Clinical Trial Protocol

Doc. No.: c02543230-04

BI Trial No.:	1315.1
BI Investigational Product:	BI 836858
Title:	A Phase I, open-label, cohort dose escalation trial with BI 836858 in patients with refractory or relapsed acute myeloid leukemia and patients with acute myeloid leukemia in complete remission with high risk to relapse
Clinical Phase:	I
Trial Clinical Monitor:	Phone: Fax:
Co-ordinating Investigator:	Phone: Fax:
Status:	Revised Protocol (based on Global Amendments 01, 02, and 03)
Version and Date:	**Version: 4.0** **Date: 28 APRIL 2016**

CLINICAL TRIAL PROTOCOL SYNOPSIS

Name of company: Boehringer Ingelheim		**Tabulated Trial Protocol**	
Name of finished product: Not applicable			
Name of active ingredient: BI 836858			
Protocol date: 21 DEC 2011	**Trial number:** 1315.1		**Revision date:** **28 APRIL 2016**
Title of trial:	A Phase I, open-label, cohort dose escalation trial with BI 836858 in patients with refractory or relapsed acute myeloid leukemia and patients with acute myeloid leukemia in complete remission with high risk to relapse		
Co-ordinating Investigator:			
Trial sites:	Multi-centre trial		
Clinical phase:	I		
Objectives:	To investigate the maximum tolerated dose (MTD), safety and tolerability, pharmacokinetics and efficacy of BI 836858 monotherapy in acute myeloid leukemia (AML) patients with refractory or relapsed AML and patients with AML in complete remission (CR) with high risk to relapse		
Methodology:	Open-label cohort dose escalation		
No. of patients:	Planned number: about 63		
total entered:	About 36 (for refractory or relapsed AML) and 27 (for AML patients in CR)		
each treatment:	About 3-6 (per dose cohort, for each patient population)		
Diagnosis :	Acute Myeloid Leukemia		
Main criteria for inclusion:	Adult patients with relapsed or refractory AML AND Patients with AML in CR with high risk to relapse defined as: a) AML patients with non-favorable genetics (according to European LeukemiaNet (ELN) classification) that are in CR after having received induction and consolidation chemotherapy and are not candidates for allogeneic hematopoietic stem cell transplantation (SCT) (e.g., no donor available, not eligible/fit enough) or b) AML patients with non-favorable genetics (according to ELN classification) that are in CR after allogeneic hematopoietic stem cell transplantation		

Name of company: Boehringer Ingelheim		**Tabulated Trial Protocol**	
Name of finished product: Not applicable			
Name of active ingredient: BI 836858			
Protocol date: 21 DEC 2011	**Trial number:** 1315.1		**Revision date:** **28 APRIL 2016**

Test product:	BI 836858
dose:	The starting dose for BI 836858 will be - 10 mg for refractory or relapsed AML patients and - 40 mg for AML patients in CR with high risk to relapse
mode of admin.:	Intravenous (i.v.) infusion
Comparator products:	Not applicable
Duration of treatment:	<u>Patients with refractory or relapsed AML</u> Patients are eligible for up to 8 repeated administrations as long as neither patient nor Investigator requests treatment discontinuation. Patients with clinical benefit, defined by the International Working Group (IWG) as having objective response (partial remission (PR) or complete remission (CR) or complete remission with incomplete blood recovery (CRi)) or subjective response (in the absence of objective response) after 8 administrations and who are tolerating the infusions, may continue until progressive disease (PD) <u>AML patients in CR with high risk to relapse</u> The first three administrations will be given every second week, on day 1 of Cycles 1, 2 and 3. From the 4th administration onwards, patients will receive monthly (every second cycle) infusions of BI 836858 (i.e. 4th infusion on Cycle 5 Day 1, 5th infusion on Cycle 7 Day 1, etc.) for overall up to one year of treatment unless these patients relapse or infusions are not tolerated. Patients are eligible for repeated administrations as long as neither patient nor Investigator requests treatment discontinuation.
Criteria for efficacy:	Progression-free survival, time to treatment failure Best overall response applies only to refractory or relapsed AML patients. applies only to AML patients in CR.
Criteria for safety:	Maximum tolerated dose, incidence and intensity of adverse events graded according to the common terminology criteria for adverse events (CTCAE, version 4.0), incidence of dose-limiting toxicity, vital signs, ECG, physical examination and laboratory parameters.
Statistical methods:	Descriptive statistics.

FLOW CHART - A (REFRACTORY OR RELAPSED PATIENTS)

Trial Periods	**Screen**	**Treatment***				**EOT**	**Further Treatment****			**FU**
	Screen	**Cycle 1 – Cycle 4 (1 Cycle = 14 days)**				**EOT**	**FTE**		**EOFT**	**FU**
Visit	**1**	**Cx V1**	**Cx V2**	**Cx V3**	**Cx V4**		**Cx V1**	**Cx V2**		
Days (in respective cycle)*	**-14 to -1**	**1**	**4 ±1[1]**	**8**	**11 ±1[1]**		**1**	**8**		
Informed consent	x									
Informed consent for pharmacogenetics	x									
Demographics and baseline conditions	x									
Medical history	x									
Review of in-/exclusion criteria	x	x [2]								
Dose assignment	x [3]									
LABS/SAFETY ASSESSMENTS										
Safety laboratory parameters incl. urinalysis[4]	x	x	x[1]	x	x[1]	x	x	x	x	x
Physical examination ECOG performance status	x	x[5]				x	x[5]		x	x
Vital signs, height[6], weight [6]	x	x	x	x	x	x	x	x	x	x
Serum pregnancy test [7]	x	x				x	x		x	
12 lead-ECG	x	x				x			x[8]	
Adverse events	x	x	x	x	x	x	x	x	x	x
Concomitant therapy	x	x	x	x	x	x	x	x	x	x[9]
DISEASE ASSESSMENTS										
Bone marrow aspiration	x	x[10]		x[10]		x[11]			x[8, 11]	x[11]
TRIAL MEDICATION										
Drug Administration		x		x			x	x		
Eligibility for further administration		x[16]		x[16]		x[16,17]	x[16, 17]	x[16, 17]		
End of active trial treatment						x				
End of further treatment									x	
Other therapy for AML										x
Vital Status										x

EOT: End of treatment evaluation, including an evaluation for further treatment. Those patients with clinical benefit, PR, CRi, or CR after 8 administrations and who are tolerating the infusions well may continue until PD or other criteria for withdrawal are met as noted in Section 3.3.4.1. For those patients who will receive more than 8 administrations, this visit is to be performed 7 days (±2 days) after the 8th administration of BI 836858. For those patients who receive ≤ 8 administrations, this visit is to be performed 14 days (±2 days) after the last administration of BI 836858.

FTE: Further treatment evaluation. Each patient who will receive more than 8 administrations will have a FTE visit for each infusion. The visit numbers are 6, 7, 8, etc. until the patient discontinues.

EOFT: End of further treatment. For each patient who receives more than 8 administrations, there will be an end of further treatment evaluation. This visit is to be performed 14 days (±2 days) after the last administration of BI 836858.

FU: Follow-up, starts after the last administration of BI 836858, visits at least every 4 weeks until 6 months after the last administration of BI 836858.

* The planned duration of a treatment cycle is 14 days; there will be two administrations of BI 836858 per cycle.

** These visits are only for those patients with clinical benefit, PR, CRi or CR after 8 administrations and who are tolerating the infusions well who continue until PD or other criteria for withdrawal are met as noted in Section 3.3.4.1.

1 Visit window of ±1 day only allowed beginning in Cycle 3 and for all subsequent cycles. In Cycles 1 and 2 visit window not allowed due to the PK schedule as outlined in Tables 1a and 2a.

2 Review of inclusion/exclusion criteria during screening and again on day of first administration.

3 After informed consent and review of inclusion/exclusion criteria (timing described in footnote 2).

4 For details refer to Section 5.2.3.1. Urine has to be measured only at screening, EOT, EOFT and FU visits. Safety laboratory assessments may be completed up to 2 days prior to administration. An additional safety lab will be collected on day 2 (i.e., 24 hours after the first administration of BI 836858). Other lab tests to be included: Haptoglobin, direct antiglobulin test, bilirubin (direct and indirect) and free hemoglobin.

5 Only every second cycle (i.e. before cycle 1, 3, 5, 7 etc.) Physical examination may be completed up to 2 days prior to administration. Eastern Cooperative Oncology Group (ECOG) score must be completed on the day of the administration. If the first administration of BI 836858 occurs within 3 days of the screening visit, these examinations do not need to be repeated.

6 Height and weight only at day 1 of first administration of BI 836858; weight also at EOT and EOFT.

7 For women of childbearing potential only. Serum pregnancy test is to be completed at odd numbered administrations only (e.g. administration 1, 3, 5, etc.).

8 ECG, bone marrow aspiration, tests will be performed at EOFT only if the patient has completed at least 2 cycles (e.g. received 4 administrations) since the EOT visit.

9 Concomitant therapy during FU is collected only if indicated for treatment of adverse event.

10 Bone marrow aspirate to assess efficacy before 5th and 9th administrations (i.e., BM performed on Day 1 (+/- 1) of cycles 3 and 5 and treatment started on day 1 (up to +3 days) of cycles 3 and 5) (see Section 5.1.2).

11 Only one sample to be collected at the time of PD or the time of initiation of other anti-leukemia therapy, which may be at the EOT/EOFT, if PD or initiation of other anti-leukemia therapy occurs during treatment, or during follow-up. If the patient is non-progressing/not receiving other anti-leukemia therapy at the end of follow-up or the trial, the sample will be obtained at the last follow-up visit for this patient.

16 Can be performed up to 2 days prior to this visit.

17 After the 8th infusion, at the end of treatment visit, patients will be evaluated to determine if they have clinical benefit, as defined by IWG objective response (PR, CRi or CR) or subjective response (in the absence of objective response) and are tolerating the infusions well and who would like to continue to receive infusions until PD or other criteria for withdrawal are met as noted in Section 3.3.4.1. For each infusion past the 8th administration, patients will continue to be assessed after each cycle for clinical benefit (objective or subjective response), and that they are tolerating the infusions well and would like to continue until PD or other criteria for withdrawal are met as noted in Section 3.3.4.1.

FLOW CHART - B (AML PATIENTS IN CR)

Trial Periods	**Screen**	**Treatment***			**Further Treatment****			**End of Treatment**	**End of Residual Effect Period and Follow-up 1**	**Follow-up**
		Cycle 1 – Cycle 3 (1 Cycle = 14 days)			**FTE (every 2nd cycle; Cycles 5, 7, 9…21)**			**EoT**	**EoR/FU1**	**FU2 to FU6**
Visit	**1**	**Cx V1**	**Cx V2**	**Cx V3**	**Cx V1**	**Cx V2**	**Cx V3**	As soon as possible but not later than one week after permanent discontinuation of trial medication	Not earlier than 30 days after permanent discontinuation of trial medication	Every 4 weeks
Days (in respective cycle)*[1]	**-14 to -1**	**1**	**2**	**8**	**1**	**2**	**8**			
Informed consent	x									
Informed consent for pharmacogenetics	x									
Demographics and baseline conditions	x									
Medical history	x									
Review of incl-/excl criteria	x	x[2]								
Dose assignment	x[3]									
LABS/SAFETY ASSESSMENTS										
Safety laboratory parameters incl. urinalysis[4]	x	x	x		x			x	x	x
Physical examination and ECOG performance status[5]	x	x[5]			x[5]			x		x
Vital signs, height[6], weight[6]	x	x	x		x			x	x	x
Serum pregnancy test [7]	x	x			x			x		
12 lead-ECG	x	x			x			x	x[8]	
Adverse events	x	x	x	x	x	x	x	x	x	x
Concomitant therapy	x	x	x	x	x	x	x	x	x	x[9]
DISEASE ASSESSMENT										
Bone marrow (BM) aspiration[10]	x	x						x		x
Disease assessment w/ PB and clinical assessment		x			x			x		
Disease assessment w/ BM or biopsy [12]		x			x			x		
TRIAL MEDICATION										
Drug Administration		x			x			x		
Eligibility for further administration		x			x[16]					
End of active trial treatment								x		
Other therapy for AML								x	x	x
Vital Status										x

EOT: End of treatment evaluation. The EOT visit will be performed as soon as possible but no later than one week (7 days) after permanent discontinuation of trial medication for any reason, or when the Investigator decides with the patient to permanently discontinue the trial medication.

FTE: Further treatment evaluation. Each patient who will receive more than 3 administrations will have a FTE visit for each infusion. The visits are completed on day 1 of every second cycle (i.e. 5, 7, 9, etc.) until the patient discontinues or completes up to 12 months of therapy. Infusions are every 2 weeks for the first 3 cycles then for FTE, these treatments are monthly.

EoR: The End of Residual End Period visit should not be performed earlier than 30 days after permanent discontinuation of the trial medication.

FU: Follow-up visits after the last administration of BI 836858 completed, at least every 4 weeks until 6 months after the last administration of BI 836858. In case patients do not visit the site, the FU visit can be conducted by phone.

* The planned duration of a treatment cycle is 14 days; there will be one administration of BI 836858

** These visits are only for those patients after 3 administrations and who are tolerating the infusions well who continue until PD or other criteria for withdrawal are met as noted in Section 3.3.4.1. These visits occur every second cycle (i.e., Cycles 5, 7, 9…21)

1 Visit window of ±1 day only allowed beginning in Cycle 9. In Cycles 1 through 7 visit window not allowed due to the PK schedule as outlined in Tables 1b and 2b.

