the clinical monitor and the investigator agree to not further pursue them.

All events, serious and non-serious, with onset within six weeks after the last application of the trial drug (observational phase) must be reported. All events, serious and non-serious, that are considered related to the trial drugs must be reported irrespective of the time of onset.

Deaths (unless they are considered drug-related or trial related) will not be reported as serious adverse events if occurring later than six weeks after last administration of the trial drugs, since death will be followed-up separately (secondary endpoints).

Definitions and requirements for documentation and reporting of AEs and serious adverse events (SAEs) during the trial are provided in Section 8.4.1.

Patients may be hospitalised for administrative reasons during the trial (e.g. days on which infusion of the trial drug takes place). These and other hospitalisations planned at the beginning of the trial will not be considered as SAE if they have been reported at the screening visit in the eCRF and performed as planned.

Changes in safety tests including blood pressure, pulse rate, electrocardiogram (ECG) and laboratory tests will be recorded as AEs, if they are not associated with an already reported AE, symptom or diagnosis, and:

! action is required and taken with the investigational drug, i.e. dose reduction or treatment discontinuation,'

or

! treatment due to the event is required (i.e. a concomitant medication is added or changed).

5.2.2 Worsening of pre-existing conditions

Expected fluctuations or expected deterioration of the underlying disease will not be recorded as an AE. If progressive disease occurs and is associated with symptoms, the signs and symptoms of progressive disease will be reported as an adverse event or a serious AE (if applicable).

Worsening of other pre-existing conditions will be recorded as an AE or SAE if one of the following criteria is met:

! the criteria for an SAE apply,
! action is required and taken with the investigational drug, i.e. dose reduction or treatment discontinuation,
! treatment is required, i.e. concomitant medication is added or changed,
! the investigator believes a patient has shown a clear, unexpected deterioration from the baseline condition.

Pre-existing conditions are not recorded as AEs if they do not meet at least one of the above criteria. Specifically, the following will not be recorded as an AE:

! pre-existing conditions present at baseline, which remain unchanged during the trial,
! expected fluctuations or expected deterioration of a pre-existing condition.

5.2.3 Dose limiting toxicity

Dose limiting toxicity (DLT) is defined as drug related CTCAE grade ≥ 3 non-haematological toxicity (excluding: untreated nausea, untreated vomiting, CTCAE grade 3

untreated diarrhoea, CTCAE grade 3 "febrile neutropenia" and CTCAE grade 3 "infection with grade 3 or 4 neutrophils").

In patients with CRi or PR, persistent CTCAE grade 4 neutropenia or thrombocytopenia until three weeks after the end of the treatment cycle will be regarded a DLT unless the respective grade 4 cytopenia was pre-existent. In patients who required platelet substitution to maintain a CTCAE grade < 4 before treatment, a CTCAE grade 4 thrombocytopenia after treatment does not constitute a DLT.

5.2.4 Maximum tolerated dose

The MTD is defined as the highest dose at which six patients have been treated and less than two patients experienced DLT within the first cycle of treatment. The MTD will be defined based on safety data from the first cycle only. However, the data from later treatment cycles will be considered for future development of BI 6727 in this indication. To determine the MTD of BI 6727 on days 1 + 15 in combination with LDAra-C (schedule A), the dose escalation starting with 150 mg BI 6727 will be conducted following the “3 + 3 design with de-escalation” as described in section 4.1.3. To determine the MTD of BI 6727 on day 1 + 15 monotherapy (schedule B), the dose escalation starting with the BI 6727 MTD determined in schedule A will be conducted following the “3 + 3 design with de-escalation” as described in section 4.1.3.

5.2.5 Laboratory investigations

Blood samples have to be collected at the time points specified in the flow chart. Safety laboratory examinations will include haematology, biochemistry and coagulation parameters.

The following parameters will be determined at the time points specified in the flow-chart:

Haematology	haemoglobin, haematocrit, red blood cell count (RBC), white blood cell count (WBC) with differential, platelets.
Biochemistry	glucose, sodium, potassium, calcium, creatinine, aspartate amino transferase (AST), alanine amino transferase (ALT), alkaline phosphatase, lactate dehydrogenase, bilirubin, urea, total protein, uric acid, creatine phosphokinase (CPK) and Troponin.
Coagulation	activated partial thromboplastin time (aPTT) and prothrombin time (PT); international normalised ratio (INR) where therapeutically indicated (i.e. vitamine K antagonist treatment)
Urine	pH, glucose, erythrocytes, leukocytes, protein, nitrite will be analysed by dipstick (semiquantitative measurements; -, +). In case of pathological findings, further evaluation should be performed and the findings documented.

After approval of Protocol Revision I, safety laboratory examinations should be done as medically indicated at discretion of the investigator. The results are not required to be entered in the eCRF; documentation in the source data is sufficient. Only in case of findings that are qualifying as an (S)AE, the respective (S)AE will be reported (eCRF and SAE form, if applicable).

5.2.6 Physical examination, height, weight, ECOG performance score

A general physical examination will be performed at screening and at the time points specified in the flow charts. Preferably, the same investigator should perform these examinations to enable comparability. Measurement of height (in cm) and body weight (in kg) and the evaluation of the ECOG performance score will be performed at the time points specified in the flow chart.

After approval of Protocol Revision I, physical examinations, weight, and ECOG performance score should be done as medically indicated at discretion of the investigator. The results are not required to be entered in the eCRF; documentation in the source data is sufficient.

5.2.7 ECG

12-lead resting ECG will be performed in all patients at the screening visit and at the EoT visit.
For patients in treatment schedules A and B ECGs will be recorded with every infusion of BI 6727 (before the start and immediately before the end of the BI 6727 infusion), additional ECGs will be recorded in cycle 1. In cycle 1 at visit 1 and 4, and at visit 1 in cycle 2 the ECGs must be performed at the related PK sampling time points. All ECGs have to be digitally recorded using dedicated equipment provided by a contract research organisation (CRO; [redacted]) at the following time points:

After approval of Protocol Revision I, ECGs should be recorded prior to and at the end of volasertib infusions. No digital and triplicate recording is required anymore. ECGs can be recorded with a local ECG machine.

- Visit 1 (day 1) of cycle 1
  - ! prior to start of infusion of BI 6727
  - ! immediately before the end of infusion of BI 6727 (1:00 hour). The infusion should not be finished yet at that sampling time point.
  - ! 2 hours after the start of infusion;
  - ! 4 -6 hours after the start of infusion
  - ! 24 hours after the start of the infusion

- Visit 4 (day 15) of cycle 1
  - ! prior to start of infusion of BI 6727

- ! immediately before the end of infusion of BI 6727 (1:00 hour). The infusion should not be finished yet at that sampling time point.
- ! 2 hours after the start of infusion;
- ! 4 -6 hours after the start of infusion

- Visit 1 (day 1) and visit 4 (day 15) of every cycle ∃ 2:
  - ! prior to start of infusion of BI 6727
  - ! immediately before the end of infusion of BI 6727 (1:00 hour). The infusion should not be finished yet at that sampling time point.

The recording will be checked for pathological results (to be recorded as AEs) by the investigator. In addition, a centralized evaluation of all 12-lead ECGs recorded will be performed by a CRO ([redacted]).

After approval of Protocol Revision I, transmissions for central ECG analysis will be discontinued.

In addition, ECGs should be done whenever the investigator deems necessary.

In case of drug related ECG changes, additional ECG monitoring will be performed in the respective and later cycles of treatment.

In case of QTcF > 470 ms prior to the planned start of infusion of BI 6727, the trial drug should not be administered.

In case of QTcF change from baseline > 60 ms with absolute QTcF < 500 ms (Grade 2 CTCAE V3.0) after receiving BI 6727, it is mandatory that patient remain at the investigative site after administration of BI 6727 for further ECG monitoring. The investigator will initiate further diagnostics (e.g. check electrolytes and check concomitant therapy that may be contributing to QTcF prolongation) and if required provide adequate treatment according to medical standards. The patient will be discharged from the investigative site after resolution of ECG findings. If the patient qualifies for a subsequent treatment course, depending on the benefit/risk ratio assessed by the investigator, the dose of BI 6727 will remain unchanged or reduced by 50 mg. For patients who will continue the BI 6727 treatment at the same dose level, in case of recurrence of the QTcF prolongation > 60 ms during the following cycles, it is mandatory that patient remains at the investigative site after administration of BI 6727 for continuous ECG monitoring. The patient will be discharged from the investigative site after resolution of ECG findings.

In case of QTcF prolongation to > 500 ms (Grade 3 CTCAE V3.0) after receiving BI 6727, it is mandatory that the patient remains at the investigative site after administration of BI 6727 for further ECG monitoring. The patient will be discharged from the investigative site after resolution of ECG findings (e.g. when the QTcF value is < 470 ms on a single observation). The investigator will initiate further diagnostics (e.g. check electrolytes and check concomitant therapy that may be contributing to QTcF prolongation) and provide adequate treatment according to medical standards. If the patient qualifies for a subsequent treatment

course (see 4.1.4), the dose of BI 6727 will be reduced according to section 4.1.4. The first BI 6727 infusion subsequent to a cycle when BI 6727 related QTcF prolongation to > 500 ms was documented must be performed in an intensive care unit with a continuous ECG monitoring under the supervision of the intensive care unit physician; in case of recurrence of the QTcF prolongation > 500 ms at the reduced BI 6727 dose, the same procedures regarding patients monitoring as at previous occurrence will apply and the treatment with BI 6727 will be permanently discontinued (see 4.1.4).

In case of occurrence of symptoms suggestive of arrhythmia related to QTcF prolongation, patient will be hospitalized, a cardiologic evaluation will be performed and treatment provided according to medical standards.