2 Review of inclusion/exclusion criteria during screening and again on day of first administration.

3 After informed consent and review of inclusion/exclusion criteria (timing described in footnote 2).

4 For details refer to Section 5.2.3.1. Urine has to be measured only at screening, FTE, EOT and FU visits. Safety laboratory assessments may be completed up to 2 days prior to administration. An additional safety lab will be collected on day 2 (i.e., 24 hours after the first administration of BI 836858). Other lab tests to be included: Haptoglobin, direct antiglobulin test, bilirubin (direct and indirect) and free hemoglobin.

5 At screening and every second cycle (i.e. before cycle 1, 3, 5, 7 etc.) Physical examination may be completed up to 2 days prior to administration. Eastern Cooperative Oncology Group (ECOG**)** score must be completed on the day of the administration. If the first administration of BI 836858 occurs within 3 days of the screening visit, these examinations do not need to be repeated.

6 Height and weight only at day 1 of first administration of BI 836858; weight also at EOT.

7 For women of childbearing potential only. Serum pregnancy test to be completed at odd numbered administrations only (e.g., administration 1, 3, 5, etc.)

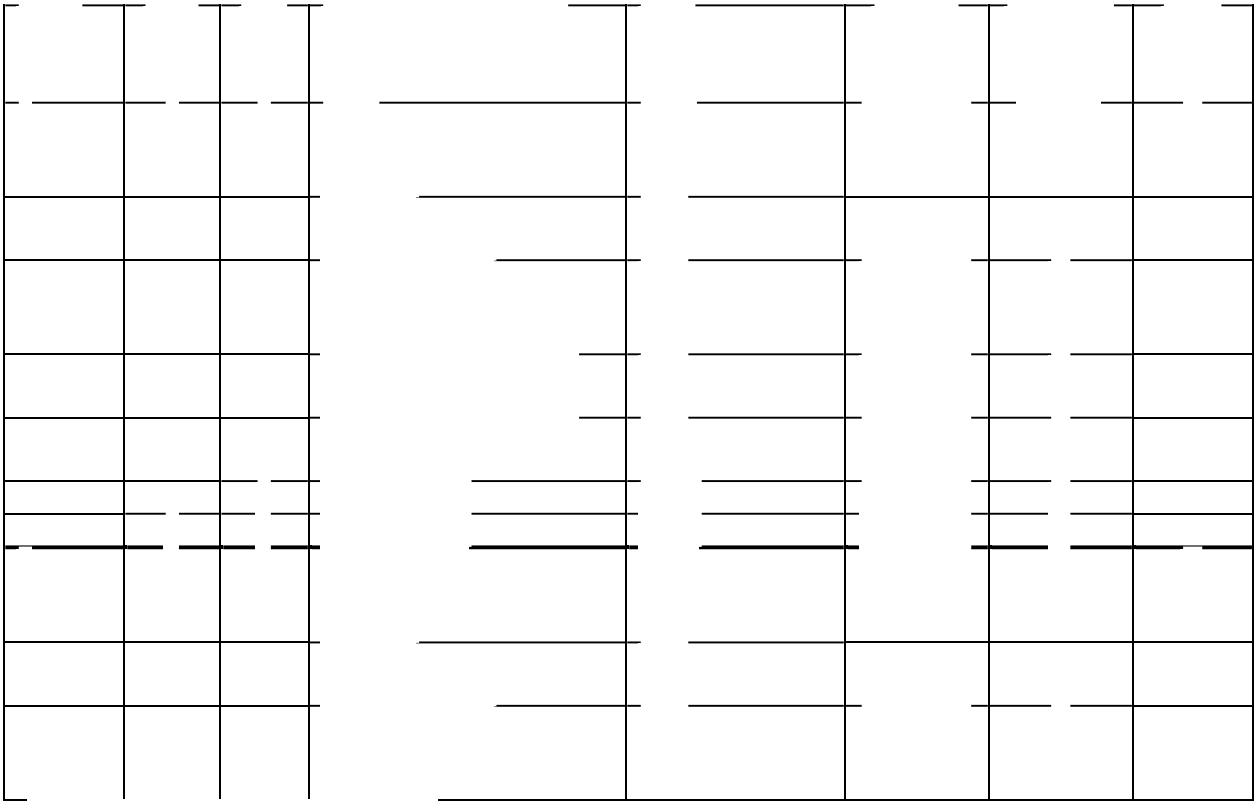
8 ECG will be performed at visit 1 of each cycle and at EoR if abnormal at EOT.

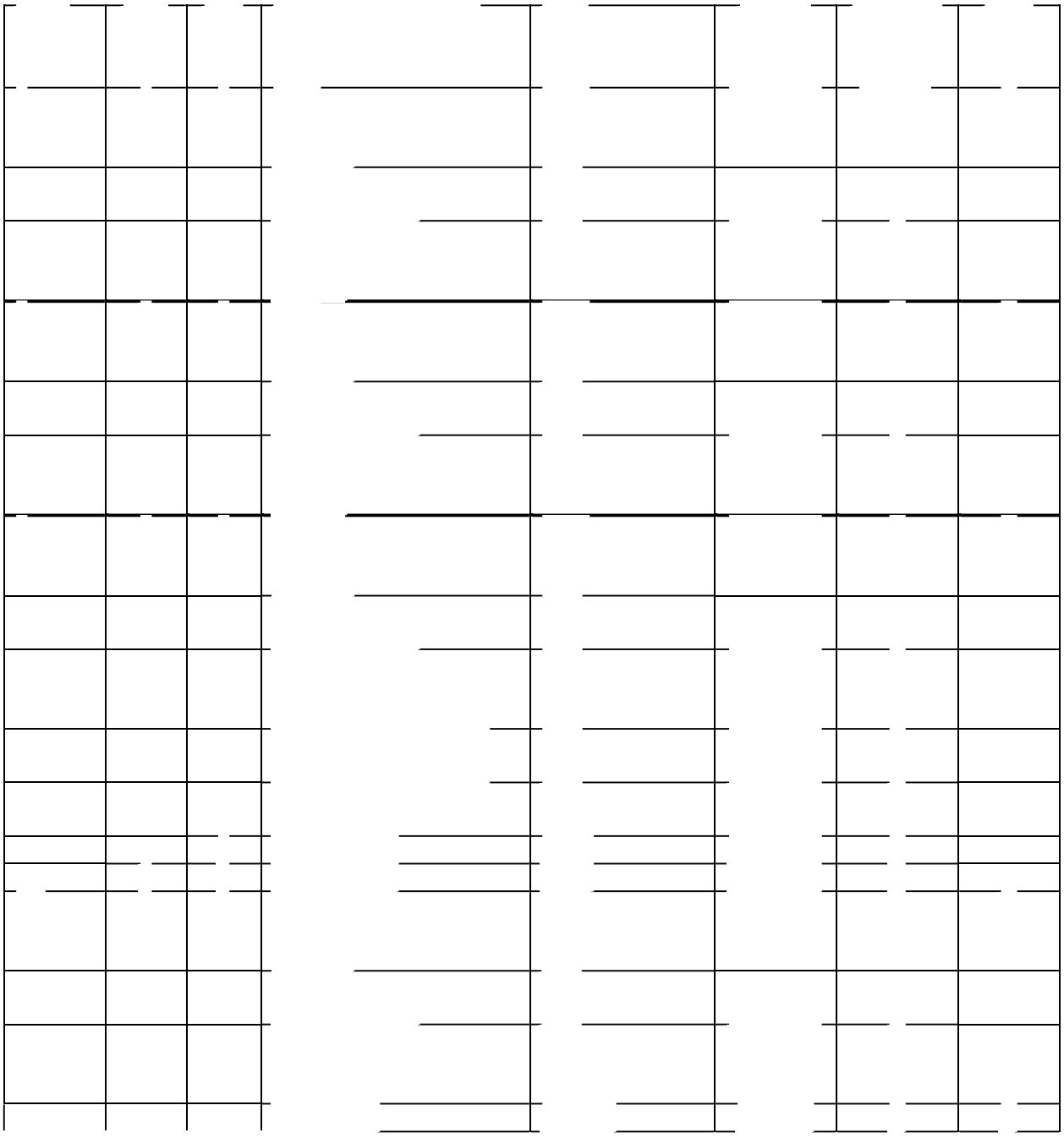
9 Concomitant therapy during FU is collected only if indicated for treatment of adverse event.

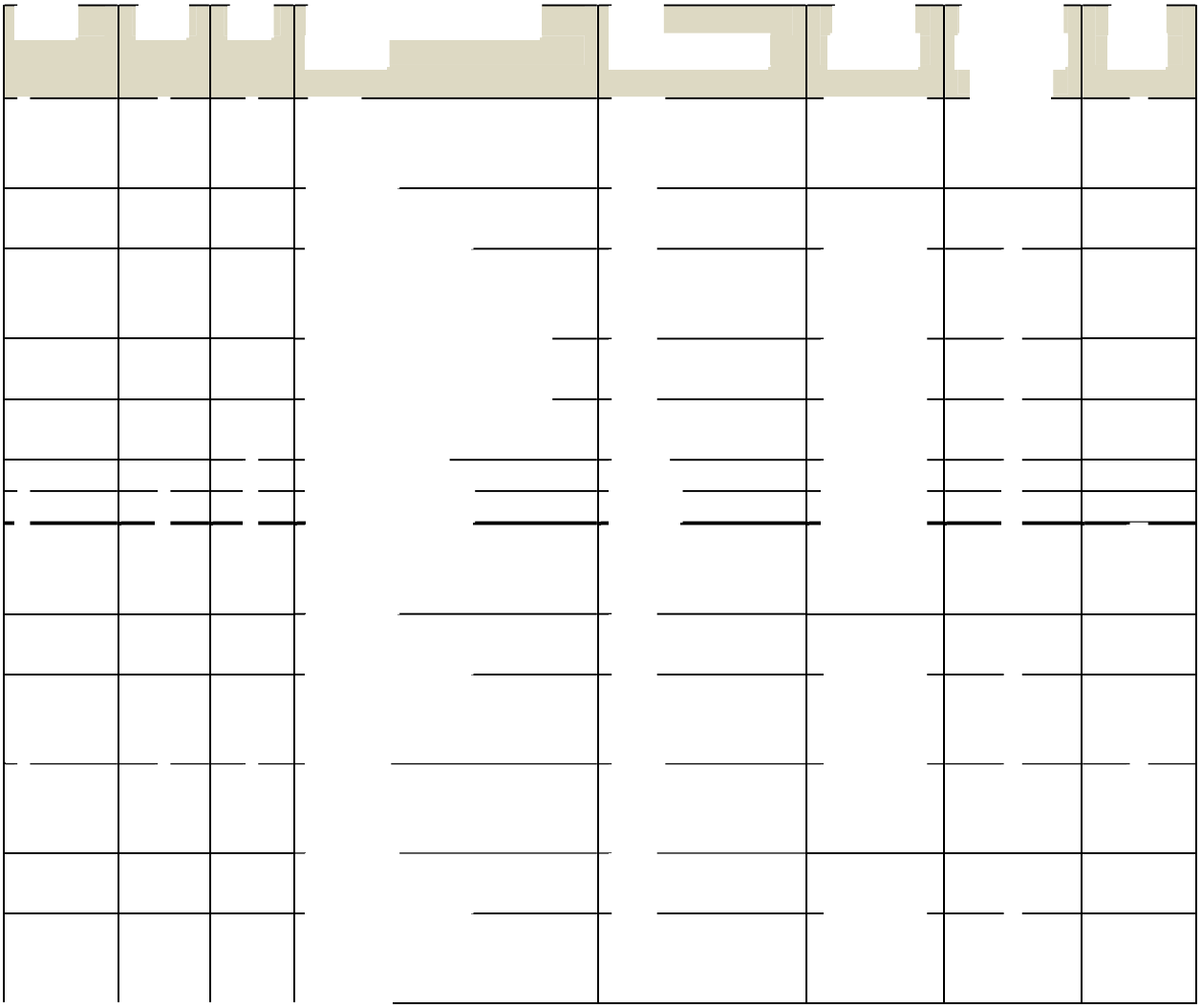
10 Bone marrow aspirate to be performed, at investigator discretion, if there is suspicion of relapse.