In case of occurrence of symptoms of left ventricular insufficiency, a cardiologic evaluation by a cardiologist and an echocardiogram must be performed.

5.2.8 Vital signs

Vital signs (blood pressure and pulse rate after two minutes supine rest) will be recorded at every visit, and during BI 6727 application at the following time points: pre-infusion, and at minutes 30 (%5), 60 (%10) and 120 (%10) after start of infusion.

After approval of Protocol Revision I, vital signs should be measured as medically indicated at discretion of the investigator. The results are not required to be entered in the eCRF; documentation in the source data is sufficient. Only in case of findings that are qualifying as an (S)AE, the respective (S)AE will be reported (eCRF and SAE form, if applicable).

5.3 OTHER

5.3.1 Demographics and history

Demographics (sex, birth date, race) and baseline conditions will be collected during the screening visit.
The WHO classification of the disease, the date of first cytological diagnosis (month and year) and cytogenetics of AML will be reported in the eCRF. In patients with relapsed/refractory AML (included only in the phase I part of the trial) the patient's history of AML will also be obtained. Previous malignant disease will be reported. Previous chemo-, immuno-, or hormone-therapy administered for malignant disease will be reported. If applicable, the total radiation dose and radiation field of any previous radiotherapy will be recorded.

5.3.2 Concomitant therapies and diagnoses

Concomitant diagnoses and / or therapies present at trial entry and / or during screening and relevant to the patient's safety during the trial as judged by the investigator, will be recorded in the eCRF.

5.3.3 Assessment of ineligibility for intensive treatment

A patient's ineligibility for intensive treatment is assessed by the investigator in agreement with the patient, based on a comprehensive documentation of the reasons for this assessment. This documentation will include the patient age, medical history, performance score, organ dysfunctions, co-morbidities, patients informed decision, and other relevant factors, supplemented with the investigators assessment what gave reason for evaluating the patient ineligible for intensive treatment.

5.3.4 Cytogenetics and molecular genetics

For central analysis of cytogenetics (chromosomal banding) and investigation of molecular genetic aberrations (mutations or deregulated expression of genes NPM1, CEBPA, FLT3 and optionally WT1, AML1, RAS, MLL, TP53, KIT, TET2, IDH1, EVI1, ERG, MN1; BAALC) a 5-10 mL bone marrow sample and a 40 mL blood sample will be collected at the screening visit. The samples will be sent via courier to the specialised laboratory for the aforementioned analysis. The samples should arrive in the lab within 24 hours after sample collection. Detailed instructions for cytogenetic sampling, handling and shipment of samples are provided in the ISF.

5.3.5 Pharmacogenetics

Pharmacogenetics investigates genetic variations in patients to explain and to predict their individual response to drugs.

To allow pharmacogenetic analyses, all patients will be asked for one blood sample. The sample will be taken and processed or stored after separate informed consent is given in accordance with local ethical and regulatory requirements.

The sample (max. 10 mL blood) will be completely anonymised. The anonymisation procedure will guarantee a very high level of data protection for the donor. Once the anonymisation has been carried out, there will be no legal way to trace back to the identity of the donor. The anonymised DNA may be analysed at a later time to identify whether there are genetic factors that could contribute to a better therapeutic outcome or a higher risk of developing treatment-related adverse drug reactions. These analyses may include genes related to efficacy, safety and pharmacokinetics.

After anonymisation, the sample (or the DNA derived thereof) will be stored at Boehringer Ingelheim for at least 10 years after the end of the clinical trial or until there is no more material available for tests.

Participation in the pharmacogenetics part is voluntary and not a prerequisite for participation in the study.

5.3.5.1 Methods and timing of sample collection

The blood sample for pharmacogenetic testing will be taken at the screening visit . A maximum of nine (9) mL of blood will be collected per EDTA blood sampling tube for those

patients who signed a separate informed consent concerning genotyping. The blood samples will be stored at a temperature of at least -20&C. Once frozen, thawing of the samples should be avoided. Detailed instructions for pharmacogenetic sampling, handling and shipment of samples are provided in the ISF.

All samples will be shipped to the logistic CRO.

5.4 APPROPRIATENESS OF MEASUREMENTS

Determination of MTD is based on toxicities graded according to CTCAE. The CTCAE criteria are commonly used in the assessment of adverse events in cancer patients.
The criteria to be used for evaluation of response are well established and scientifically accepted.

5.5 DRUG CONCENTRATION MEASUREMENTS - PHARMACOKINETICS

Blood will be collected at specified time points during the first treatment cycle of each treatment schedule (see appendix 10.1) to determine the plasma concentration of BI 6727 and cytarabine. Further exploratory analysis for identification of drug metabolites could be done if applicable. If these additional analyses are performed, the results will be reported separately. The actual sampling date and time for blood samples will be documented in the eCRF. These actual sampling times will be used for determination of pharmacokinetic parameters. Also, for a valid PK analysis, it is of utmost importance to document the exact clock time of trial medication administration. The duration of the BI 6727 infusion (planned 1 hours) will be documented (start and end time of the infusion) in the eCRF. Every attempt will be made to adhere to an infusion time of 1 hours for BI 6727 with a constant infusion rate.

5.5.1 Methods and timing of sample collection

5.5.1.1 Plasma sampling for pharmacokinetics

For pharmacokinetic purposes the following blood volumes will be taken per subject during the initial treatment cycle:

In treatment schedule A, a total amount of around 90 mL blood will be taken per subject. In treatment schedule B around 54 mL blood and in treatment schedule C around 35 mL blood will be taken per subject in the first cycle. In cycle 2, about 16 or 6 mL of blood will be drawn for pharmacokinetic purposes in treatment schedule A or B, respectively. The samples have to be taken from the opposite arm, not from the infusion arm. For patients having central venous access, BI 6727 may be administered using this device and PK samples obtained from either forearm.

For quantification of BI 6727 plasma concentrations, around 3 mL of venous blood will be taken in an EDTA (ethylendiaminetetraacetic acid)-anticoagulant blood drawing tube (e.g. [redacted] at the time points specified in the flow charts and in appendix 10.1. The sampling tube has to be mixed immediately with the anticoagulant by gently inverting about 10 times. Vigorous shaking should be avoided to prevent haemolysis.

The whole blood is to be centrifuged immediately at 4-25°C at approximately 3000 rpm (~2100 g) for at least 15 minutes. Please store the PK samples in an ice bath (up to 30 minutes) until centrifugation if they cannot be centrifuged immediately.

Transfer immediately two aliquots of EDTA plasma (at least 500 µL each) into carefully and unique labelled cryovials. Please check the patient number and planned sampling time. The visit, the exact time (hh:mm, 24 h-clock time) and date (month in letter) of sampling are to be recorded in the eCRF.

The plasma samples have to be stored at -20°C or below at the clinical site until shipment on dry ice to the logistic CRO.

They also will be stored at the analytical laboratory at -20°C or below until analysis.

Detailed handling instructions for plasma samples are provided in the ISF.

For quantification of cytarabine plasma concentrations, around 5 mL of venous blood will be taken in a lithium heparin -anticoagulant blood drawing tube (e.g. Vacutainer® or Monovette) at the time points specified in the flow charts and in appendix 10.1. THU (tetrahydrouridine) will be added immediately to the sampling tube in order to prevent catabolism of cytarabine. The sampling tube has to be mixed with the anticoagulant by gently inverting about 10 times. Vigorous shaking should be avoided to prevent haemolysis.

The whole blood is to be centrifuged at 4-25°C at approximately 3000 rpm (~2100 g) for at least 15 minutes. Please store the PK samples in an ice bath (up to 30 minutes) until centrifugation if they can’t be centrifuged immediately.

Transfer immediately two aliquots of heparinized plasma (at least 600 µL each) into carefully and unique labelled cryovials. Please check the patient number and planned sampling time. The visit, the exact time (hh:mm, 24 h-clock time) and date (month in letter) of sampling are to be recorded in the CRF.

The plasma samples have to be stored at -20°C or below at the clinical site until shipment on dry ice to the logistic CRO.

They also will be stored at the analytical laboratory at -20°C or below until analysis.

Detailed handling instructions for plasma samples are provided in the ISF.

[redacted]

5.6 BIOMARKER - PHARMACODYNAMIC SAMPLING

5.6.1 Methods and timing of sample collection

For direct analysis of effects of BI 6727 and/or cytarabine on the leukaemia cells, bone marrow aspirate samples (or peripheral blood if no bone marrow can be obtained, e.g. punctio sicca) will be collected at screening (all treatment schedules), at visit 2, i.e. 5±1 days after the end of the first BI 6727 infusion (treatment schedules A and B only), and on day 28 in the first cycle only (all treatment schedules). A total of about 5 mL of bone marrow aspirate from each patient (or 5 mL of peripheral blood if no bone marrow can be obtained) will be required for the pharmacodynamic analysis. The sampling of bone marrow will be performed according to standard procedure and only by experienced persons of the respective trial site. Bone marrow aspirate and peripheral blood from samples taken for screening and for response assessment at the end of the first treatment cycle will be used for comparison.

[redacted]

5.7 PHARMACOKINETIC - PHARMACODYNAMIC RELATIONSHIP

If the data suggest a pharmacokinetic / pharmacodynamic relationship of special parameters (e.g. neutrophil count), a detailed analysis may be performed.

5.8 DATA QUALITY ASSURANCE

The trial will be conducted in compliance with the protocol, the principles laid down in the Declaration of Helsinki version 1996 (please, refer to section 8), local law and according to the principles of GCP and the company standard operating procedures (SOPs). An investigator meeting will be performed prior to start of the trial to inform all investigators about the trial drugs and the procedures of the trial. Instead, each investigator could also be visited individually by the clinical monitor and the clinical research associate (CRA). Each investigator will receive an ISF with all information relevant for the performance of the trial.

Investigators will be visited at regular intervals for on-site monitoring by a Boehringer Ingelheim employee or a CRA authorised by BI. At these occasions, source data verification

(SDV) will be performed and a check will be done whether the eCRFs are kept current. The information in the eCRF and information in source documents will be cross-checked as described in section 8.2.4.

An audit may be performed if required or if Boehringer Ingelheim would decide to perform an audit.

The data management procedures to ensure the quality of the data are described in detail in the trial data management and analysis plan (TDMAP) available in the CTMF. Coding of the data obtained will be done by using the medical dictionary for regulatory activities (MedDRA) and the WHO dictionary for concomitant medication.

Data quality review meetings will be performed at regular intervals to evaluate the quality of the data collected. Discrepancies in data will be queried.

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

For the first treatment cycle it is recommended that the patients are hospitalised for the

treatment days until 24 hours after application of BI 6727. The decision concerning further hospitalisation is left to the discretion of the investigator.

In case a patient misses a visit and the patient belatedly reports to the investigator between the missed and the next scheduled visit, the delayed visit should be made and documented with the date of and the reason for the delayed visit. The next visit, should still take place at the scheduled time.

6.2 TRIAL PROCEDURES AT EACH VISIT

The investigations as outlined in the flow charts will be performed at the respective visits as described in detail in the following sections.

6.2.1 Screening and run-in phase

6.2.1.1 Screening Visit

The screening phase, i.e. the phase after informed consent and before the very first administration of the trial drug, may be as long as 14 days.
The following will be obtained and / or performed:

! Informed consent

! Demographics (sex, birth date, race)

! Medical history (oncological and relevant non-oncological)

! Review of inclusion and exclusion criteria (patient eligibility)

! Documentation of reasons why the patient is considered ineligible for intensive treatment

! Resting 12 lead-ECG (digital, triplicate)

! Blood sample for pharmacogenetic investigations (optional, only after signed separate informed consent)

! Physical examination, body height, weight, vital signs and ECOG performance score

! Concomitant therapy

! Safety laboratory, including coagulation parameters and urinalysis (see section 5.2.5)

! Serum pregnancy test for women of childbearing potential

! Disease assessment: peripheral blood and bone marrow evaluation for leukaemia, pharmacodynamics (FACS and cytospins see section 5.6), AML cytogenetics and molecular genetics (see section 5.3.4). Bone marrow aspiration performed before inclusion in the trial may be accepted as baseline assessment if done within fourteen days before first treatment administration
If applicable imaging (or other appropriate means of assessment) of extramedullary manifestation of leukaemia.

! Assignment / Randomisation

6.2.2 Treatment phase

6.2.2.1 Visit 1 – day 1

On the treatment days, the following will be obtained and / or performed:

! Review of inclusion and exclusion criteria (patient eligibility), in the first cycle only

! Body weight and ECOG performance score

! Vital signs at time points specified in the flow charts

! Adverse events (AEs)

! Changes in concomitant therapies

! ECG recording (digital, triplicate) at the following time points in treatment schedule A and B only (ECGs in cycle 1 are performed precisely at the related PK sampling time points)

- prior to start of infusion of BI 6727 (every treatment cycle)
- immediately before the end of infusion of BI 6727 (every treatment cycle)
- 2 hours after the start of infusion (= 1 hour after end of BI 6727 infusion) (1st treatment cycle only)
- 4 -6 hours after the start of infusion (= 3-5 hours after end of BI 6727 infusion) (1st treatment cycle only)
- 24 hours after the start of the infusion (= 23 hours after end of BI 6727 infusion) (1st treatment cycle only)

! Administration of BI 6727 after final confirmation of dose tier (schedules A and B)

! Administration of cytarabine (schedules A and C)

! Safety lab parameters before trial drug administration as specified in the flow charts and section 5.2.5

! Pharmacokinetic blood samples according to Tables 10.1.2: 1 - 10.2.1: 3 (Appendix 10.1) The date and time of blood sampling must be recorded in the eCRF.

! Disease assessment (clinical and in the blood)

! Bone marrow aspiration for pharmacodynamic analyses in treatment schedules A and B (FACS and cytospins see section 5.6) 24 hours after administration of BI 6727. **Pharmacodynamic bone marrow sampling only in the first cycle!**

6.2.2.2 Visit 2 – day 5±1

At visit 2 the following will be obtained and / or performed:

! Vital signs

! Adverse events

! Changes in concomitant therapy

! Administration of cytarabine (schedules A and C)

! Compliance check for and documentation of cytarabine administration on the scheduled previous days

! Safety lab as specified in the flow charts and section 5.2.5

! Pharmacokinetic blood samples according to Tables 10.1.2: 1 - 10.1.2: 2 (Appendix 10.1) (only schedules A and B). The date and time of blood sampling must be recorded in the eCRF.

! Disease assessment (clinical and in the blood)

After approval of Protocol Revision I, visit 2 is optional.

6.2.2.3 Visit 3 – day 10±2

At visit 3 the following will be obtained and / or performed:

! Vital signs

! Adverse events

! Changes in concomitant therapy

! Administration of cytarabine (schedules A and C)

! Compliance check for and documentation of cytarabine administration on the scheduled previous days (schedules A and C)

! Safety lab as specified in the flow charts and section 5.2.5

! Pharmacokinetic blood samples according to Tables 10.1.2: 1 - 10.1.2: 2 (Appendix 10.1) (only schedules A and B). The date and time of blood sampling must be recorded in the eCRF.

! Disease assessment (clinical and in the blood)

! After approval of Protocol Revision I, visit 2 is optional.

6.2.2.4 Visit 4 – day 15

6.2.2.4.1 Visit 4 – day 15 (for treatment schedules A and B)

At visit 4 the following will be obtained from and / or performed in patients allocated to treatment schedules A and B:

! Vital signs at time points specified in the flow charts

! Adverse events

! Changes in concomitant therapy

! Compliance check for and documentation of cytarabine administration on the scheduled previous days until day 10 (schedule A)

! ECG recording (digital, triplicate) at the following time points in treatment schedule A and B only (ECGs in cycle 1 are performed precisely at the related PK sampling time points)

- prior to start of infusion of BI 6727 (every cycle)
- immediately before the end of infusion of BI 6727 (every cycle)
- 2 hours after the start of infusion (= 1 hour after end of BI 6727 infusion) (1st treatment cycle only)
- 4 -6 hours after the start of infusion (= 3-5 hours after end of BI 6727 infusion) (1st treatment cycle only)

! Safety lab as specified in the flow charts and section 5.2.5

! Administration of the trial drug BI 6727

! Pharmacokinetic blood samples according to tables 1 (schedule A) and table 2 (schedule B) respectively in section 10.1.2 (Appendix 10.1) The date and time of blood sampling must be recorded in the eCRF.

! Disease assessment (clinical and in the blood)

6.2.2.4.2 Visit 4 – day 15±2 (for treatment schedule C)

At visit 4 the following will be obtained from and / or performed in patients allocated to treatment schedule C:

! Vital signs

! Adverse events

! Changes in concomitant therapy

! Compliance check for and documentation of cytarabine administration on the scheduled previous days until day 10

! Safety lab as specified in the flow charts and section 5.2.5

! Disease assessment (clinical and in the blood)

6.2.2.5 Visit 5 – day 19±2

At visit 5 the following will be obtained and / or performed:

! Vital signs

! Adverse events

! Changes in concomitant therapy

! Safety lab as specified in the flow charts and section 5.2.5

! Disease assessment (clinical and in the blood)

! After approval of Protocol Revision I, visit 2 is optional.

6.2.2.6 Visit 6 – day 23±2

At visit 6 the following will be obtained and / or performed:

! Vital signs

! Adverse events

! Changes in concomitant therapy

! Safety lab as specified in the flow charts and section 5.2.5

! Disease assessment (clinical and in the blood)

! After approval of Protocol Revision I, visit 2 is optional.

6.2.2.7 Visit 7 – day 28 + 3

A visit will be performed at the end of each treatment cycle, i.e. on day 28 (plus up to three days). This visit may coincide with day 1 of the following treatment cycle. A subsequent treatment cycle should not start earlier than day 29 of the 4-week cycle. Any delay of more than three weeks between the previous and the next treatment cycle should be discussed with the clinical monitor of BI.
If this visit coincides with day 1 of the following treatment cycle the examinations which are due at both visits need to be documented only in the eCRF pages of visit 7 and do not need to be replicated in the eCRF pages of visit 1.

! Physical examination including body weight and ECOG performance score

! Vital signs

! Adverse events

! Changes in concomitant therapy

! Safety lab as specified in the flow charts and section 5.2.5

! Serum pregnancy test for women of childbearing potential after every other cycle

! Pharmacokinetic blood samples according to Tables 10.1.2: 1 - 10.1.2: 2 (Appendix 10.1) (only schedules A and B). The date and time of blood sampling must be recorded in the eCRF.