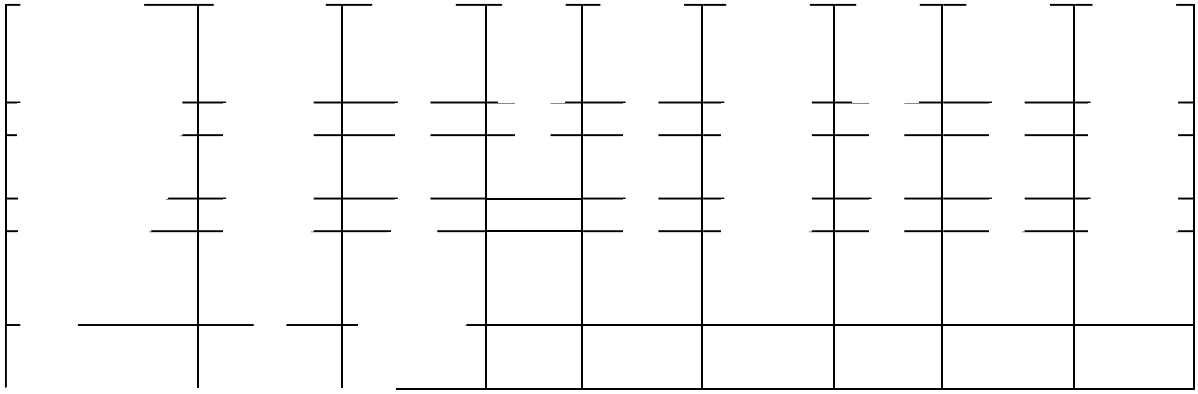
12 Disease assessment with bone marrow (or biopsy) is to be performed if suspicion of relapse

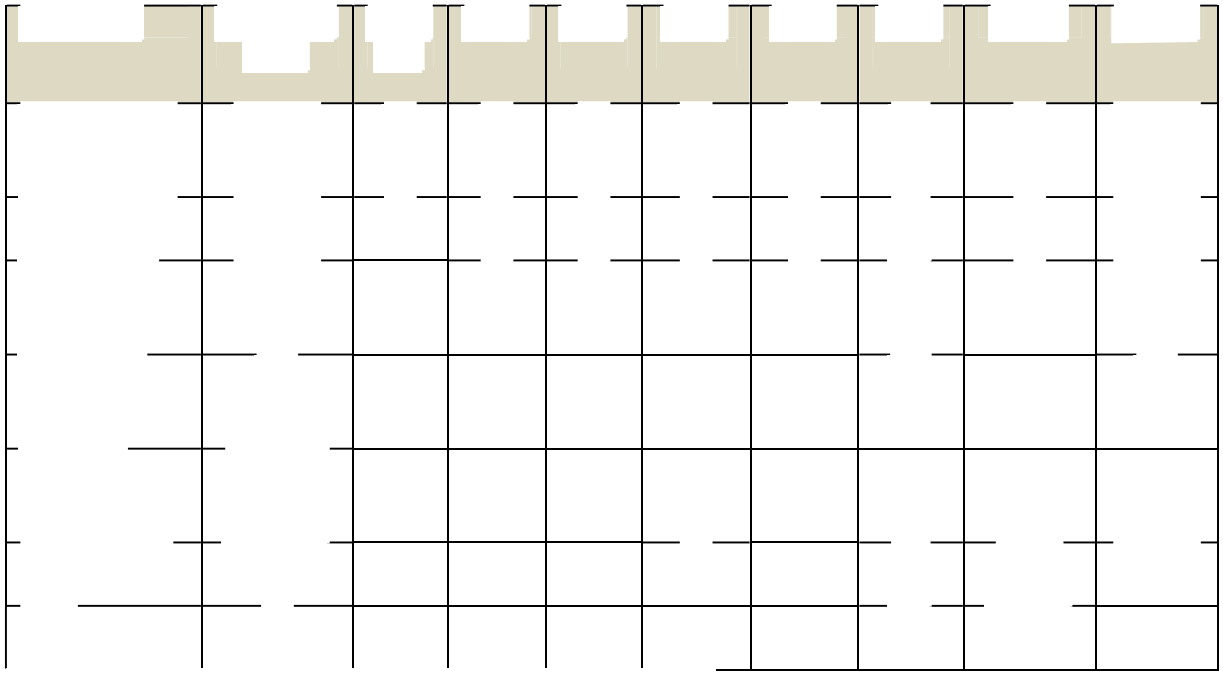
16 Can be performed up to 2 days prior to this visit.











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ABBREVIATIONS

AE	Adverse Event
AESI	Adverse event of special interest
ALT	Alanine amino transferase
AML	Acute myeloid leukemia
AMP	Auxiliary medicinal product
ANC	Absolute neutrophil count
anti-HB	Hepatitis B surface antibody
anti-HCV	Hepatitis C antibody
AP	Alkaline phosphatase
APL	Acute promyelocytic leukemia
aPTT	Activated partial thromboplastin time
AST	Aspartate amino transferase
ASCT	Allogeneic stem cell transplantation
BI	Boehringer Ingelheim
BLQ	Below the lower limit of quantification
BM	Bone marrow
CA	Competent Authority
◦C	Degree Celcius
CL	Total plasma clearance
C_{max}	Maximum measured plasma concentration
CML	Local Clinical Monitor
CNS	Central nervous system
CR	Complete Remission

CRi	Complete Remission with incomplete blood recovery
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Clinical Research Organization
CTCAE	Common Terminology Criteria for Adverse Events
CTMF	Clinical Trial Master File
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
DEDP	Drug exposure during pregnancy
DILI	Drug Induced Liver Injury
DLT	Dose Limiting Toxicity
DNA	Deoxyribonucleic-acid
eCRF	Electronic Case Report Form
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDTA	Ethylen-diamine-tetraacetic acid
ELN	European LeukemiaNet
EOFT	End of further treatment
EoR	End of Residual Effect Period
EOT	End of active treatment
FDA	Food and Drug Administration
FTE	Further treatment evaluation
FU	Follow-up
GCP	Good Clinical Practice
G-CSF	Granulocyte colony stimulating factor
GvHD	Graft versus Host Disease
HBsAg	Hepatitis B surface antigen
HIV	Human immunodeficiency virus

IB	Investigator's Brochure
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
INR	International normalized ratio
IRB	Institutional Review Board
IRR	Infusion-related reaction
ISF	Investigator Site File
i.v.	Intravenous
IWG	International Working Group
LDH	Lactate dehydrogenase
LFT	Liver function test
mAB	Monoclonal antibody
mg	milligram
MTD	Maximum Tolerated Dose
MedDRA	Medical Dictionary for Drug Regulatory Activities
MRT	Mean residence time
NBE	New biological entity
NC	Not calculated
NIMP	Non-investigational medicinal product
NK	Natural killer (cells)
NOA	Not analyzed
NOP	No peak detectable
NOR	No valid result
NOS	No sample available
OPU	Operative Unit
ORR	Objective Response Rate

PD	Progressive disease
PFS	Progression free survival
PK	Pharmacokinetics
PLT	Platelets
PR	Partial Remission
PT	Prothrombin time
REP	Residual Effect Period; after the last dose of medication with measureable drug levels or pharmacodynamic effects still likely to be present
RNA	Ribonucleic-acid
RTPCR	Reverse transcription polymerase chain reaction
SAE	Serious Adverse Event
sCD33	Soluble CD33
SCT	Stem cell transplantation
SD	Stable disease
SDV	Source data verification
SOP	Standard Operating Procedure
SUSAR	Suspected unexpected serious adverse reaction
TCM	Trial Clinical Monitor
TDMAP	Trial Data Management and Analysis Plan
TF	Treatment Failure
TNF	Tissue necrosis factor
TTF	Time to treatment failure
ULN	Upper limit of normal
WBC	White blood cell count
WHO	World Health Organization

1. INTRODUCTION

1.1 MEDICAL BACKGROUND

Acute myeloid leukemia (AML) is a heterogeneous clonal disorder of hematopoietic progenitor cells and represents the most common malignant myeloid disorder in adults, with a prevalence of 3.8 cases per 100,000 rising to 17.9 cases per 100,000 adults aged 65 years and older (R07-2768). The median age at presentation is about 70 years, and three men are affected for every two women. Without therapeutic intervention the disease progresses and leads to death within months after initial diagnosis (R07-2768).

Genetic alterations in leukemic cells constitute the most important factor for the prognosis of AML (R07-2768, R07-2770, R07-2774). AML patients are classified in groups of favorable, intermediate, and unfavorable 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, induction treatment, most commonly consists of cytarabine and an anthracycline, is aiming to reach a CR. The second phase, post-remission treatment, is aiming to consolidate remission. AML patients under the age of 60 years achieve complete remission rates of up to75 % following intensive treatment regimens, 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).

While the majority of younger AML patients receive intensive treatment, a substantial number of elderly patients are 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 of the entire group of elderly AML patients. For AML patients considered ineligible to receive intensive treatment investigational treatments is widely regarded as the preferred therapeutic option (R07-2769**,** R07-2772). With these non-approved drugs CR rates up to 20 % are observed in randomized Phase III trials. Although patients who 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 performed regularly for every single patient based on the specialised physician's clinical experience and the comprehensive review of factors such as patient age, performance score, organ dysfunctions and co-morbidities, as well as the patient's informed decision.

The median overall survival (OS), for patients not achieving a CR is <1 year, even with best palliative treatment. Even for patients who have received induction and consolidation treatment the OS and cure rate are poor: Over 60 % will die due to their disease within 5 years. The risk of leukemic relapse along with the poor prospects of long-term survival after a relapse calls for novel therapeutic strategies to maintain CR in AML.

AML patients in CR who have been initially diagnosed with non-favorable genetics and either have received induction and consolidation treatment and are not candidates for allogeneic hematopoietic stem cell transplantation (e.g. no donor available, not eligible/fit enough) or have received an allogeneic hematopoietic stem cell transplantation have a very high risk to relapse. For those patients no standard therapy to maintain the CR is currently available.

For refractory or relapsed AML patients, outside of treatment in clinical trials, re-induction followed by allogeneic stem cell transplantation is the most common regimen. However many are not eligible for such an intensive treatment. For those patients with refractory or relapsed AML ineligible for intensive treatment, or for those with refractory or relapses disease after allogeneic stem cell transplantation, no approved or standard treatment is available.

Evidence that targeting of CD33 can result in clinical benefit for patients suffering from AML is provided by the unconjugated, humanized IgG1 monoclonal antibody lintuzumab (SGN-33, HuM195) which showed signs of clinical efficacy as monotherapy in a Phase I clinical trial in relapsed / refractory AML patients with an objective response rate (ORR) of 17 % (R11-1481). Objective response was defined as either CR, CRi or PR.

Lintuzumab was also explored in a Phase I study in patients with acute promyelocytic leukemia (APL) after remission induction. Multiple doses of lintuzumab could be administered safely and appeared to eliminate minimal residual disease detectable by RTPCR in some patients. (R11-4695)

Currently, major efforts are focused on the improvement of the therapy in these subgroups of patients with unfavourable prognosis.

1.2 DRUG PROFILE

BI 836858 is a fully human IgG1 antibody specific for human CD33 which is Fc-engineered for increased binding to FcγRIIIa. Please see full details in latest version of Investigator's Brochure (c02324887-03).

CD33 is a myeloid differentiation antigen which is expressed on the cell surface of non-malignant leukocytes of the myeloid lineage and with high frequency on malignant cells in AML, chronic myeloid leukemia and myelodysplastic syndrome (R11-1467, R11-1468, R11-1470, R11-2960). In addition to expression on malignant myeloid blast cells, CD33 expression was reported for leukemic stem cells (R11-1469). For normal leukocytes, CD33 expression was reported for monocytes, macrophages, dendritic cells, and to a lower extent, granulocytes (R11-1467), but not for $CD34^{+}CD38^{-}$ hematopoietic stem cells in the bone marrow (R11-1469). Based on the expression profile of CD33, transient pharmacodynamic effects of CD33 antibody treatment on CD33 positive normal cell types may be expected.

BI 836858 is Fc-engineered for increased binding to FcγRIIIa, which results in increased antibody dependent cellular cytotoxicity (ADCC) activity of BI 836858 as compared to a non-Fc-engineered IgG1-type of antibody. The ADCC activity of BI 836858 was assessed on a panel of AML-derived cell lines and primary AML cells and compared to the ADCC activity of lintuzumab, a humanized CD33-specific antibody which has been in clinical development for AML (R11-1471).

The CD33 antigen is known to internalize upon antibody binding (R11-4256).

Preliminary data from this first-in-human dose escalation study with BI 836858 (trial number 1315.1) in patients with relapsed or refractory acute myeloid leukemia investigating a weekly dose (q1w) is available. As of the data cut-off date 12 April 2016, 26 patients were treated with BI 836858, all with doses of 10, 20 and 40 mg, respectively. The most frequent drug-related AE Preferred Term (PT) was infusion-related reaction (IRR) in eleven out of 26 patients (42 %). Adverse events considered a sign or symptom of an IRR by the investigator included back pain, chest pain, chills, dyspnea, fever and hypotension. All patients recovered from their IRRs with adequate symptom-oriented therapy. Drug-related transient increase of liver function tests was reported in four patients: one patient with grade 1 aspartate amino

transferase (AST) and alanine amino transferase (ALT), one patient with grade 1 ALT, grade 3 AST and grade 3 bilirubin, one patient with grade 3 AST, grade 3 ALT and no increase of bilirubin and another one (not yet entered in the database) with grade 3 AST, grade 1 ALT and no increase of bilirubin.

2. RATIONALE, OBJECTIVES, AND BENEFIT - RISK ASSESSMENT

2.1 RATIONALE FOR PERFORMING THE TRIAL

New therapeutic strategies are needed to significantly improve the prognosis of AML patients with relapsed/refractory disease, but also for AML patients in CR with a high risk to relapse. 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 antibodies.

CD33 is a valid target to treat patients with AML, as CD33 is expressed on the majority of AML cells (R11-1472) and on leukemic stem cells, but not outside of the hematopoietic system (R11-1473).