! Disease assessment:

- peripheral blood evaluation for leukaemia
- bone marrow evaluation after the first treatment cycle for leukaemia and pharmacodynamics (FACS and cytospins see section 5.6), after first treatment cycle bone marrow evaluation according to 5.1.1. The bone marrow aspiration may be performed up to 3 days earlier depending on logistic requirements to allow for a timely continuation of therapy
- clinical assessment of disease
- if applicable imaging (or other appropriate means of assessment) of extramedullary manifestation of leukaemia

! Assessment of eligibility for a further treatment cycle

After approval of Protocol Revision I, physical examinations, weight, ECOG performance score, and safety laboratory examinations should be done as medically indicated at discretion of the investigator. The results are not required to be entered in the eCRF; documentation in the source data is sufficient. Only in case of findings that are qualifying as an (S)AE, the respective (S)AE will be reported (eCRF and SAE form, if applicable).
ECGs should be recorded prior to and at the end of volasertib infusions. No triplicate digital recording is required anymore. ECGs can be recorded with a local ECG machine. Transmission for central analysis will be discontinued.
Bone marrow aspirations and disease assessments only have to be done per local standard of practice to support the decision on further treatment with volasertib. These efficacy data will not be entered in the eCRF; documentation in the source data is sufficient.

6.2.3 End of treatment and follow-up

6.2.3.1 Visit at the End of treatment

The end of treatment (EoT) information has to be obtained when the patient discontinues the treatment along with the information obtained at the visit scheduled for that time point. If the patient concludes the trial within a treatment cycle and not at the end of a treatment cycle, the information required to be collected at the end of a cycle shall be obtained also (please refer to 6.2.2.7). Disease assessment needs to be done only if not yet performed within the past four weeks.

The following will be obtained and / or performed

! Resting 12-lead ECG (digital, triplicate)

! Physical examination, ECOG score, body weight

! Adverse events

! Outcome: in case the patient had PD the date of first diagnosis of PD has to be recorded

! Trial completion (including reason for conclusion or if applicable premature discontinuation of trial, date of last administration of the trial drug)

6.2.3.2 Follow-up visit

Follow-up visits will be performed after the EoT visit in case patients are not eligible for further treatment cycles until death, lost to follow-up or agreement between sponsor and coordinating investigator not to pursue further follow up visits. Follow-up visits should be performed at 12 weeks intervals or earlier if appropriate. Follow-up visits may also be performed by telephone interview in case the patient is unable to visit the investigator.
The following will be obtained and / or performed.

! ECOG performance score

! AEs since last visit in case they occurred during the observational period (6 weeks after the last trial drug administration) or are considered drug-related (see 5.2.1 and 8.4.1)

! Follow-up of AEs in case they were not yet recovered at EoT

! Outcome: date death (if applicable), date of progression (in case, the patient experienced PD)

! Treatment with any other antileukaemia drug (report date of treatment and drug)

After approval of Protocol Revision I, Follow-up is completed 21 days after discontinuation of study drug.

6.2.3.3 End of the whole trial

The clinical trial will be analyzed and reported after all patients enrolled in the phase II part have either stopped treatment or have been treated for at least four months (i.e. are expected to have received at least four treatment cycles). The timepoint for the report is chosen, because no major changes in the readout of the primary endpoint of phase II (response rate) are expected after patients have received ≥4 cycles. If patients are still ongoing in the trial or phase I schedule B is not yet completed at the time of the report, the clinical trial database will be kept open to collect additional data that will be reported in a revised report. If patients are still ongoing on treatment ~2 years after randomization of the last patient in phase II a revised clinical trial report might be generated with the clinical trial database still kept open to collect additional data. The trial will be completed as soon as the last patient has completed his / her last visit. The final results will be reported in a revised report.

In case the trial is ended by the sponsor when patients are still being treated with a clinical benefit from BI 6727, the patients will be offered to be treated in a follow-up trial which will be set up and allow patients to receive therapy with BI 6727.

6.3 REMOVAL OF PATIENTS FROM THERAPY OR ASSESSMENT

A patient has to be withdrawn from the trial in case one of the following criteria applies:

! A patient withdraws consent (patients are free to discontinue their participation in this trial at any time without the need to justify this decision).

! A treatment cycle has been delayed for more than three weeks for other than medical reasons

! A patient is no longer able to participate in the trial (e.g. AEs unrelated to therapy or disease progression, surgery, concomitant diagnoses, concomitant therapies or administrative reasons). The investigator may also stop a patient’s participation, if the patient is no longer able to attend trial visits.

! A patient is being administered forbidden concomitant medication (refer to section 4.2.2)

A patient can be withdrawn after discussion between the sponsor and the investigator if eligibility criteria are violated and / or the patient fails to comply with the protocol.

All withdrawals will be documented and the reason for withdrawal recorded and discussed, as necessary, in the final report of the trial. As soon as a patient is withdrawn from the trial, the next scheduled visit and the EoT have to be performed if feasible. Every effort should be made to follow-up patients in case an AE is still ongoing at the time of withdrawal. Patients who withdraw after assignment / randomisation and prior to the first treatment will not be included in the analysis data set for efficacy evaluation. They will be entered into the trial database, the reason for withdrawal will be documented and reported descriptively as well as by patient listing in the final trial report.

A patient has to discontinue trial drug administration in case

! DLT occurs which does not recover to a degree that allows treatment continuation or a second episode of DLT occurs in this patient or

! PD develops, including deterioration of general condition due to disease progression

Patients included in the phase I part who have not completed at least one cycle will be replaced unless they discontinued the trial due to drug-related AEs.
Patients allocated to treatment schedules A or B in the phase I part of the trial who for administrative reasons omitted the second infusion in the first 4-week cycle and were unable to receive the missed infusion within the next two days will be replaced.
Patients allocated to treatment schedules A in the phase I part of the trial who for administrative reasons omitted more than two doses of cytarabine in the first 4-week cycle will be replaced.

None of the patients randomized in the phase II part of the trial will be replaced for any reason.

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

The trial will be performed in two parts, a phase I part and a phase IIa part. In the phase I part of the trial, BI 6727 will be investigated as monotherapy and in combination with LD-Ara-C in patients with relapsed/refractory AML. In the phase I part, the dose of BI 6727 will be escalated to determine the maximum tolerated dose (MTD) of BI 6727 monotherapy and BI 6727 in combination with LD-Ara-C in relapsed/refractory AML patients who are ineligible for other treatment options.

In the phase IIa part, the combination of BI 6727 at MTD with LD-Ara-C and LD-Ara-C monotherapy will be investigated to determine the efficacy of the combination schedule in comparison to LD-Ara-C monotherapy in previously untreated AML patients that are considered ineligible for intensive treatment.

7.1 STATISTICAL DESIGN - MODEL

The trial will be performed as an open label study. In phase I patients will not be randomized; they will be assigned to the treatment schedule that is being filled at the time the patient is ready to enter the trial (BI 6727 monotherapy and BI 6727 in combination with LD-Ara-C, respectively). In phase IIa 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 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 (R04-0569) (see section 4.1.3). Intra-individual dose escalation will be allowed according to the rules specified in section 4.1.4.

7.2 NULL AND ALTERNATIVE HYPOTHESES

The analyses will thoroughly explore all aspects of the efficacy and safety of BI 6727 in combination with LD-Ara-C. 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.

7.3 PLANNED ANALYSES

Two analysis populations are defined for efficacy and safety analyses. For the phase I part the full analysis 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 BI 6727 will be considered, including the patients who have been replaced for any reason (see section 6.3).

For the phase II part the full analysis 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.

7.3.1 Primary analyses

7.3.1.1 Assessment of the MTD and derived variables for first cycle only

One primary objective for this study is the tolerability and safety of BI 6727 as monotherapy and in combination with cytarabine, respectively, as reflected by the MTD (for definition of MTD please refer to 5.2.4).

In addition, to determine the MTD, an analysis on conditional probabilities for a DLT given the dose will be done, based on the logistic regression model.

For the analysis of the tolerability and safety, please refer to section 7.3.3.

7.3.1.2 Assessment of the primary efficacy endpoint and derived variables

The primary endpoint for efficacy is best objective response derived from the data of all cycles. The primary analysis will be done for all patients of the full analysis set (phase II) for all treatment schedules separately. Each patient will be assigned to one of the response categories described in section 5.1.1.1.

Each patient's best response will be used as a primary measure. To describe response over time, the proportions of patients in each response category will be tabulated at specified time intervals.

The number of patients with objective response (best response is CR or CRi) will be summarised. Patients will be followed up for assessment of response and progression until they progress, receive any other anti-leukaemia therapy, die, or until the trial ends. The observed length of follow-up and the number of patients available for analysis at each time point will determine the period of time covered in tables and figures.

7.3.1.3 Statistical group comparison

All statistical group comparisons will be performed with respect to the full analysis 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. The conditional power for showing superiority of a treatment schedule with respect to the control schedule at a later time point will be evaluated. The conditional power will be compared to a given fixed value that is based on assumptions for the information time and for the significance level of the (hypothetical) statistical test at a later time point (see also section 7.6.2).

Odds ratios, confidence intervals, and Fisher's exact test will be used to compare treatments in an exploratory manner if appropriate. Additionally, the conditional power for showing superiority at a later time point will be evaluated. 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.

7.3.2 Secondary analyses

7.3.2.1 Assessment of the secondary endpoints and derived variables

Secondary endpoints related to efficacy will be event free survival, overall survival, relapse-free survival, and remission duration.

Event free survival, overall survival, relapse-free survival

Event free survival (EFS) is defined as the duration of time from randomisation to time of treatment failure (i.e. PD), relapse from CR, or death from any cause, whichever comes first. Overall survival is the time from randomisation until death. Relapse-free survival is defined only for patients who achieve CR and is measured from the date of attaining CR until the date of recurrence or death from any cause, whichever occurs first.

In case there is no occurrence of death or treatment failures until the last visit of the trial the time will be censored. The percentage of patients who are event free will be displayed at monthly or greater time intervals as appropriate.

The causes of death will be summarised, along with whether death was plausibly related to disease progression.