CD 33 targeting approaches have been evaluated in clinical trials in AML patients. Gemtuzumab Ozogamicin (Mylotarg®), an immunoconjugate of a CD 33 mAb and calicheamicin, was approved by the Food and Drug Administration (FDA) in 2000 for patients over the age of 60 with relapsed AML, or those who are not considered candidates for standard chemotherapy. In June 2010 Mylotarg® was withdrawn by FDA request, due to a negative benefit risk assessment in a Phase III trial. As Mylotarg is an immunconjugate of a CD 33 mAb and a toxin, the MoA and also the safety profile are different to BI 836858. Clinical data of relapsed/refractory AML patients who were treated with the humanized CD33 IgG1 monoclonal antibody (mAb) lintuzumab are published (R11-1474, R01-1267, R11-1481). In these trials, administration of lintuzumab was safe and has shown signs of clinical efficacy (ORR) of 17 % in a Phase I trial in relapsed / refractory AML (R11-1481). Lintuzumab was also explored in a Phase I study in patients with APL after remission induction. Multiple doses of lintuzumab could be administered safely and appeared to eliminate minimal residual disease detectable by RTPCR in some patients. (R11-4695)

The clinical experience with lintuzumab supports the assumption that targeting CD33 with an IgG1-type antibody may translate into clinical benefit in patients with AML with an acceptable side effect profile.

BI 836858 is a monoclonal antibody which mechanistically relies on effector-cell mediated immune mechanisms, in particular ADCC (antibody dependent cellular cytotoxicity) and ADCP (antibody dependent cellular phagocytosis). ADCC predominantly depends on the presence of natural killer (NK) cells and ADCP on the presence of myeloid derived effector cells (i.e. monocytes and macrophages). In a recent publication, where NK cell phenotype and function was assessed in 32 consecutive AML patients including 12 achieving complete remission, it was reported that NK cells in relapsed and refractory AML patients have impaired functionality. It was also shown that phenotypic and functional abnormalities of NK cells are partially restored in AML patients achieving a CR. (R15-6192).

It is likely that BI 836858 requires the presence of functional NK cells and monocytes to achieve clinical benefit in AML patients. AML patients who have achieved a CR have an improved effector cell profile (NK cells and monocytes) and may have a higher likelihood to benefit from the pharmacological activity of BI 836858.

This trial was the first administration of BI 836858 in humans.

2.2 TRIAL OBJECTIVES

The primary objective of this trial is to determine the maximum tolerated doses (MTDs) of BI 836858. BI 836858 is a new biological entity (NBE) and the MTD may not be reached. To learn more about the safety and preliminary efficacy there will be an expansion cohort either at the MTD or the highest tested dose (e.g. 320 mg). Secondary objectives are to document the safety and tolerability of BI 836858,
and to evaluate efficacy (see Section 5).

2.3 BENEFIT - RISK ASSESSMENT

Although considerable progress has been achieved in understanding the etiology and biologic behavior of AML and the development of more effective treatment regimens are ongoing,

most patients with refractory or relapsed AML have a very poor prognosis. Re-induction followed by allogeneic stem cell transplantation is the most common regimen for refractory or relapsed AML patients, however many are not eligible for such an intensive treatment. For those patients with refractory or relapsed AML ineligible for intensive treatment, or for those with refractory or relapsed disease after allogeneic stem cell transplantation, no approved or standard treatment is available.

AML patients in CR who have been initially diagnosed with non-favorable genetics and either have received induction and consolidation treatment and are not candidates for allogeneic hematopoietic stem cell transplantation (e.g. no donor available, not eligible/fit enough) or have received an allogeneic hematopoietic stem cell transplantation have a very high risk to relapse. For those patients no standard therapy to maintain the CR is currently available.

BI 836858 is a monoclonal antibody, which specifically targets CD33. Targeting CD33 in patients with AML may potentially offer a benefit to those patients since CD33 is expressed on AML blasts in the majority of AML patients (see Section 1.2). *In vitro*, BI 836858 is a potent inducer of ADCC, which results in cytolysis of AML-derived cell lines and primary AML blasts from peripheral blood and bone marrow. In the clinical setting, these effects may potentially result in anti-leukemic activity as a monotherapy, but also offer potential for combination with other drugs in patients with AML.

CD33 is not known to be expressed outside of the hematopoietic system. The anticipated side effect profile of BI 836858 based on the CD33 expression profile comprises predominantly hematologic adverse events such as neutropenia. These hematological adverse events are frequently reported in patients with hematological diseases and may be due to the underlying disease, the treatment or both. The preclinical safety assessments for BI 836858 have revealed TNF-alpha and INF-gamma release, suggesting a potential for infusion reactions.

Clinical data from 26 patients are available from this first in human study 1315.1.

Infusion reactions were the most frequently observed drug related adverse event in this first in human study and is newly classified as a listed (expected) adverse event. Infusion-related reactions are frequently observed with monoclonal antibodies in hematological indications, and signs/symptoms of IRRs reported for BI 836858 are in line with AEs reported for other antibodies approved in hematology indications. To mitigate the risk for IRRs, protocol specified precautions must be adhered to, i.e. premedication, rate-controlled infusion schedule and symptom monitoring. If an IRR occurs the infusion of BI 836858 should be paused and additional supportive measures are recommended based on standard of care, e.g. additional corticosteroid or non-steroidal analgesics and/or opioids.in. So far no case of life-threatening IRR was reported; however in case a patient is developing a life-threatening IRR despite appropriate premedication the patient should discontinue the treatment with BI 836858 permanently. Drug-related transient increase of LFT was reported in 4 patients. In none of these cases Hy´s law criteria were met. Frequent testing of LFTs is mandated during treatment with BI 836858 (frequency defined in the clinical trial protocols). In case of

alterations of liver laboratory parameters the clinical evaluation of liver disease and follow up on liver laboratory parameters should be done as outlined in the clinical trial protocol.

Patients with refractory or relapsed AML with limited or no standard treatment options may benefit from blast cell reduction and disease stabilization following treatment with BI 836858. AML patients in CR who have been initially diagnosed with non-favorable genetics with a very high risk to relapse with limited or no standard treatment options may benefit from targeting CD33 positive leukemic stem cells and maintenance of achieved complete remission to initial standard therapy.

The potential benefit of therapy with BI 836858 is expected to outweigh the treatment-related risks.

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

This trial will be performed in two separate patient populations: 1) Patients diagnosed with relapsed or refractory AML who have failed at least one prior line of therapy and 2) patients with AML who are in complete remission (CR) with a high risk to relapse. It will be performed in an open, non-randomized, 3+3 design followed by an expansion cohort. A cycle will comprise of 14 days.

For patients with refractory or relapsed AML, one cycle is 14 days with two administrations of BI 836858 (i.e. administrations on Days 1 and 8). Patients with clinical benefit, defined by the International Working Group (IWG) as having objective response (partial remission (PR) or complete remission (CR) or complete remission with incomplete blood recovery (CRi)) or subjective response (in the absence of objective response) after 8 administrations and who are tolerating the infusions, may continue until progressive disease (PD) and as long as neither patient nor Investigator requests treatment discontinuation.

For AML patients in CR, one cycle is 14 days with one administration of BI 836858 (i.e. administrations on Days 1) in Cycles 1, 2 and 3. From the 4th cycle onwards, patients will receive monthly (every second cycle) infusions of BI 836858 (i.e. 4th infusion on Cycle 5 Day 1, 5th infusion on Cycle 7 Day 1) for overall up to one year of treatment unless these patients relapse or infusions are not tolerated.

To determine separate MTDs for each patient population, cohort dose escalation will be conducted following the 3+3 design for the refractory or relapsed AML patients and the patients with AML in CR with high risk to relapse, respectively. The dose level will be escalated with each new cohort until at least one out of three patients of a cohort experiences a dose limiting toxicity (DLT; for definition see Section 5.2.1.1) during the first two cycles (DLT evaluation period). If exactly one out of the three patients of the cohort experiences a DLT, three additional patients will be treated at the same dose level. If none of the three additional patients experiences a DLT, then the cohort dose escalation will be continued by treating the next 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). The MTD is defined as the dose of BI 836858 that is one dose cohort below the dose at which two or more out of six patients experienced DLT. At the maximum tolerated dose, no more than one patient out of six patients may experience DLT, i.e., the MTD is defined as the highest dose studied for which the incidence of dose-limiting toxicity is no more than 17% (i.e. 1/6 patients) during the first two cycles.

Patients are considered to have completed the first two cycles if they have reached end of cycle 2 and have received all planned administrations of BI 836858 (i.e. 4 administrations for patients with relapsed or refractory AML and 2 administrations for patients in CR).

However, for those patients who receive more than two cycles of BI 836858, all DLT occurring after end of cycle 2 will be taken into consideration for further development of BI 836858.

Table 3.1: 1 Table of action taken in response to DLTs

Patients experiencing a DLT	Number of patients in cohort	Action taken by Sponsor
0	3	Open the next cohort
1	3	Add 3 additional patients (see below) at same dose level
1	6	If there are no new DLTs in additional 3 patients, open next cohort
2	6	If there is at least one new DLT in additional 3 patients, MTD is exceeded, expansion cohort opened at next lower dose level.

During the dose escalation phase, each patient will receive up to 2 repeated treatment cycles before DLT assessment.

For both patient populations the dose is planned to be escalated in cohorts at pre-defined dose levels based on a multiplication factor of 2. The dose levels are 10 mg, 20 mg, 40 mg, 80 mg, 160 mg, and 320 mg as outlined in Section 4.1.3. However, for AML patients in CR, the dose escalation will start with the 40 mg dose cohort and follow the same dose escalation levels. Intermediate dose levels and dose levels higher than 320 mg may be investigated if agreed upon between Investigator and Sponsor.

After definition of the MTD, it is planned to enroll an expansion cohort of 12 patients to better characterize the safety of BI 836858. In case no MTD is reached up to the highest planned dose (e.g., 320 mg), 12 additional patients will be treated with each respective schedule at the highest test dose (i.e., 320 mg) of BI 836858.

The primary analysis will take place when all patients from the cohort dose escalation and dose expansion cohorts have had a minimum of 4 cycles or have discontinued from the trial prior to reaching end of cycle 4 due to meeting the criteria for withdrawal as outlined in Section 3.3.4.1.

3.1.1 Administrative structure of the trial

Boehringer Ingelheim is the Sponsor of this trial. The Coordinating Investigator will be participating Investigators will be physicians experienced and specialized in the treatment of AML and in the conduct of Phase I trials.

In regular telephone conferences between the participating Investigators and the Sponsor, there will be discussions of safety assessments, recommendations for cohort dose escalation, to reach a consensus on DLT, and whether to continue or modify the trial.

All safety laboratory analyses will be performed locally at each clinic site in the schedule outlined in the Flow Charts. All of the biomarker analyses will be performed at with the exception of cytokine analyses which will be performed in locations noted in Section 5.6.3.

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

The primary objective of this trial is to determine the MTD for both patient populations separately. The most important secondary objective is to assess the safety of BI 836858. This can be achieved by an open label, single arm design without a control group.

Adult patients with refractory/relapsed AML are considered eligible for this trial. Relapsed AML is defined as recurrent disease after prior remission of any duration. Refractory disease is defined as failure to achieve remission to most recently administered therapy. Patients with primary refractory disease, defined as failure to achieve remission to initial therapy, are eligible. Typically patients with primary refractory disease are defined as refractory after failure of two cycles of intensive induction. Patients with failure of a single cycle of induction are eligible for this trial if they refuse to receive a second induction cycle or if they are not candidates for a second intensive induction cycle. Patients receiving hypomethylating agents as initial induction should receive at least two cycles of induction before designation as refractory.

AML patients in CR who have been initially diagnosed with non-favorable genetics have a very high risk to relapse. Eligible patients for this trial should either have received induction and consolidation treatment and are not candidates for allogeneic hematopoietic stem cell transplantation (e.g. no donor available, not eligible/fit enough) or have received allogeneic hematopoietic stem cell transplantation. For those patients no standard therapy to maintain the CR is currently available.

These AML patient groups were selected for inclusion in this trial, because these patients constitute groups with unfavourable prognosis for whom currently no satisfactory standard treatment exists.

The trial design will follow a 3+3 design with cohort dose escalation and de-escalation for both patient groups. Once the MTD has been defined, an expansion cohort of 12 patients is planned to be enrolled to better characterize the safety profile and tolerability of the MTD. In case no MTD is reached up to the highest planned dose (e.g., 320 mg), 12 additional patients will be treated with the respective schedule of the highest tested dose (e.g., 320 mg) of BI 836858. This trial design is accepted for hematology Phase I studies.

For patients with refractory or relapsed AML, the first efficacy assessment via bone marrow aspirate will be performed after 2 cycles (4 administrations). Subsequent disease assessment will be performed after 4 cycles (8 administrations) and at the discretion of the Investigator.

For AML patients in CR, disease status will be followed up on a regular basis with peripheral blood count and a bone marrow assessment will be performed if suspicion of relapse. Patients with a MRD marker will be followed up on this marker as well, however this is explorative.

Intra-patient dose escalation will be allowed for selected patients in case the next higher dose cohort is free of DLT and considered safe. This is not considered a safety risk because it will be restricted to patients who have tolerated at least three cycles of BI 836858 at the time of dose escalation and may offer a potential benefit to patients enrolled at a lower dose.

Each patient will be closely monitored for infusion-related reactions, as this is a potential side-effect for mAbs.

Safety assessments will be performed at all visits during the treatment phase.

The trial shall allow the investigation of BI 836858 in AML with regard to safety and the definition of the optimal dose for the future clinical development program in this disease.

3.3 SELECTION OF TRIAL POPULATION

Approximately 50 patients with relapsed or refractory AML and about 35 AML patients in CR with high risk to relapse will be screened. Of these patients, approximately 36 with refractory or relapsed AML and approximately 27 patients with AML in CR with high risk to relapse will be included in this trial from a target of 5 sites. Each site will screen a target of about 10 patients.

A log of all patients included into the study (i.e. having given informed consent) will be maintained in the investigator site file (ISF) at the investigational site irrespective of whether they have been treated with investigational drug or not.

3.3.1 Main diagnosis for study entry

Patients with relapsed or refractory AML as defined according to the World Health Organization (WHO) criteria will be eligible for this trial (see Section 3.2),

AND

Patients with AML in CR with high risk to relapse will be eligible for this trial (see also Section 3.2). AML in CR with high risk to relapse is defined as follows:

a) AML patients with non-favorable genetics (according to European LeukemiaNet (ELN) classification) that are in CR after having received induction and consolidation chemotherapy and are not candidates for allogeneic hematopoietic stem cell transplantation (SCT) (e.g., no donor available, not eligible/fit enough)

or

b) AML patients with non-favorable genetics (according to ELN classification) that are in CR after allogeneic hematopoietic stem cell transplantation.

CR is defined as following: Morphologically leukemia free state (i.e. bone marrow with <5% blasts by morphologic criteria and no blasts with Auer rods, no evidence of extramedullary leukemia) and absolute neutrophil count ≥1000 /µL and platelets ≥100,000 /µL. However, for being eligible for this trial, patients in CR must **not** be independent of red blood cell transfusions.

3.3.2 Inclusion criteria

1. Two patient populations: Patients with diagnosis of relapsed or refractory AML with at least one prior treatment for AML and patients with diagnosis of AML in CR with high risk to relapse.

2. For patients with refractory or relapsed AML: Expression of CD33 on more than 30% of bone marrow blasts per central laboratory assessment at the Ohio State University.

   For AML patients in CR with high risk to relapse: Patients should have had a CD33 positive expression of bone marrow blasts at the time of initial AML diagnosis. No CD33 expression confirmation at screening is required.

3. Eastern Cooperative Oncology Group (ECOG) Performance Status ≤2. See Section 10.2
4. Age ≥18 years.
5. Written informed consent which is consistent with International Conference on Harmonization – Good Clinical Practice (ICH-GCP) guidelines and local legislation.

3.3.3 Exclusion criteria

1. Patients with acute promyelocytic leukemia according to WHO definition
2. Patients with refractory or relapsed AML, >5,000 blasts in the peripheral blood.
3. Anti-leukemia therapy within two weeks before first treatment with BI 836858; however, parallel treatment with Hydroxyurea is allowed for patients with relapsed/refractory AML. (See Section 4.2.2.1)
4. Allogeneic stem cell transplantation within the last 28 days before first treatment with graft versus host disease requiring more than 20 mg of steroids per day. Steroid dosage must be stable within two weeks prior to start of treatment.
5. Patients who are candidates for allogeneic stem cell transplantation (for patients with refractory or relapsed AML).
6. Second malignancy currently requiring active therapy. However, patients with organ-confined prostate cancer with no evidence of recurrent or progressive

disease based on prostate-specific antigen values are also eligible for this study if hormonal therapy has been initiated, or a radical prostatectomy or definitive radiotherapy has been performed.

7. Symptomatic central nervous system involvement (see Section 4.2.2)
8. 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 for those with Gilbert syndrome.
9. Prothrombin time (PT) >1.5 x ULN for subjects not on therapeutic vitamin K antagonists (phenprocoumon, warfarin)
10. Bilirubin greater than 1.5 mg/dl (>26 µmol/L) unless elevation is thought to be due to hepatic infiltration by AML, Gilbert syndrome, or hemolysis.
11. Serum creatinine greater than 2.0 mg/dl
12. Known human immunodeficiency virus (HIV) infection or active hepatitis B virus or hepatitis C virus infection. Patients with any serological evidence of current or past hepatitis B exposure are to be excluded unless the serological findings are clearly due to vaccination
13. Concomitant intercurrent illness, or any condition which in the opinion of the Investigator, would compromise safe participation in the study, e.g. active severe infection, unstable angina pectoris, new onset of exacerbation of a cardiac arrhythmia
14. Psychiatric illness or social situation that would limit compliance with trial requirements
15. Concomitant therapy, which is considered relevant for the evaluation of the efficacy or safety of the trial drug (see Section 4.2.2)
16. Female patients of childbearing potential who are sexually active and unwilling to use a medically acceptable method of contraception during the trial and for 6 months after the last administration of BI 836858, i.e. combination of two forms of effective contraception (defined as hormonal contraception, intrauterine device, condom with spermicide, etc.). Subjects will be considered to be of childbearing potential unless surgically sterilized by hysterectomy, or bilateral tubal ligation/salpingectomy or post-menopausal for at least two years
17. Male patients with partners of childbearing potential who are unwilling to use condoms in combination with a second effective method of contraception (defined as hormonal contraception, intrauterine device, condom with spermicide, etc.) during the trial and for 6 months after the last administration of BI 836858
18. Pregnant or nursing female patients
19. Treatment with another investigational agent under the following conditions:
    a) Within two weeks (for biologics 4 weeks or 5 half-lives, whichever is longer) of first administration of BI 836858; or
    b) Patient has persistent toxicities from prior anti-leukemic therapies which are determined to be relevant by the Investigator.
    c) Concomitant treatment with another investigational agent while participating in this trial.
20. Prior treatment with a CD33 antibody
21. Patient unable or unwilling to comply with the protocol.

3.3.4 Removal of patients from therapy or assessments

3.3.4.1 Removal of individual patients

An individual patient is to be withdrawn from the trial if:

- The patient withdraws consent. Patients are free to discontinue their participation in this trial at any time without the need to justify the decision.
- The patient needs to take concomitant drugs which may interfere with the investigational product (please refer to Section 4.2.2).
- The patient is no longer able to participate for other medical reasons (e.g. adverse events unrelated to therapy or disease progression, concomitant diagnoses, pregnancy, surgery 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 can be withdrawn from the trial after discussion between the Investigator and the Sponsor 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 refractory or relapsed AML patient is withdrawn from the trial treatment, the end of active treatment (EOT) visit has to be performed if feasible. For patients with AML in CR, as soon as a patient is withdrawn from the trial treatment, the end of active treatment (EOT) visit and the End of Residual Effect Period (REP) visit (EoR visit) must be performed if feasible. Every effort should be made to follow-up with patients in case an adverse event (AE) is still ongoing at the time of withdrawal. If a patient is withdrawn from the trial due to consent withdrawal, no further visits will be completed and no further trial data will be collected. However, if information about survival status is available in the public domain, then the Investigator is requested to report this information in the eCRF.

A patient has to discontinue trial drug administration in case:

- A DLT occurs which does not recover to a degree that allows treatment continuation (see Section 4.1.4).
- Progressive disease (PD) or any other concomitant diagnosis/symptom develops resulting in an indication to start any other therapy for AML, including deterioration of general condition.

Patients not completing the first two cycles (with all planned BI 836858 administrations) for reasons other than DLT will be replaced.

3.3.4.2 Discontinuation of the trial by the sponsor

Boehringer Ingelheim reserves the right to discontinue the trial overall or at a particular trial site at any time for the following reasons:

1. Violation of GCP, the Clinical Trial Protocol (CTP), or the contract by a trial site or Investigator, disturbing the appropriate conduct of the trial,
2. Emergence of any efficacy/safety information that could significantly affect continuation of the trial,
3. Failure to meet expected enrolment goals overall or at a particular trial site.
4. Any other administrative reasons, including discontinuation of the clinical development program with BI 836858**.**

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

4. TREATMENTS

4.1 TREATMENTS TO BE ADMINISTERED

BI 836858 will be administered as rate-controlled intravenous infusion. In case a patient experiences an adverse event during the infusion, the duration of the infusion may be expanded until the use-by date and use-by time indicated on the label is reached. The actual duration of the infusion needs to be documented in the electronic case report form (eCRF) including actual start and end time, actual time points for interruption and restart of the infusion and the actual infusion rates.

Adverse events during the infusion will be thoroughly documented and characterized to allow differentiation between infusion-related reactions (R10-4428, R10-4517).

4.1.1 Identity of BI investigational product and comparator product

The characteristics of the test product are below.

- Substance (INN): BI 836858
- Pharmaceutical form: Solution for infusion after dilution
- Source: Boehringer Ingelheim Pharma GmbH & Co. KG
- Unit strength: 10 mg/mL (vials with 10mL)
- Daily dose: See Section 4.1.3
- Duration of use: Single administration every 7, 15, or 29 days (depending on patient population)
- Route of administration: Intravenous
- Posology: Rate controlled infusion (Volume: 250 mL)

The first and second infusion will be started at a rate of 10 mL/h. The infusion rate should be increased every 30 (+/-10) minutes by 10 mL/h to a maximum of 80 mL/h as long as tolerated by the patient. Infusion should not exceed 8 hours. If considered safe by the Investigator, the stepwise increase of infusion rate during the third and subsequent infusions may be faster or steps may be omitted, but the maximum infusion rate must not exceed 120 mL/h. If symptoms of an infusion-related reaction occur, the infusion should be temporarily stopped. Upon recovery, it should be infused at 50% of the rate at which the reaction occurred and should not be dose escalated from this dose for at least 30 minutes. Lower rates may be selected if clinically indicated. Depending on the time of occurrence and the severity of the reaction, the investigator may consider administering additional supportive medication, e.g. corticosteroids. A stepwise re-increase of the infusion rate to a maximum of 80 mL/h is possible. For medical reasons, in case a patient experiences an adverse event during the infusion, the duration of the infusion may be expanded until the use-by date and use-by time indicated on the label is reached. The actual duration of the infusions and infusion steps need to be documented in the eCRF including actual start and end time, actual time points for interruption and restart of the infusion and the actual infusion rates.

4.1.2 Method of assigning patients to treatment groups

Not applicable. This is a single-arm, open-label, cohort dose escalation trial.

4.1.3 Selection of doses in the trial

BI 836858 will be administered as a rate-controlled intravenous infusion every 7 days to refractory or relapsed AML patients.

For AML patients in CR, the first three administrations will be given every second week, on day 1 of Cycles 1, 2 and 3. From the 4th administration onwards, patients will receive monthly (every second cycle) infusions of BI 836858 (i.e. 4th infusion on Cycle 5 Day 1, 5th infusion on Cycle 7 Day 1…) for overall up to 12 months of treatment unless these patients relapse or infusions are not tolerated.

Patients with refractory or relapsed AML have a high medical need and a bad prognosis. To treat this patient population with a sub saturating dose is not warranted and therefore a starting dose close to the full saturation of all CD33 sites is chosen. The starting fixed dose of 10 mg which is a dose level expected to provide near to the full saturation of all CD33 sites at maximum measured plasma concentration (C_{max}) based on estimated receptor occupancy (i.e. 94.3% estimated CD33 occupancy). For lintuzumab, a CD33 monoclonal antibody, in a Phase I trial no MTD was reached up to 8mg/kg/week (R11-1481). A fixed dose regimen was chosen instead of a dose per m^2 based a recent publication by Wang et al. The individual and population performance of body size-based and fixed dosing in adults were compared for 12 oncology approved mAbs (R10-6267). Although both dose regimens demonstrated similar performance, the fixed dose was recommended since it offered advantages in the ease of dose preparation and a lower chance of dosing errors.

For details please refer to the Investigator's Brochure, Section 5.3.6 (c02324887-03).

The dose is planned to be escalated in cohorts at pre-defined dose levels based on a multiplication factor of 2. The dose levels are 10 mg, 20 mg, 40 mg, 80 mg, 160 mg, and 320 mg. Intermediate dose levels and dose levels higher than 320 mg may be investigated if agreed upon between Investigator and Sponsor. In an ongoing Phase I study BI 836858 is administered to lower risk MDS patients every 14 days. In the 20 and 40 mg cohort no DLT occurred and the 80mg cohort is currently ongoing. The dose escalation in AML patients in CR will begin with infusions at the dose level of 40 mg. The dose will be escalated to the next pre-defined or intermediate dose levels as needed.

When a cohort dose escalation is to be performed, the data of all previous dose cohorts will be reviewed and discussed between the participating Investigators and the Sponsor. This assessment will determine if each patient population is able to continue treatment with BI 836858.

During the cohort dose escalation phase, enrolment into the first dose cohort (10 mg) will be allowed at the earliest 7 days after the first administration of BI 836858 between patient 1

and 2 and subsequently between patient 2 and 3. In case the 10 mg cohort has to be expanded to 6 patients, a one week observation period must be followed between the first administration of BI 836858 and the start of the subsequent patient. For subsequent cohorts (i.e., 20 mg, 40 mg, 80 mg, 160 mg, and 320 mg), consecutive screening is allowed; however, there has to be an interval of at least 3 days between the 1st administration of BI 836858 for each patient.

Enrolment into the next higher dose cohort is allowed after the previous dose cohort was found to be safe for the initial administration for all patients in this cohort (e.g. at least 28 days after the first administration of drug in the last patient entered into the cohort).