Remission duration, response rate at different time points

Exploratory analyses will be performed to determine the remission duration and the response rate after specified time intervals. Analysis of remission duration will only be done for patients who achieve CR.

7.3.3 Safety analyses

The occurrence of dose limiting toxicity (DLT) as well as the incidence and intensity of adverse events graded according to CTCAE, laboratory parameters, vital signs and duration of neutropenia will be evaluated.

All patients of the full analysis set (both phase I and phase II) will be included in the safety analyses.

Two analyses will be performed. The first analysis of safety will be performed for the first part of the trial (determination of the MTD, first cycle only, treatment regime=initial dose at the start of the treatment, full analysis set (phase I only)). This descriptive analysis will evaluate the MTD for each treatment schedule. The second analysis will be performed with

respect to all cycles and will act as a support for the determination of the MTD (full analysis set (both phase I and phase II)).

Incidence and intensity of adverse events

The severity, and timing of adverse events will indicate how well the treatment regimen is tolerated. Toxicities will be evaluated using the CTCAE grading scheme.

The overall incidence and intensity of adverse events, as well as relatedness of adverse events to treatment with BI 6727 monotherapy and in combination with cytarabine, respectively, will be reported for all treatment schedules.

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.

Descriptive statistics will be used to describe changes in laboratory tests over time. In addition, all abnormalities of potential clinical relevance will be reported.

Events that started within the period starting with first administration of the trial drug and ending six weeks after the first treatment administration in the last treatment cycle will be considered as having occurred during treatment. In general, later events will be attributed to the post-study period and will be presented separately. However, post-study events will be examined to determine whether they need to be combined with on-treatment events in an additional table.

ECG measurements

Prolonguation of QT/QTc times will be analysed descriptively and exploratory based on the ECG measurements described in Section 5.2.7. Further details of the analysis of ECG data will be specified in the statistical analysis plan.

7.3.4 Interim analyses

Early analyses of response to therapy will be performed before completion of recruitment in order to support internal strategic decision making and planning for future clinical trials. In order to avoid bias of these early efficacy analyses on trial conduct, the results will not be distributed to trial sites before database lock for the CTR (see section 6.2.3.3). The analyses will be performed when approximately 50% of planned patients in the phase II part of the trial have either stopped treatment or completed at least two treatment cycles. Details of the early analyses of response to therapy will be specified in the interim trial statistical analysis plan. The early efficacy analyses will be documented and archived. If considered necessary for internal strategic decision making the early efficacy analysis may be repeated once when approximately 70% of planned patients in the phase II part of the trial have either stopped treatment or completed at least two treatment cycles.

After all patients of treatment schedule A that are contained in the full analysis set (phase I) have either completed at least one course of BI 6727 in combination with cytarabine or

dropped out of the study, a safety analysis will be performed. For this purpose a database snapshot will be performed. The safety analysis will summarize results regarding safety of the patients in the phase I part and will contain the determination of the MTD as well as a recommendation for the dose of BI 6727 to be used in the phase II part of the study. The selection of the recommended dose for the phase II part will consider overall safety observed during all treatment cycles. No efficacy comparisons will be performed in this phase I safety analysis. Detailed specifications of the phase I safety analysis are provided in the TSAP. The phase I safety analysis will be documented and archived.
For other safety purposes database snapshots can be performed as deemed appropriate.

7.3.5 Pharmacokinetic methods

7.3.5.1 Pharmacokinetic analyses

The following basic pharmacokinetic parameters will be calculated in cycle 1 for BI 6727 in plasma for schedules A and B on visits 1 and 4 and for cytarabine in plasma for schedule C on visits 1 and 3 (refer to section 10.1).

Additional parameters may be determined if deemed necessary:

- C_{max} (maximum measured concentration of BI 6727 or cytarabine in plasma)
- t_{max} (time from dosing to maximum measured concentration)
- $AUC_{0-\infty}$ (area under the concentration-time curve of BI 6727 or cytarabine in plasma over the time interval from 0 extrapolated to infinity)
- AUC_{0-24} (area under the concentration-time curve of BI 6727 or cytarabine in plasma over the time interval from 0 to 24)
- $t_{1/2}$ (terminal half-life of BI 6727 or cytarabine in plasma)
- MRT (mean residence time of BI 6727 or cytarabine in the body after intravenous or subcutaneous administration, respectively)
- CL (total clearance of BI 6727 in plasma after intravascular administration)
- CL/F (total clearance of cytarabine in plasma after subcutaneous administration)
- V_z (apparent volume of distribution during the terminal phase λ_z following a intravascular dose of BI 6727)
- Vz /F (apparent volume of distribution during the terminal phase λ_z following a subcutaneous dose of cytarabine)
- V_{ss} (apparent volume of distribution at steady state following intravascular administration of BI 6727)

Pharmacokinetic parameters after first and second administration will be compared in a descriptive manner.

The pharmacokinetic parameters C_{max}, $AUC_{0-\infty}$ and AUC_{0-24} will be explored with respect to dose proportionality (if more than 2 doses are investigated).

All evaluable patients will be included in the pharmacokinetic analysis. A patient is considered to be not evaluable if the subject has an important protocol violation relevant to the evaluation of pharmacokinetics or has insufficient data. Patients who are considered as not evaluable will be listed with their individual plasma concentrations and individual pharmacokinetic parameters, however, will not be included in descriptive statistics for plasma concentrations, pharmacokinetic parameter evaluation or other statistical assessment.

The following descriptive statistics will be calculated for BI 6727 and cytarabine concentrations as well as for all pharmacokinetic parameters: N, arithmetic mean, standard deviation, minimum, median, maximum, arithmetic coefficient of variation, geometric mean, geometric coefficient of variation. Descriptive statistics of concentrations at specific time points will be calculated only when at least 2/3 of the individuals have concentrations within the validated concentration range. The overall sample size to decide whether the “2/3 rule” is fulfilled will be based on the total number of samples intended to be drawn for that time point. Descriptive statistics of parameters will be calculated only when at least 2/3 of the individuals have parameters. The overall sample size to decide whether the “2/3 rule” is fulfilled will be based on the total number of patients included in the analysis of the parameter.

Pharmacokinetic parameters of cytarabine dosed along with BI 6727 will be compared in a descriptive manner to those of cytarabine dosed alone to assess the effect of BI 6727 on cytarabine pharmacokinetics. Similarly, pharmacokinetic parameters of BI 6727 obtained in treatment schedule A will be compared to the parameters obtained in treatment schedule B to assess the effect of cytarabine on BI 6727 pharmacokinetics.

Refer to Appendix 10.1 for details concerning derivation of pharmacokinetic parameters.

7.3.5.2 Pharmacogenetic analyses

Pharmacogenetic analyses will be carried out using an explorative approach on anonymised samples, if they are deemed helpful to interpret the pharmacokinetics, efficacy, and safety data of BI 6727.

7.4 HANDLING OF MISSING DATA

Every effort will be made to obtain complete information on all AEs, with particular emphasis on potential dose limiting toxicities.

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

The occurrence of missing data should be minimised by follow-up of patients for both disease progression and mortality after end of trial for an individual patient. Both response and progression status for patients who are lost to follow-up or who die before progression has been documented, will be assessed at the end of the trial.

Laboratory value: Missing baseline laboratory values will be imputed by respective values from the screening visit.

Pharmacokinetic parameters

Concentration data identified with NOS (no sample), NOR (no valid result), NOA (not analyzed), BLQ (below the limit of quantification), and NOP (no peak detectable) will be ignored and not replaced by zero at any time point (applies also to the lag phase). Descriptive statistics of concentrations at specific time points will be calculated only when at least 2/3 of the individuals have concentrations within the validated concentration range. The overall sample size to decide whether the "2/3 rule" is fulfilled will be based on the total number of samples intended to be drawn for that time point (i.e. BLQ, NOR, NOS, NOA, NOP are included).

In the noncompartmental analysis, concentration data identified with NOS, NOR, and NOA will not be considered. BLQ and NOP values in the lag phase will be set to zero. The lag phase is defined as the period between time zero and the first time point with a concentration above the quantification limit. All other BLQ/NOP values of the profile will be ignored.

If the predose concentration is less than or equal to 5 percent of C_{max} value in that subject, the subject's data without any adjustments can be included in all pharmacokinetic measurements and calculations (i.e. the predose value will not be changed to zero). If the predose value is greater than 5 percent of C_{max}, the subject should be dropped from all statistical evaluations. The individual pharmacokinetic parameters can be calculated and listed separately.

Every effort will be made to include all concentration data in an analysis. If not possible, a case to case decision is required whether the value should only be excluded from half-life estimation or the complete analysis.

- If a concentration is only excluded from half-life determination, it will be used for all other calculations (e.g. descriptive statistics) and for graphical presentation

- If a concentration value is excluded from all calculations, it will not be presented graphically or used for the calculation of descriptive statistics and parameter determination. However, the excluded concentration itself will be listed in the tables in section 15 of the clinical trial report associated with an appropriate flag.

Descriptive statistics of parameters are calculated only when at least 2/3 of the individual parameter estimates of a certain parameter are available. If the actual sampling time will not be recorded or will be missing for a certain time point, the planned time will generally be used for this time point instead. Pharmacokinetic parameters which cannot be determined will be identified by "not calculated" (NC).

7.5 RANDOMISATION

In the phase I part of the trial patients will be assigned, not randomized, into escalating dosage groups by order of admission into the trial.

Randomisation will be performed in the phase IIa part of this trial. In phase IIa, equal numbers of patients will be randomised to the respective treatment schedules. The medical data service will provide randomisation envelopes that are generated using a validated system.