Once the MTD for one of the patient populations is defined, a dose for treatment of the expansion cohort in this patient population will be determined, which will not exceed the MTD. In case no MTD is reached up to the highest tested dose (e.g. 320 mg), 12 additional patients will be treated with the respective schedule of the highest tested dose (e.g. 320 mg) of BI 836858 in the expansion cohort. During treatment of the expansion cohort, new patients may be enrolled at any time.

Table 4.1.3: 1 Entry of patients into trial, by cohort

Cohort	Day first patient in cohort receives infusion	Earliest day next patient can be enrolled
10 mg*	Day 1	Day 8
All other dose levels in cohort** dose escalation	Day 1	Day 4
Dose Expansion	Day 1	Any time

* a one week observation period must be followed between the first administration of BI 836858 and the start of the subsequent patient - for all patients with refractory or relapsed AML in the 10 mg cohort
**This entry schedule also applies to AML patients in CR, starting at 40 mg cohort.

4.1.4 Drug assignment and administration of doses for each patient

Prior to inclusion of a new patient during the cohort dose escalation phase, the Investigator has to confirm the actual dose tier of BI 836858 for the patient with the Sponsor who oversees the cohort dose escalation steps and the safety data of patients from all trial sites. BI 836858 will be administered as an intravenous infusion under the supervision of the Investigator or designated personnel.

BI 836858 may be administered at any time during the day. However, to it is recommended to start the infusion during the morning hours.

For refractory or relapsed AML patients: BI 836858 will be administered as weekly i.v. infusions in 14-day cycles (i.e., Days 1 and 8; 2 infusions per cycle).

For AML patients in CR: the first three administrations will be given once every second week on day one of 14-day Cycles 1, 2 and 3 (i.e., Days 1, 15 and 29). From the 4th administration onwards, patients will receive monthly (every second cycle) infusions of BI 836858 (i.e. 4th administration on Cycle 5 Day 1, 5th administration on Cycle 7 Day 1 …) for overall up to 12 months of treatment.

Premedication
Premedication to prevent infusion-related reactions is obligatory 30 minutes (up to 120 min before start of administration of BI 836858 is permissible) prior to the first three administrations of BI 836858, unless a contraindication for premedication exists, and should include:

- Acetaminophen/Paracetamol 650 mg - 1000 mg p.o., or equivalent
- Antihistamine p.o. or i.v., equivalent to Diphenhydramine 50 mg i.v.
- Glucocorticoid i.v., equivalent to prednisolone 100 mg

For patients with refractory or relapsed AML:
If BI 836858 has been well tolerated without signs of infusion-related reactions in the first administration, glucocorticoid premedication may be reduced to a dose equivalent to 50 mg prednisolone for the second through fourth administrations, and in case this is well tolerated reduce the steroids with the 5th infusion (25 mg with the 5th and 0 mg with the 6th infusion.)

For AML patients in CR**:**
If BI 836858 has been well tolerated without signs of infusion-related reactions in the first administration, glucocorticoid premedication may be reduced to a dose equivalent to 50 mg prednisolone for the second administration, and in case this is well tolerated steroids can be omitted with the 3rd infusion.

For both patient populations, however, in case an administration of BI 836858 was not well tolerated, the premedication with prednisolone can be re-escalated up to 100 mg.

Retreatment
Before the next administration of BI 836858, adverse events and safety laboratory will be assessed. To continue treatment with further administrations, all of the following criteria must be met:

Refractory or relapsed AML patients

(1) 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 thrombocytopenia was preexistent prior to trial entry. Patients with active leukemia who go from Grade 3 neutropenia to Grade 4 neutropenia after treatment may continue on study provided there is no evidence of infection or febrile neutropenia. Patients with active leukemia who go from

Grade 3 to Grade 4 thrombocytopenia after treatment may continue on study provided that post-transfusion platelet count is at least 20,000/µL before therapy is given.

(2) Acceptable tolerability (in case of an AE at the planned start of a further administration, patients may continue therapy only after recovery to a level which would allow further therapy, i.e. CTCAE grade 1 or pre-treatment value); no febrile neutropenia (≥38.5°C and ANC <1000/µL) and no uncontrolled infection. Patients who do not meet these criteria for further therapy should be discussed with the TCM and/or the Coordinating Investigator and may be eligible to continue if the toxicity is not clinically significant.

AML patients in CR

(1) Neutrophils ≥750 /µL (0.75 x 10^9/L) and platelets ≥50,000 /µL (50 x 10^9/L).

(2) Acceptable tolerability (in case of an AE at the planned start of a further administration, patients may continue therapy only after recovery to a level which would allow further therapy, i.e. CTCAE grade 1 or baseline value.)

(3) Patients with GvHD, with a CTCAE grade 1 or 2 and taking steroids, may continue further administration. GvHD patients with a steroid-refractory (≥2 mg/Kg) CTCAE grade 3 or higher, independent of receiving steroids, should be discontinued from study.

In case criteria 1 and 2 are not fulfilled, blood counts and/or the adverse event should be re-evaluated for up to three weeks. In case of a treatment delay, the Sponsor must be notified. If criterion 1 is not fulfilled and the patient has <5% blasts in the bone marrow, absence of myelodysplastic changes, and/or absence of evidence of disease by flow cytometry in the bone marrow then no further treatment should be administered until discussion with the Sponsor.

Administration of the trial drug has to be stopped temporarily in case of a DLT (see Section 5.2.1.1). Patients may continue therapy only after recovery from the DLT to a CTCAE level which allows further therapy based on Investigator assessment and only with a reduced dose of BI 836858. The new dose of BI 836858 must be finally agreed on between the Sponsor 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 836858 dose, the treatment has to be permanently discontinued. Likewise, treatment has to be discontinued in case the DLT is not reversible.

Intra-patient dose escalation
Intra-patient dose escalation may be considered in agreement between investigator and sponsor for selected patients. It is restricted to patients who have received at least 3 treatment cycles and tolerate the treatment well at the time of dose escalation. Intra-patient dose escalation can only be performed at a time when the next higher dose cohort has been

reviewed and considered safe by the sponsor and investigators. The dose escalation step is limited to the dose which has been administered to the next higher cohort. In addition, after the first dose at the higher dose level, patients have to be monitored for at least 24 hours after the end of the infusion, including safety laboratory 24 hours after the first administration of the escalated dose of BI 836858.

A log of all patients enrolled into the study (i.e. having given informed consent) will be maintained in the Investigator Site File (ISF) at the investigational site irrespective of whether they have been treated with investigational drug or not.

4.1.5 Blinding and procedures for unblinding

4.1.5.1 Blinding

This Phase I trial will be performed according to an open label, single arm design. It will recruit two separate patient populations: 1) Patients with relapsed and refractory AML and active disease; and 2) AML patients in CR with high risk to relapse. This trial will be handled in an open fashion by the Sponsor throughout, i.e. also for the purpose of data cleaning and preparation of the analysis. The eCRF will contain information on the treatment and the dose.

4.1.5.2 Procedures for emergency unblinding

Not applicable.

4.1.6 Packaging, labelling, and re-supply

BI 836858 will be supplied in 10 mL vials containing 100 mg BI 836858. For details of packaging and the description of the label, refer to the ISF. Medication 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 BI 836858 infusion solution, the content of the vial of BI 836858 will be diluted in 0.9% sodium chloride. The content of several vials may be needed for administration of the requested dose. For further details, please refer to the instructions included in the ISF. The full volume of the diluted compound will be 250 mL.

4.1.7 Storage conditions

BI 836858 has to be stored in a limited access area at the temperature indicated on the trial drug label - stored in a refrigerator 36-46°F (2-8°C); do not freeze. If the storage conditions are found to be outside the specified range, immediately contact the local clinical monitor (CML) as provided in the list of contacts. For more details on BI 836858, please refer to the Investigator's Brochure (IB) and the ISF.

4.1.8 Drug accountability

Drug supplies of BI 836858, which will be provided by the Sponsor or a Clinical Research Organization (CRO) appointed by the Sponsor, must be kept in a secure, limited access storage area under the storage conditions defined by the Sponsor. A temperature log must be maintained to make certain that the drug supplies are stored at the correct temperature.

Each Investigator and/or pharmacist will receive the investigational drugs delivered by the Sponsor when the following requirements are fulfilled:

- approval of the study protocol by the IRB / ethics committee,
- availability of a signed and dated clinical trial contract between the sponsor and the Head of Trial Centre,
- approval/notification of the regulatory authority, e.g. competent authority,
- availability of the curriculum vitae of the principal Investigator,
- availability of a signed and dated CTP or immediately imminent signing of the CTP,
- availability of the proof of a medical licence for the principal investigator,
- availability of the Form 1572.

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 and/or pharmacist must maintain records of the product's delivery to the trial site, the inventory at the site, the use for each patient, and the return to the Sponsor or alternative disposition of unused product. The Investigator/pharmacist will maintain records that document adequately that the patients were provided these doses specified by the CTP and reconcile all investigational product received from the Sponsor. At the time of return to the sponsor, the investigator 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.

4.2 CONCOMITANT THERAPY, RESTRICTIONS, AND RESCUE TREATMENT

4.2.1 Rescue medication, emergency procedures, and additional treatments

Rescue medication to reverse the action of BI 836858 is not available. Potential side effects of BI 836858 have to be treated symptomatically. Patients should receive supportive care according to the local guidelines regarding treatment of infusion-related reactions, blood product support, antibiotics, antivirals, 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 during the first 2 cycles for better assessment of safety and response parameters.

Anti- bacterial and fungal prophylaxis should be given according to local standards or available guidelines.

All concomitant non-anti-leukemia therapies to provide adequate care may be given as clinically necessary. All concomitant treatments will be recorded in the eCRF except for vitamins and nutrient supplements. Trade name, indication and dates of administration of concomitant therapies will be documented. For parenteral nutrition during the trial, the components need not be specified in detail. It should be indicated as 'parenteral nutrition'. If a patient needs anesthesia, it will be sufficient to indicate 'anesthesia' without specifying the details.

Concomitant therapy will be recorded in the eCRF during the screening and treatment period, starting at the date of signature of informed consent, and ending at the EOT-visit. After the EOT-visit, only concomitant therapy indicated for treatment of an adverse event needs to be reported.

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

Prior anti-leukemia therapy must have been discontinued at least two weeks before the first administration of the trial drug (Hydroxyurea may be given during study participation) and the patient must have recovered from all clinically relevant reversible toxicities as determined by the investigator. A time interval of at least 2 weeks (four weeks for biologics) must have elapsed from the last administration of any other investigational treatment for AML to the first administration of BI 836858.

For peripheral blood blast control, as this may correlate with the risk of occurrence of infusion related symptoms, hydroxyurea will be allowed (maximum dose of hydroxyurea 3gm daily) before and during study participation. Blasts must be ≤ 5,000/µl at start of each administration of BI 836858.

No other anti-neoplastic therapy concomitantly is allowed.

Short term glucocorticoid medications may be used up to 20 mg per/day continuously are allowed (see exclusion criterion 4) and up to 2 mg/kg bodyweight for short term. All other indications for steroids have to be discussed and agreed upon between Investigator and Sponsor.

Intrathecal treatment to control symptoms associated with central nervous system (CNS) involvement is allowed but must be discussed and agreed upon between Investigator and Sponsor. All concomitant therapy will be recorded in the eCRF.

4.2.2.2 Restrictions on diet and life style

No restrictions apply with regard to diet or life style.

4.3 TREATMENT COMPLIANCE

BI 836858 will be administered as a single intravenous infusion under supervision of the Investigator or dedicated clinic personnel. Compliance may also be verified by pharmacokinetic assessment. Any discrepancies will be explained in the eCRF by the Investigator or designee.

5. VARIABLES AND THEIR ASSESSMENT

5.1 EFFICACY – PHARMACODYNAMICS

5.1.1 Endpoints of efficacy

The efficacy endpoints will be assessed at the time points specified in the Flow Charts.
Efficacy endpoints will be secondary in this trial.

Secondary endpoints of efficacy are:

For patients with refractory or relapsed AML:

- Best overall response according to International Working Group (IWG) criteria (please see Section 5.1.2.3) (R06-0452)
- Progression free survival
- Time to treatment failure

For AML patients in CR with high risk to relapse:

- Progression free survival
- Time to treatment failure

5.1.2 Assessment of efficacy

5.1.2.3 Assessment and definition of best overall response

For patients with refractory or relapsed AML, response will be assessed according to the criteria from the IWG based on laboratory data from the peripheral blood, bone marrow examination, clinical examination (at the end of each cycle), at the evaluation for further treatment-visit and the EOT-visit. Bone marrow examination will be performed before the Cycle 3 and Cycle 5 (5th and 9th administration of BI 836858) (i.e., BM performed on Day 1 (+/-1) of cycles 3 and 5 and treatment started on Day 1 (up to +3) of cycles 3 and 5) and at the discretion of the Investigator, e.g. in case clinical and laboratory examinations of peripheral blood demonstrate that a CR has been achieved, or for assessment of persistent neutropenia, anemia or thrombocytopenia.

For AML patients in CR, response will be assessed clinically and in the peripheral blood (on Day 1 of each cycle). In the case of suspected relapse based on peripheral blood counts a bone marrow examination will be performed.

Assessment and definition of best overall response

Response will be evaluated according to the following criteria (modified from the IWG criteria, R06-0452):

- Complete remission (CR)

  Morphologically leukemia free state (i.e. bone marrow with <5% blasts by morphologic criteria and no blasts with Auer rods, no evidence of extramedullary leukemia) and absolute neutrophil count ≥1000 /µL and platelets ≥100,000 /µL. Patient must be independent of transfusions (no transfusion for 1 week prior to the assessment).

- Complete remission with incomplete blood count recovery (CRi)

  All of the above criteria for CR must be met, except that absolute neutrophils <1000 /µL or platelets <100,000 /µL in the blood.

- Partial remission (PR)

  All of the criteria for CR must be met, except that leukemic blasts in the bone marrow may range from 5 to 25% as long as the count has decreased by at least 50% from pre-study treatment, or <5% blasts in the presence of Auer rods or abnormal morphology.

- Stable disease (SD)

  Patient alive with no CR, CRi, PR or PD.

- Treatment failure (TF)

  Patient survives ≥7 days following completion of initial 2 treatment cycles (e.g. 28 days) with persistent leukemia in the last peripheral blood smear or bone marrow (>25% blasts), or with persistent extramedullary disease, but without further clinical deterioration due to leukemia or increase of blast population in the bone marrow or peripheral blood.

  Resistant disease: Patient survives ≥7 days post-course of treatment; persistent leukemia in blood or bone marrow.

  Aplasia: Patient survives ≥7 days post-course of treatment; death while cytopenic, with aplastic bone marrow

  Indeterminate cause: Patients who die < 7 days post therapy. Patients who die > 7 days post therapy with no peripheral blood blasts, but no bone marrow examination. Patients who do not complete the first course of therapy.

  Morphologic relapse (recurrence): Reappearance of blasts post-CR or CRi in peripheral blood or bone marrow. That is, bone marrow leukemic blasts ≥ 5% or reappearance of blasts in the blood not attributable to any other cause (e.g. bone marrow regeneration), or development of extramedullary disease.

- Progressive disease (PD)

  Patient survives ≥7 days following completion of initial 2 treatment cycles (e.g. 28 days) with increase of blast population in the bone marrow or peripheral blood by >50% or aggravation or new development of extramedullary disease or further deterioration or death due to leukemia. 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 'clinically progressive disease'. Every effort should be made to document the objective PD even after discontinuation of treatment.

Definition of best overall response

Best overall response is defined as the best overall response (CR, CRi, PR, TF, PD or not evaluable in this order) recorded since first administration of BI 836858.

5.1.2.4 Progression free survival (PFS)

- PFS is defined as the time from first treatment with BI 836858 until disease progression, relapse or death.

- The date of progression/relapse will be the earliest of the dates of the disease assessment (blood sample, bone marrow sample, or clinical assessment) in which the

progression/relapse was observed. For patients who did not progress, relapse, or die, PFS will be censored at the date of last disease assessment.

5.1.2.5 Time to treatment failure (TTF)

Some patients will receive the next line of therapy, although no formal PD may be diagnosed at the time when the next treatment is indicated according to Investigator assessment. In addition to PFS, the TTF will be calculated.

- TTF is defined as the time from first treatment with BI 836858 until ~~objective~~ disease progression, relapse or death or start of next AML therapy.

- The date of progression/relapse will be the earliest of the dates of the disease assessment (blood sample, bone marrow sample, or clinical assessment) in which the progression/relapse was observed. For patients who did not progress, relapse, die, or receive next AML therapy TTF will be censored at the date of last disease assessment.

5.2 SAFETY

5.2.1 Endpoints of safety

Primary endpoints:

- Maximum tolerated dose (MTD)
- Number of patients with Dose Limiting Toxicity (DLT) during the MTD evaluation period:
    - For patients with refractory or relapsed AML, the first two cycles (i.e. patient has received at least 4 administrations of BI 836858 and reached end of cycle 2).
    - For AML patients in CR with high risk to relapse, the first two cycles (i.e. patient has received at least 2 administrations of BI 836858 and reached end of cycle 2).

As this trial is the first in human use of BI 836858, the primary objective is to determine the MTD of BI 836858 and assess the safety of the drug in humans. For details on determination of MTD, please refer to Section 3.1, Section 5.2.1.1 and Section 7.3.1.

The safety of BI 836858 will be assessed by a descriptive analysis of incidence and intensity of adverse events (AE) graded according to the CTCAE version 4.0, the incidence of DLT, laboratory data and results of physical examination.

The Sponsor will review the safety data with the participating Investigators at regular intervals and as ad hoc if needed.

The safety endpoints will be assessed in a descriptive way without confirmatory analyses.

5.2.1.1 Dose limiting toxicity (DLT) for refractory or relapsed AML patients

DLT is defined as any non-disease-related non-hematological AE of CTCAE grade 3 or higher. Expected non-hematological disease related AE´s such as complications resulting from haematological AEs include:

- bleeding and complications from bleeding due to thrombocytopenia as defined by the investigator
- infection and complications from infections due to neutropenia as defined by the investigator

- constitutional symptoms due to anemia as defined by the investigator

Infusion-related reactions (IRRs, CTCAE grade 3 or higher) associated with the administration of BI 836858 should be reported as Adverse Event of Special Interest (AESI, refer to Section 5.2.2.1), but will not be regarded as a DLT. The exception is anaphylaxis which occurs despite premedication with glucocorticoid or which does not resolve with glucocorticoid (i.e. such cases of anaphylaxis will be regarded as a DLT).

Infection will not constitute a DLT unless it is felt that the infection resulted from unexpectedly complicated myelosuppression; degree of severity and/or duration as assessed by the Investigator.

Hematological AEs, e.g. neutropenia, thrombocytopenia and anemia are frequently pre-existing in AML patients and are therefore AEs not considered as DLT. Failure to recover neutrophil count (ANC>500/uL) or platelet count (>25000/uL) at the first bone marrow evaluation after 2 cycles of BI 836858 in patients with < 5% blasts in the bone marrow, absence of myelodysplastic changes, and/or absence of evidence of disease by flow cytometry in the bone marrow will be considered a DLT. For patients with ≥ 5% blasts, myelodysplastic changes, or evidence of disease by flow cytometry/cytogenetics, failure to recover neutrophil or platelet count may not be considered DLT as this could be the result of persistent disease.

Patients who have not completed at least 4 administrations (2 cycles) of BI 836858 due to BI 836858 related toxicity will be considered as a DLT.

5.2.1.2 Dose limiting toxicity (DLT) for AML patients in CR

DLT is defined as any non-disease-related AE of CTCAE grade 3 or higher. Patients in remission are not expected to have disease-related AEs. In case of any hematological AE of CTCAE grade 3 or higher, relapse of AML has to be excluded. Infusion-related reactions (IRRs) associated with the administration of BI 836858 should be reported as Adverse Events of Special Interest (AESI, refer to Section 5.2.2.1), but will not be regarded as a DLT. The exception is anaphylaxis which occurs despite premedication with glucocorticoid or which does not resolve with glucocorticoid (i.e. such cases of anaphylaxis will be regarded as a DLT).

Occurrence of and/or worsening of GvHD will not be considered as a DLT; however, these cases will be reviewed carefully during the safety assessment meetings.

AML patients in CR who have not completed at least 2 administrations (2 cycles) of BI 836858 due to BI 836858 related toxicity will be considered as a DLT.

Once each patient of a cohort has completed 2 treatment cycles of BI 836858 all available safety data will be reviewed by the Sponsor, Coordinating Investigator and other participating Investigators who enrolled at least one patient. Safety data will be discussed via a

teleconference, initiated by Sponsor, to reach a consensus on DLT, in order to allow dose escalation, cohort expansion or suspension of further dose escalation.

All DLTs occurring at any time will be reported as an adverse event of special interest (AESI, see Sections 5.2.2.1 for definitions and 5.2.2.2 for reporting requirements).

5.2.2 Assessment of adverse events

5.2.2.1 Definitions of AEs

Adverse event

An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Adverse reaction
An adverse reaction is defined as a response to a medicinal product which is noxious and unintended. Response in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility. Adverse reactions may arise from use of the product within or outside the terms of the marketing authorisation or from occupational exposure. Conditions of use outside the marketing authorization include off-label use, overdose, misuse, abuse and medication errors.

Serious adverse event

A serious adverse event (SAE) is defined as any AE which:

- results in death,
- is life-threatening, this refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if more severe.
- requires inpatient hospitalisation or
- prolongation of existing hospitalisation,
- results in persistent or significant disability or incapacity, or
- 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 judgment which may jeopardise the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions.

Medical and scientific judgement should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be

immediately life threatening or result in death or hospitalisation but might jeopardise the patient or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation or development of dependency or abuse. Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

AEs considered "Always Serious"

Every new occurrence of cancer of new histology must be reported as a serious event regardless of the duration between discontinuation of the drug and the occurrence of the cancer.

Cancers of new histology and exacerbations of existing cancer must be reported as a serious event regardless of the duration between discontinuation of the drug and the occurrence of the cancer.

In accordance with the European Medicines Agency initiative on Important Medical Events, Boehringer Ingelheim has set up a list of further AEs, which by their nature, can always be considered to be "serious" even though they may not have met the criteria of an SAE as given above.

The latest list of "Always Serious AEs" can be found in the RDC system. A copy of the latest list of "Always Serious AEs" will be provided to you upon request. These events should always be reported as SAEs as described above.

Adverse events of special interest (AESIs)
The term AESI relates to any specific AE that has been identified at the project level as being of particular concern for prospective safety monitoring and safety assessment within this trial, e.g. the potential for AEs based on knowledge from other compounds in the same class. AESI need to be reported to the sponsor's Pharmacovigilance Department within the same timeframe that applies to SAE, please see above.

The following are considered as AESIs:

- infusion-related reactions (CTCAE grade 3 or higher),
- any event that qualifies for DLT, and
- hepatic injury (DILI).

Hepatic injury
A hepatic injury (DILI) is defined by the following alterations of hepatic laboratory parameters:

- an elevation of AST and/or ALT $\geq$3 fold ULN combined with an elevation of total bilirubin $\geq$2 fold ULN measured in the same blood draw sample, and/or
- marked peak aminotransferase (ALT, and/or AST) elevations $\geq$10 fold ULN

These lab findings constitute a hepatic injury alert and the patients showing these lab abnormalities need to be followed up according to the "DILI checklist" provided in the ISF. In case of clinical symptoms of hepatic injury (icterus, unexplained encephalopathy, unexplained coagulopathy, right upper quadrant abdominal pain, etc.) without lab results (ALT, AST, total bilirubin) available, the Investigator should make sure these parameters are analysed, if necessary in an unscheduled blood test. Should the results meet the criteria of hepatic injury alert, the procedures described in the DILI checklist should be followed

Intensity of AEs

The intensity of adverse events should be classified and recorded in the CRF according to the Common Terminology Criteria for Adverse Events (CTCAE, version 4.0, R09-2850).

Causal relationship of AEs

The definition of an adverse reaction implies at least a reasonable possibility of a causal relationship between a suspected medicinal product and an adverse event. An adverse reaction, in contrast to an adverse event, is characterised by the fact that a causal relationship between a medicinal product and an occurrence is suspected.

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.

Arguments that may suggest that there is a reasonable possibility of a causal relationship could be:

- The event is consistent with the known pharmacology of the drug
- The event is known to be caused by or attributed to the drug class.
- A plausible time to onset of the event relative to the time of drug exposure.
- Evidence that the event is reproducible when the drug is re-introduced
- No medically sound alternative aetiologies that could explain the event (e.g. pre-existing or concomitant diseases, or co-medications).
- The event is typically drug-related and infrequent in the general population not exposed to drugs (e.g. Stevens-Johnson syndrome).
- An indication of dose-response (i.e. greater effect size if the dose is increased, smaller effect size if dose is diminished).

Arguments that may suggest that there is no reasonable possibility of a causal relationship could be:

- No plausible time to onset of the event relative to the time of drug exposure is evident (e.g. pre-treatment cases, diagnosis of cancer or chronic disease within days / weeks of drug administration; an allergic reaction weeks after discontinuation of the drug concerned)
- Continuation of the event despite the withdrawal of the medication, taking into account the pharmacological properties of the compound (e.g. after 5 half-lives). Of note, this criterion may not be applicable to events whose time course is prolonged despite removing the original trigger.

- Additional arguments amongst those stated before, like alternative explanation (e.g. situations where other drugs or underlying diseases appear to provide a more likely explanation for the observed event than the drug concerned).
- Disappearance of the event even though the study drug treatment continues or remains unchanged.