An eligible patient is reported by fax to the clinical monitor at Boehringer Ingelheim; in phase I the patient will be assigned to the treatment schedule (according to 4.1.2), in the phase IIa part the clinical monitor will open the next randomisation envelope in the predetermined order. The result of the assignment / randomisation along with the appropriate starting dose (in phase I part) will be communicated to the investigator by the clinical monitor (for more information please refer to section 4.1.2 and the ISF).

7.6 DETERMINATION OF SAMPLE SIZE

7.6.1 Determination of the maximum tolerated dose

In oncology trials, the “standard design” is a rule-based up-and-down scheme using cohorts of three patients (e.g. 3+3 design, or the modified Fibonacci dose escalation, see Edler and Burkholder in Crowley (R07-0220)). The operating characteristics of the standard design are discussed in different papers and are summarized by Storer in Crowley (R07-0220). The standard design and all other designs, that approach the MTD from below, will tend to yield a low estimate of the MTD. In addition, it is “robust”, that means that the design will determine a reasonable MTD and that escalation will be sensible, given the observed DLTs (see Potter R07-0223).

Table 7.6: 1 shows the probabilities of two or more out of six patients to be observed with DLT for some assumed probabilities of experiencing DLT in a certain dose group. There will be a probability of at least 80 % for two or more patients to exhibit DLT, if the underlying individual probability for a patient in that dose group to reach DLT is 42 % or larger.

Table 7.6: 1 Probability of observing DLT in patients experiencing dose limiting toxicity, from binomial distribution

Individual probability of observing DLT	0.40	0.42	0.45
Probability of observing DLT in two or more out of six patients	0.77	0.80	0.84

Thus, the determined MTD is defined as the highest dose of the treatment drug (BI 6727 for the two different schedules) at which no more than one out of six patients experience DLT in the first cycle.

For the planned sample size it is assumed that 5 different dosage groups are needed per treatment schedule with 2 additional dosage tiers of 3 patients (3+3 design). It is assumed that the average number of patients in a dosage group as well as in a dosage tier will be 3 (including replacement patients).

Altogether this leads to an estimated sample size of 21 patients per treatment schedule. Note that this calculation does so far not include any additional patients to be included at the presumptive MTD. Naturally, the calculated sample size of 21 patients per treatment schedule represents only a rough estimation since the number of patients needed is induced by the 3+3 design and is subject to different influencing factors.

7.6.2 Calculation of phase II sample size based on stopping for futility

Sample size calculation for phase II of this trial are based on the comparison between the treatment schedules (BI 6727 combined with cytarabine) and the control schedule (cytarabine mono therapy)

The calculation of the phase II sample size is based on a stopping for futility approach (R07-2799, R07-2798). The calculated sample size is based on the assumption that the actual phase II trial represents an interim analysis of a (hypothetical) phase III trial that tests on stopping for futility. The test decision (with respect to phase II) is made by looking at the conditional p-value obtained at the time of interim analysis and comparing it to a given fixed value, the critical p-value. Obviously, in this setting, the critical p-value equals the type I error probability. A characteristic that can be derived from the critical p-value is the conditional power. It provides quantitative information about the probability that a treatment schedule will show superiority compared to a control schedule subject to the response information available at interim analysis.

It is assumed that the response rate of the mono treatment schedule (control schedule) is given as 15%, whereas the response rate of a combination therapy is 30%. The overall type I error is chosen as 5% (one-sided), the overall power as 65%, and the information fraction (number of patients at interim analysis divided by total number of patients) as 60%. Altogether this leads to a sample size of 86 patients for the interim analysis, i.e. 43 per treatment schedule. With respect to the (hypothetic) interim analysis, which is the actual phase II comparison, a power of 78.3% and a type I error (the critical p-value) of 18.9% is achieved with a critical conditional power value of 23.6% (under the current trend hypothesis, see R07-2799; all calculations performed with EAST 5).

In summary, this means that with a total sample size of 86 patients (43 patients per treatment schedule) a power of 78.3% can be achieved with a type I error of 18.9 % and a critical conditional power of 23.6%.

If the response rate of the combination therapy is assumed to be 25 % instead of 30 % the calculated sample size, leading to the identical power values and error probabilities as above, rises to 174 patients (87 per treatment schedule).

8. ADMINISTRATIVE MATTERS

The trial will be carried out in compliance with the protocol, the principles laid down in the Declaration of Helsinki, version as of October 1996 (as long as local laws do not require to follow other versions), in accordance with the ICH Harmonised Tripartite Guideline for Good Clinical Practice (GCP) and relevant BI SOPs. Standard medical care (prophylactic, diagnostic and therapeutic procedures) remains in the responsibility of the treating physician of the patient.

Insurance Cover: The terms and conditions of the insurance cover are made available to the investigator and the patients via documentation in the ISF (Investigator Site File).

8.1 ETHICS

8.1.1 Independent Ethics Committee or Institutional Review Board

The trial will not be initiated before the protocol and informed consent and patient information form have been reviewed and received approval / favourable opinion from the local Independent Ethics Committee (IEC) and approval by the Competent Authority (CA), as required by local laws and regulations. Should a CTP amendment be made that needs IRB / IEC approval and authority notification/approval, the changes in the CTP will not be instituted until the amendment and revised informed consent (if appropriate) have been reviewed and received approval / favourable opinion from the local IEC and the CA, as required by local laws and regulations. A CTP amendment intended to eliminate an apparent immediate hazard to patients may be implemented immediately providing that the regulatory authority and IRB / IEC are notified as soon as possible and an approval is requested. CTP amendments exclusively for logistical or administrative changes may be implemented with notification to the IEC and CA only.

The constitution of the IEC must meet the requirements of ICH GCP and of the participating country / countries. A list of the IEC members who attended the meeting when the CTP / CTP amendment was discussed, including names and qualifications, needs to be provided by the IEC to the sponsor. The sponsor must provide to the regulatory authorities the name and address of the IEC along with a statement from the IEC that it is organised according to GCP and the applicable laws and regulations. The IEC must perform all duties outlined by the requirements of ICH GCP and of the participating country / countries.

8.1.2 Patient Information and Informed Consent

Prior to patient participation in the trial, written informed consent must be obtained from each patient (or the patient's legally accepted representative) according to ICH GCP and to the regulatory and legal requirements of the participating country. Each signature must be personally dated by each signatory and the informed consent and any additional patient-information form retained by the investigator as part of the trial records. A signed copy of the informed consent and any additional patient information must be given to each patient or the patient's legally accepted representative.

The patient must be informed that his/her personal trial-related data will be used by Boehringer Ingelheim in accordance with the local data protection law. The level of disclosure must also be explained to the patient.

The patient must be informed that his / her medical records may be examined by authorised monitors (CML/CRA) or Clinical Quality Assurance auditors appointed by Boehringer Ingelheim, by appropriate IEC members, and by inspectors from regulatory authorities.

Should a CTP amendment become necessary, the patient consent form and patient information form may need to be revised to reflect the changes to the CTP. It is the responsibility of the sponsor to ensure that an amended consent form is reviewed and has received approval / favourable opinion from the IEC and CA, as required by ICH GCP and by local laws and regulations, and that it is signed by all patients subsequently entered in the trial and those currently in the trial, if affected by the amendment.

8.2 RECORDS

8.2.1 Drug accountability

Drug supplies, which will be provided by the sponsor and a CRO appointed by the sponsor, must be kept in a secure, limited access storage area under the storage conditions defined by the sponsor. Where necessary, a temperature log must be maintained to make certain that the drug supplies are stored at the correct temperature.

The investigator or pharmacist or her/his delegate must maintain records of the product's delivery to the trial site, the inventory at the site, the use by each patient, and the return to the sponsor or alternative disposition of unused product(s). These records will include dates, quantities, batch/serial numbers, expiry ('use by') dates, and the unique code numbers assigned to the investigational product(s) and trial patients. The investigator or pharmacist will maintain records that document adequately that the patients were provided the doses specified by the CTP and reconcile all investigational products received from the sponsor. At the time of return to the sponsor or the appointed CRO, the investigator or pharmacist must verify that all unused or partially used drug supplies have been returned by the clinical trial patient and that no remaining supplies are in the investigator's possession.

8.2.2 Emergency code break

Not applicable.

8.2.3 Case Report Forms (CRFs)

All of the clinical data will be captured via electronic data capture (EDC) using ~~athe Oracle Clinical~~ Remote Data Capture system, a web-based tool. The investigator site staff will enter and edit the data via a secure network, with secure access features (username, password and secure identification or username and password – an electronic password system). A complete electronic audit trail will be maintained. The investigator will approve the data using an electronic signature (Ref: 21 CFR Part 11), and this approval is used to confirm the accuracy of the data recorded.

Electronic CRFs (eCRFs) will be used for all patients. The investigator's data will be accessible from the investigator's site throughout the trial. Relevant medical history prior to enrolment will be documented at the baseline visit. Thereafter during the trial, narrative statements relative to the patient's progress during the trial will be maintained. The electronic CRFs must be kept current to reflect patient status at each phase during the course of the trial. The patients must not be identified on the electronic CRF by name. Appropriate coded identification (i.e. Patient Number) must be used. The investigator must make a separate confidential record of these details (patient identification code list) to permit identification of all patients enrolled in a clinical trial in case follow-up is required. While a trial is ongoing and until the access to the database has been terminated, there will be no Documentation of Changes (DOCs). All changes will be requested from the investigator through the EDC system. If a change is necessary once the investigator has no further access to the database, a DOC will be sent to the investigator for confirmation of the change. The investigator's signature is requested to show he/she agrees with the change that was made. The original DOC is kept by the investigator.

Copies of the electronic CRF together with all data changes made will be supplied to the investigator at the end of the trial. The investigator will be responsible for retaining all records pertaining to the trial as specified in the appropriate contract.

8.2.4 Source documents

Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data reported on the CRFs or entered in the eCRFs that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the trial; also current medical records must be available.

For eCRFs all data must be derived from source documents.

8.2.5 Direct access to source data - documents

The investigator / institution will permit trial-related monitoring, audits, IRB / IEC review and regulatory inspection, providing direct access to all related source data / documents. CRFs/eCRFs and all source documents, including progress notes and copies of laboratory and medical test results must be available at all times for review by the sponsor's clinical trial monitor, auditor and inspection by health authorities (e.g. FDA). The Clinical Research Associate (CRA) / on site monitor and auditor may review all CRFs/eCRFs, and written informed consents. The accuracy of the data will be verified by reviewing the documents described in Section 8.2.4.

8.3 QUALITY ASSURANCE AUDIT

A quality assurance audit of this trial may be conducted by the sponsor or sponsor's designees. The quality assurance auditor will have access to all medical records, the

investigator's trial-related files and correspondence, and the informed consent documentation of this clinical trial.

8.4 PROCEDURES

8.4.1 Adverse events

An adverse event (AE) is defined as any untoward medical occurrence, including an exacerbation of a pre-existing condition, in a patient in a clinical investigation who received a pharmaceutical product. The event does not necessarily have to have a causal relationship with this treatment.

All adverse events occurring during the course of the clinical trial (i.e., from signing the informed consent onwards through the observational phase) will be collected, documented and reported to the sponsor by the investigator according to the specific definitions and instructions detailed in the 'Adverse Event Reporting' section of the Investigator Site File.

A serious adverse event (SAE) is defined as any AE which results in death, is immediately life-threatening, results in persistent or significant disability / incapacity, requires or prolongs patient hospitalisation, is a congenital anomaly / birth defect, or is to be deemed serious for any other reason if it is an important medical event when based upon appropriate medical judgement which may jeopardise the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions.

All adverse events, serious and non-serious, will be fully documented on the appropriate eCRFs. For each adverse event, the investigator will provide the onset, end, intensity, treatment required, outcome, seriousness and action taken with the investigational drug. The investigator will determine the relationship of the investigational drug to all AEs as defined in the 'Adverse Event Reporting' Section of the Investigator Site File.

The basis for judging the intensity of the AE will be based on the CTCAE criteria version 3.0 (R04-0474). The basis for judging the causal relationship between the investigational product and the AE is described below.

Causal relationship

Medical judgment should be used to determine the relationship, considering all relevant factors, including pattern of reaction, temporal relationship, de-challenge or re-challenge, confounding factors such as concomitant medication, concomitant diseases and relevant history. Assessment of causal relationship should be recorded in the case report forms.

- Yes: There is a reasonable causal relationship between the investigational drug administered and the AE.
- No: There is no reasonable causal relationship between the investigational drug administered and the AE.

If a SAE is reported from a still blinded trial, the causal relationship must be provided by the investigator for all potential trial drugs, i.e. the BI trial drug and for all other trial drugs (i.e. any active comparator or placebo according to the trial design).

The investigator has the obligation to report AEs during the specified observational phase. If defined in the CTP, the investigator also has the responsibility to report AEs occurring in a certain period after a patient completes the trial. Any AEs reported to the sponsor during this phase must be documented in the safety database.

If not stipulated differently in the ISF, SAEs are to be reported to the sponsor using the BI Serious Adverse Event Report Form including a documented causal relationship assessment and providing as much detail regarding the SAE as possible. With receipt of follow-up information, all remaining fields on the SAE form are to be completed or updated.

Any serious or significant AE, whether or not considered related to the investigational product, and whether or not the investigational product has been administered, must be reported immediately by telephone / fax to the sponsor. Expedited reporting of serious adverse events, e.g. suspected unexpected serious adverse reactions (SUSARs), will be done according to local regulatory requirements. Further details regarding this reporting procedure are provided in the ISF.

Following every such telephone / fax report, the Clinical Monitor must provide a written report of the serious or significant AE and any sequelae to Corporate Drug Safety according to the appropriate Corporate SOP(s). These narratives, which confirm the information collected by telephone, may give additional information not available at the time of the initial report.

8.4.2 Emergency procedures

Not applicable.

8.5 RULES FOR AMENDING PROTOCOL

All CTP amendments must be documented, dated and signed by all signatories (or their successors) of the original protocol. This also applies to any local amendment that may become necessary. Amendments (excluding those exclusively for administrative or logistical changes) need to be submitted to the IEC for approval and to the competent authority (CA) for approval. Local Amendments will only be submitted in the countries / centres concerned.)

8.6 DISCONTINUATION OF THE TRIAL BY THE SPONSOR

Boehringer Ingelheim reserves the right to discontinue the trial at any time for the following reasons:

1.) Failure to meet expected enrolment goals overall or at a particular trial site,

2.) emergence of any efficacy/safety information that could significantly affect continuation of the trial

3.) violation of GCP, the CTP, or the contract by a trial site or investigator, disturbing the appropriate conduct of the trial.

The investigator / the trial site will be reimbursed for reasonable expenses incurred in case of trial termination (except in case of the third reason).

8.7 STATEMENT OF CONFIDENTIALITY

Individual patient medical information obtained as a result of this trial is considered confidential and disclosure to third parties is prohibited with the exceptions noted below. Patient confidentiality will be ensured by using patient identification code numbers.

Treatment data may be given to the patient's personal physician or to other appropriate medical personnel responsible for the patient's welfare. Data generated as a result of the trial need to be available for inspection on request by the participating physicians, the sponsor's representatives, by the IEC and the regulatory authorities, i.e. the CA.

8.8 PUBLICATION POLICY

Boehringer Ingelheim is as much as possible dedicated to support process of free exchange of relevant scientific information. Any publication of the result of this trial must be consistent with the Boehringer Ingelheim publication policy. The rights of the investigator and of the sponsor with regard to publication of the results of this trial are described in the investigator contract. As a general rule, no trial results should be published prior to finalisation of the Clinical Trial Report (CTR).

8.9 COMPLETION OF TRIAL

The EC/competent authority in each participating EU member state needs to be notified about the end of the trial (last patient/patient out, unless specified differently in Section 6.2.3 of the CTP) or early termination of the trial.

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10. APPENDICES

10.1 PHARMACOKINETIC METHODS

10.1.1 Derivation of pharmacokinetic parameters

BI 6727 or Cytarabine plasma concentrations will be plotted graphically versus time for all subjects as listed in the plasma concentration-time tables for both analytes. For the presentation of the mean profiles, the arithmetic/geometric mean and the planned blood sampling times will be used.

Concentrations will be used for calculations in the format that is reported in the bioanalytical report. The data format for descriptive statistics of concentrations will be identical with the data format of the respective concentrations. For the calculation of pharmacokinetic parameters, only concentrations within the validated concentration range will be used. The descriptive statistics of pharmacokinetic parameters will be calculated using the individual values with the number of decimal places as provided by the evaluation program. Then the individual values as well as the descriptive statistics will be reported with three significant digits in the clinical trial report. The actual sampling times will be used. For predose samples, the actual sampling time will be set to zero.

Concentration data identified with NOS (no sample available), NOR (no valid result), NOA (not analyzed), BLQ (below the limit of quantification), and NOP (no peak detectable) will be ignored and not replaced by zero at any time point (applies also to the lag phase including the pre-dose value). Descriptive statistics of concentrations at specific time points will be calculated only when at least 2/3 of the individuals have concentrations within the validated concentration range. The overall sample size to decide whether the "2/3 rule" is fulfilled will be based on the total number of samples intended to be drawn for that time point (i.e., BLQ, NOR, NOS, NOA, NOP are included).

Non-compartmental pharmacokinetic parameters will be determined using WinNonlin or another validated program.

In the non-compartmental analysis, concentration data identified with NOS, NOR, and NOA will not be considered. BLQ and NOP values in the lag phase will be set to zero. The lag phase is defined as the period between time zero and the first time point with a concentration above the quantification limit. All other BLQ and/or NOP values of the profile will be ignored.

If the predose concentration before the first dose is less than or equal to 5% of C_{max} value in that subject, the subject's data without any adjustments can be included in all pharmacokinetic measurements and calculations (i.e., the predose value will not be changed to zero). If the predose value is greater than 5% of C_{max}, the subject should be dropped from all statistical evaluations. The individual pharmacokinetic parameters can be calculated and listed separately.
Every effort will be made to include all concentration data in an analysis. If not possible, a

case to case-to-case decision is required whether the value should only be excluded from half-life estimation or the complete analysis.

- If a concentration is only excluded from half-life determination, it will be used for all other calculations (e.g., descriptive statistics) and for graphical presentation.

- If a concentration value is excluded from all calculations, it will not be presented graphically or used for the calculation of descriptive statistics and parameter determination. . However, the excluded concentration itself will be listed in the clinical trial report associated with an appropriate flag.

Descriptive statistics of parameters are calculated only when at least 2/3 of the individual parameter estimates of a certain parameter are available. If the actual sampling time will not be recorded or will be missing for a certain time point, the planned time will generally be used for this time point instead. Pharmacokinetic parameters which cannot be determined will be identified by "not calculated" (NC).

C_{max} and t_{max}: Individual C_{max} and t_{max} values will be directly determined from the plasma concentration time profiles of each subject. If the same C_{max} concentration occurs at different time points, t_{max} is assigned to the first occurrence of C_{max}.

Estimation of λ_z: The apparent terminal rate constant λ_z will be estimated from a regression of ln(C) versus time over the terminal log-linear disposition portion of the concentration-time profiles. The log-linear profiles, which include the regression line through the terminal points, will be checked via visual inspection, and it will be determined whether the regression appropriately represents the terminal slope. A minimum of three points will be used in the determination of λ_z. If the last concentration-time point increases, this time point may be included if the $t_{1/2}$ estimate is reasonable. If λ_z is not determinable then consequently only parameters not requiring λ_z will be reported. In addition, the lower ($t_{\lambda z,start}$) and upper ($t_{\lambda z,end}$) limit on time for values to be included in the calculation of λ_z will be listed.

$t_{1/2}$: The terminal half-life will be calculated from the terminal rate constant using the equation

$$t_{1/2} = \frac{\ln 2}{\lambda_z}$$

AUC: The area under the curve will be calculated using the linear up/log down algorithm. If an analyte concentration is equal to or higher than the preceding concentration, the linear trapezoidal method will be used. If the analyte concentration is smaller than the preceding concentration, the logarithmic method will be used.

Linear trapezoidal rule ($t_2 > t_1$ and $C_{t2} \geq C_{t1}$):

The area of the trapezoid between the two data points (t_1, C_{t1}) and (t_2, C_{t2}) will be computed by:

$$AUC_{t1\text{-}t2} = 0.5 \times (t_2 - t_1) \times (C_{t1} + C_{t2})$$

Logarithmic trapezoid rule ($t_2 > t_1$ and $C_{t2} < C_{t1}$):

The area of the trapezoid between the two data points (t_1, C_{t1}) and (t_2, C_{t2}) will be computed by:

$$AUC_{t1-t2} = \frac{(t_2 - t_1) \times (C_{t2} - C_{t1})}{\ln(C_{t2}/C_{t1})}$$

$AUC_{0\text{-}\infty}$: The area under the plasma concentration-time curve over the time interval from 0 extrapolated to infinity will be calculated according to the following equation

$$AUC_{0\text{-}\infty} = AUC_{0\text{-}tz} + \frac{C'_{tz}}{\lambda_z}$$

where C'_{tz} is the concentration predicted by the regression line for the time t_z (time of last measurable concentration of the analyte in plasma). The area under the concentration-time curve over the time interval from 0 to the last quantifiable plasma concentration ($AUC_{0\text{-}tz}$) will be calculated by the linear up/log down method as described above.

$\%AUC_{tz\text{-}\infty}$: The percentage of the $AUC_{0\text{-}\infty}$ will be obtained by extrapolation according to the following equation:

$$\%\,AUC_{tz-\infty} = \frac{AUC_{0\text{-}\infty} - AUC_{0\text{-}tz}}{AUC_{0\text{-}\infty}} \times 100$$

MRT: The mean residence time after intravenous bolus injection will be calculated as follows:

$$MRT = \frac{AUMC_{0-\infty}}{AUC_{0-\infty}}$$

In order to compare the mean residence time after intravenous bolus administration (MRT) and intravenous infusion (MRT_{inf}), the following equation will be used in addition, where T represents the infusion time.

$$MRT = MRT_{inf} - (T \times 0.5)$$

The area under the first moment curve from time 0 to infinity ($AUMC_{0-\infty}$) is calculated according to:

$$AUMC_{0-\infty} = AUMC_{0-tz} + \frac{C'_{tz} \times tz}{\lambda_z} + \frac{C'_{tz}}{\lambda_z^2}$$

CL: The total clearance after intravenous administration will be determined according to the following equation:

$$CL = \frac{Dose}{AUC_{0-\infty}}$$

(F = absolute bioavailability factor)

V_z: The apparent volume of distribution during the terminal phase after intravascular administration will be determined according to the following equation:

$$V_z = \frac{CL}{\lambda_z}$$

V_{ss}: After single intravenous bolus administration or intravenous infusion when the mean residence time has been adapted as described above, the distribution volume in the steady state will be calculated according:

$$V_{ss} = CL_{ss} \times MRT_{ss}$$

gMean, gCV: The geometric mean (gMean) and coefficient of variation, gCV (given in %), will be calculated by the formulae:

$$gMean = \exp\left[\frac{1}{n}\sum_{i=1}^{n}\ln(x_i)\right] = \exp\left[\overline{\ln(x_i)}\right]$$

$$gCV(\%) = 100 \cdot \sqrt{\exp\left[Var(\ln(x_i))\right] - 1}$$

where

$$Var(\ln(x_i)) = \frac{1}{n-1}\sum_{i=1}^{n}\left[\ln(x_i) - \overline{\ln(x_i)}\right]^2 .$$

10.1.2 Blood sampling time schedule

Table 10.1.2: 1 Time schedule for blood sampling during treatment schedule A, treatment with both, BI 6727 on days 1 and 15 and cytarabine on Days 1 to 10

Treatment Period	Visit	Day	CRF Time/PTM	Event	Sample No	Analysed for BI 6727	Analysed for cytarabine
Cycle 1	1	1	-0:05	PK Blood + ECG	C1 S1	X	X
			0:00 Start of admin .	Drug admin			
			0:30	PK Blood	C1 S2	X	X
			1:00 Just before end of BI 6727 infusion	PK Blood + ECG	C1 S3	X	X
			1:30	PK Blood	C1 S 4	X	X
			2:00	PK Blood + ECG	C1 S5	X	X
			3:00	PK Blood	C1 S6	X	X
			4:00[1]	PK Blood + ECG	C1 S7	X	X
			24:00	PK Blood + ECG	C1 S8	X	
	2	5	96:00	PK Blood	C1 S9	X	
	3	10	216:00 Last dose of cytarabine	PK Blood	C1 S10	X	
	4	15	335:55	PK Blood +	C1 S11	X	

Treatment Period	Visit	Day	CRF Time/PTM	Event	Sample No	Analysed for BI 6727	Analysed for cytarabine
				ECG			
			336:00 Start of BI 6727 infusion	Drug admin			
			336:30	PK Blood	C1 S12	X	
			337:00 Just before end of BI 6727 infusion	PK Blood + ECG	C1 S13	X	
			337:30	PK Blood	C1 S14	X	
			338:00	PK Blood + ECG	C1 S15	X	
			339:00	PK Blood	C1 S16	X	
			340:00[1]	PK Blood + ECG	C1 S17	X	
	7	28	648:00[2]	PK Blood	C1 S18	X	
Cycle 2	1	1	-0:05	PK Blood + ECG	C2 S1	X	X
			0:00 Start of BI 6727 infusion	Drug admin			
			1:00 Just before end of BI 6727 infusion	PK Blood + ECG	C2 S2	X	X

[1] sampling between 4 and 6 hours after dose administration of BI 6727
[2] Sample taken any time during visit 7 at the end of cycle 1

Please note: Blood samples during and at the end of infusion have to be taken from the opposite arm than the infusion arm.

Table 10.1.2: 2 Time schedule for blood sampling during treatment schedule B, treatment with BI 6727 on days 1 and 15

Treatment Period	Visit	Day	CRF Time/PTM	Event	Sample No	Analysed for BI 6727
Cycle 1	1	1	-0:05	PK Blood + ECG	C1 S1	X
			0:00 Start of BI 6727 Infusion	Drug admin		
			0:30	PK Blood	C1 S2	X
			1:00 Just before end of BI 6727 infusion	PK Blood + ECG	C1 S3	X
			1:30	PK Blood	C1 S4	X
			2:00	PK Blood + ECG	C1 S5	X
			3:00	PK Blood	C1 S6	X
			4:00[1]	PK Blood + ECG	C1 S7	X
			24:00	PK Blood + ECG	C1 S8	X
	2	5	96:00	PK Blood	C1 S9	X
	3	10	216:00	PK Blood	C1 S10	X
	4	15	335:55	PK Blood + ECG	C1 S11	X
			336:00 Start of BI 6727 Infusion	Dose admin		
			336:30	PK Blood	C1 S12	X
			337:00 Just before end of BI 6727 infusion	PK Blood + ECG	C1 S13	X
			337:30	PK	C1 S14	X

Treatment Period	Visit	Day	CRF Time/PTM	Event	Sample No	Analysed for BI 6727
				Blood		
			338:00	PK Blood + ECG	C1 S15	X
			339:00	PK Blood	C1 S16	X
			340:00[1]	PK Blood + ECG	C1 S17	X
	7	28	648:00[2]	PK Blood	C1 S18	X
Cycle 2	1	1	-0:05	PK Blood + ECG	C2 S1	X
			0:00 Start of BI 6727 infusion	Drug admin		
			1:00 Just before end of BI 6727 infusion	PK Blood + ECG	C2 S2	X

[1] Sampling between 4 and 6 hours after dose administration of BI 6727
[2] Sample taken any time during visit 7 at the end of cycle 1

Please note: Blood samples during and at the end of infusion have to be taken in the opposite arm of the infusion arm.

Table 10.1.2: 3 Time schedule for blood sampling during treatment schedule C, treatment with cytarabine on Days 1 to 10

Treatment Period	Visit	Day	CRF Time/PTM	Event	Sample No	Analysed for cytarabine
Cycle 1	1	1	-0:05	PK Blood	C1 S1	X
			0:00 Start of cytarabine administration.	Drug admin		
			0:30	PK Blood	C1 S2	X
			1:00	PK Blood	C1 S3	X
			1:30	PK Blood	C1 S4	X
			2:00	PK Blood	C1 S5	X
			3:00	PK Blood	C1 S6	X
			4:00[1]	PK Blood	C1 S7	X

[1] sampling between 4 and 6 hours after dose administration of cytarabine