5.2.2.2 Adverse event collection and reporting

AE Collection
The Investigator shall maintain and keep detailed records of all AEs in their patient files. The following must be collected and documented on the appropriate CRF(s) by the Investigator:

- From signing the informed consent onwards through the Residual Effect Period (REP), until individual patient's end of trial:

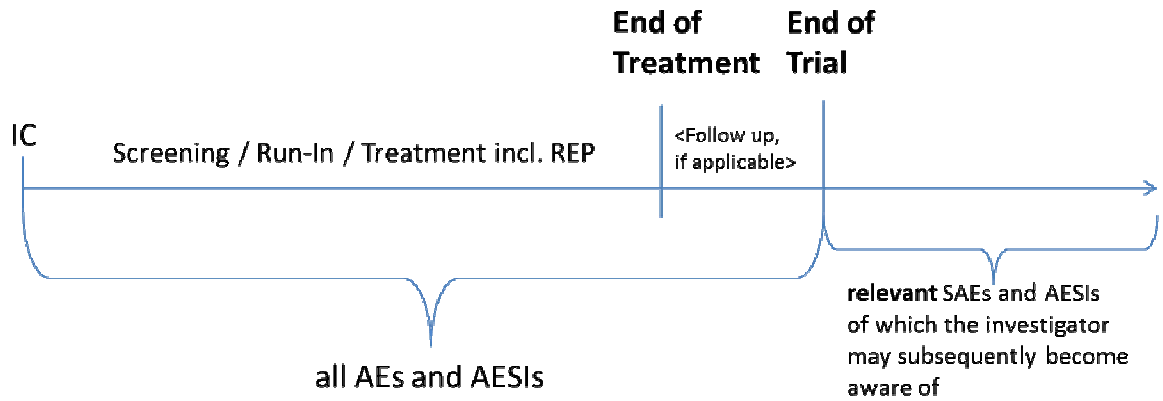
  All AEs (serious and non-serious) and all AESIs.

- However, if an individual patient discontinues trial medication prematurely but stays in the trial (i.e. if further visits incl. telephone visits, or vital status assessments are planned) from then on and until the individual patient's end of the trial the Investigator must report related SAEs and related AESIs.

- After the individual patient's end of trial:

  The Investigator does not need to actively monitor the patient for AEs but should only report relevant SAEs and relevant AESIs of which the Investigator may become aware of.

The rules for Adverse Event Reporting exemptions (see below in paragraph "Exemptions to (S)AE Reporting") still apply.



The REP is defined as 30 days after the last trial medication application. All AEs which occurred through the treatment phase and throughout the REP will be considered as "on treatment," please see Section 7.3.3. Events which occurred after the REP will be considered as "post-treatment" events.

AE reporting to sponsor and timelines

The Investigator must report SAEs, AESIs, and non-serious AEs which are relevant for the reported SAE or AESI, on the BI SAE form via fax immediately (within 24 hours) to the sponsor's unique entry point (country specific contact details will be provided in the ISF). The same timeline applies if follow-up information becomes available. In specific occasions the Investigator could inform the sponsor upfront via telephone. This does not replace the requirement to complete and fax the BI SAE form.

With receipt of any further information to these events, a follow-up SAE form has to be provided. For follow-up information the same rules and timeline apply as for initial information.

Information required

For each AE, the Investigator should provide the information requested on the appropriate CRF pages and the BI SAE form. The Investigator should determine the causal relationship to the trial medication and any possible interactions between the investigational drug(s) and a Non-Investigational Medicinal Product (NIMP) / Auxiliary Medicinal Product (AMP).

The following should also be recorded as an (S)AE in the CRF and SAE form (if applicable):

- Worsening of the underlying disease or of other pre-existing conditions
- Changes in vital signs, ECG, physical examination and laboratory test results, if they are judged clinically relevant by the Investigator.

If such abnormalities already pre-exist prior trial inclusion they will be considered as baseline conditions.

All (S)AEs, including those persisting after individual patient's end of trial must be followed up until they have resolved, have been sufficiently characterised, or no further information can be obtained.

Pregnancy

In rare cases pregnancy may occur in a clinical trial. Once a patient has been enrolled into this clinical trial and has taken trial medication, the Investigator must report immediately (within 24 h) a potential drug exposure during pregnancy (DEDP) in a female patient or in a partner to a male patient to the sponsor's unique entry point (country-specific contact details will be provided in the ISF). The Pregnancy Monitoring Form for Clinical Trials (Part A) should be used.

The outcome of the pregnancy associated with the drug exposure during pregnancy must be followed up and reported to the sponsor's unique entry point on the Pregnancy Monitoring Form for Clinical Trials (Part B).

As pregnancy itself is not to be reported as an AE, in the absence of an accompanying SAE, only the Pregnancy Monitoring Form for Clinical Trials and not the SAE form is to be completed. If there is an SAE associated with the pregnancy then the SAE has to be reported on the SAE form in addition.

The ISF will contain the Pregnancy Monitoring Form for Clinical Trials (Part A and B).

Exemptions to (S)AE Reporting
Disease Progression in oncology trials is a study endpoint for analysis of efficacy, and as such is exempted from being reported as an SAE. Progression of the patient's underlying malignancy will be recorded on the appropriate pages of the eCRF as part of efficacy data collection only and will not be reported on the SAE Form. It will therefore not be entered in the safety database (Adverse Reactions Information System global, ARISg) and hence not get expeditiously reported. Death due to disease progression is also to be recorded on the appropriate eCRF page and not on the SAE Form.

Examples of exempted events of PD may be:

- Progression of underlying malignancy (Progressive disease [PD]): if PD is clearly consistent with the suspected progression of AML as defined by the respective response criteria.
- Hospitalization/Procedures due solely to the progression of underlying malignancy (PD)
- Clinical symptoms and/or signs of progression (without confirmation by objective criteria e.g. imaging, clinical measurement): If the symptom can exclusively be determined to be due to the progression of the underlying malignancy and does meet the expected pattern of progression for the disease under study.

However, when there is evidence suggesting a causal relationship between the trial drug and the progression of the underlying malignancy, the event must be reported as an (S)AE on the SAE Form and on the eCRF.

5.2.3 Assessment of safety laboratory parameters

5.2.3.1 General safety laboratory parameters

Blood samples and urine have to be collected at the time points specified in the Flow Charts. Safety laboratory examinations will include hematology, biochemistry, coagulation and qualitative urine analysis:

Hematology	Hemoglobin, white blood cell count (WBC) with differential, platelets (PLT)
	Reticulocytes have to be measured only at Visit 1 of every second cycle, EOT, Visit 1 of every second cycle in FTE, at the EOFT visit (in refractory or relapsed AML patients) and

	during follow-up.
Biochemistry	Glucose, sodium, potassium, calcium, inorganic phosphate, creatinine, AST, ALT, alkaline phosphatase (AP), lactate dehydrogenase (LDH), bilirubin, urea, total protein, albumin, uric acid
	Serum immunoglobulin levels (IgG, IgM, IgA) and direct antiglobulin test have to be measured only every 8 weeks, at the EOT visit and during follow-up.
Coagulation	Activated partial thromboplastin time (aPTT), prothrombin time (PT), international normalised ratio (INR) where indicated (e.g. treatment with vitamin K antagonists)
Urine	pH, glucose, erythrocytes, leukocytes, protein, nitrite will be analysed by dipstick and reported as semiquantitative measurements. In case of pathological findings, further evaluation should be performed and results documented.
Pregnancy test	A serum pregnancy test needs to be obtained at the time points indicated in the Flow Chart in patients of childbearing potential.

An additional safety lab will be collected on day 2 of Cycle 1 (i.e., 24 hours after the first administration of BI 836858). Other lab tests to be included: haptoglobin, direct antiglobulin test, bilirubin (direct and indirect) and free hemoglobin. Non pre-existing abnormal laboratory values (CTCAE Grade 3 or higher) will be followed up every 48 hours until these laboratory values are back to at least CTCAE Grade 1.

In case an administration is delayed due to an AE, the patient should visit the site at least once a week for assessment of safety laboratory and AEs. More frequent visits may be appropriate as assessed by the Investigator.

5.2.4 Electrocardiogram

A 12-lead resting ECG will be performed in all patients according to the schedule in the Flow Charts. The ECG will be assessed for pathological results (to be recorded as either concomitant disease or AE) by the Investigator. Additional examinations should be done whenever the Investigator deems necessary.

5.2.5 Assessment of other safety parameters

5.2.5.1 Vital signs

Vital signs (blood pressure, heart rate and body temperature) will be recorded at every visit during screening, treatment (including the EOT visit) and follow-up. Additional time points for blood pressure and heart rate at the day of administration of BI 836858 are: prior to the start of premedication, prior to the start of BI 836858 infusion, and in 30 (±10) minute intervals throughout the course of the infusion of BI 836858 and 60 (±10) minutes after the end of the infusion, thereafter every 4-8 hours until at least 24 hours after start of the infusion. In case of an infusion-related reaction, the Investigator should decide whether to intensify or prolong monitoring of vital signs of the patient.

Beginning with infusion 2, blood pressure and heart rate will be assessed at the same time points as during infusion 1 with the exception that they will not be assessed every 4-8 hours until at least 24 hours after the start of the infusion.

5.2.5.2 Physical examination

A physical examination including height, weight and ECOG performance score will be performed at screening and at the time points specified in the Flow Charts. During the physical examination, the patient should be assessed for possible AEs.

5.4 APPROPRIATENESS OF MEASUREMENTS

Determination of MTD is based on toxicities graded according to CTCAE (R09-2850). The CTCAE criteria are commonly used in the assessment of AEs in cancer patients. The criteria

to be used for evaluation of response (R06-0452) are well established and scientifically accepted.

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

During the treatment phase, patients with refractory or relapsed AML will receive administration with BI 836858 every 7 days. For AML patients in CR, The first three administrations will be given once every second week on day 1 of Cycles 1, 2 and 3. From the 4th administration onwards, patients will receive monthly (every second cycle) infusions of BI 836858 (i.e. 4th infusion on Cycle 5 Day 1, 5th infusion on Cycle 7 Day 1 …) for overall up to 12 months of treatment.

Patients are required to be hospitalized under close surveillance with access to intensive care for at least 24 hours after the first administration of BI 836858 to allow close monitoring for infusion-related reactions or other AEs. After good tolerability of the first administration of BI 836858, the Investigator may evaluate the risk for an infusion-related reaction and other AEs in view of relevant co morbidities or AML-related symptoms, and as a result, the patient may receive subsequent infusions in the out-patient setting.

In case a patient misses a visit within one treatment cycle and the patient comes to the clinic between the missed and the next scheduled visit, the delayed visit should be scheduled as soon as possible and documented with the actual date and the reason for the delayed visit. The next visit, should still take place at the time it was originally scheduled in this treatment cycle.

However, in case the day of treatment administration (Visit 1 of a cycle) is delayed, all subsequent visits of a cycle will be recalculated based on the actual date of Visit 1 of the delayed cycle.

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

The investigations as outlined in the Flow Charts A and B will be performed at the respective visits as described in detail in the following sections.

6.2.1 Screening and run-in period

The screening period (Visit 1), i.e. the phase after informed consent and before the first administration of the trial drug, may be as long as 14 days.

The following parameters and investigations will be obtained and / or performed for both patient populations:

- Informed consent
- Informed consent for pharmacogenetics
- Demographics (sex, birth date, race) and baseline conditions
- Medical history (oncological and relevant non-oncological)
- Review of inclusion and exclusion criteria (patient eligibility)

- Dose assignment (during cohort dose escalation phase only, before the first administration of the trial drug and after informed consent and review of in- and exclusion criteria)
- Safety laboratory (hematology, biochemistry including serum immunoglobulin levels and direct antiglobulin test, coagulation, urine; for details please refer to Section 5.2.3.1)
- Physical examination, height, weight, vital signs and ECOG performance score
- Serum pregnancy test in women of childbearing potential
- 12-lead ECG
- Concomitant therapy
- Bone marrow aspiration for disease assessment (for refractory or relapsed AML patients)

6.2.1.1 Re-screening

Sites will be allowed to re-screen patients after 1 week from when they screen failed. If more than 4 weeks have elapsed prior to re-screening, all screening procedures must be repeated.

6.2.2 Treatment periods for refractory or relapsed AML patients

6.2.2.1 Visit 1 and Visit 3 – day of BI 836858 administration (administrations 1-8)

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

- Review of inclusion and exclusion criteria (patient eligibility), prior to the first administration only
- Safety lab parameters before trial drug administration as specified in Section 5.2.3.1. An additional safety lab will be collected on day 2 of Cycle 1 (i.e., 24 hours after the first administration of BI 836858). Other lab tests to be included: haptoglobin, direct antiglobulin test, bilirubin (direct and indirect) and free hemoglobin. Non pre-existing abnormal laboratory values (CTCAE Grade 3 or higher) will be followed up every 48 hours until these laboratory values are back to at least CTCAE Grade 1.
- Physical examination completed every second cycle beginning with cycle 1. Physical exam may be completed up to 2 days prior to administration and ECOG must be completed on the day of the administration. Height and weight (only at Day 1 of first cycle). If the first administration is completed within 3 days of the screening visit, these examinations do not need to be repeated.
- Vital signs at time points specified in Section 5.2.5.1
- Serum pregnancy test in women of childbearing potential (required at odd-numbered administrations e.g. 1, 3, 5, 7).
- 12-lead ECG (required at Visit 1 of each cycle)
- Adverse events (AEs)

- Changes in concomitant therapies
- Bone marrow aspiration (Required before the 5th and 9th administration of BI 836858 and at the discretion of the Investigator).

- Administration of BI 836858 after final confirmation of dose tier
- Eligibility for further administration may be performed up to 2 days prior to this visit (at administration 2 and beyond).

6.2.2.2 Visit 2 and Visit 4 (± 1 day window allowed beginning in Cycle 3), following administration of BI 836858

In Cycles 1 and 2, visits will occur at Day 4 and Day 11 after the administration. Beginning in Cycle 3 and thereafter, patients will come to the clinic only for infusions and will not be required to complete the visits on Day 4 and Day 11 unless medically indicated. On the Visit 2 and Visit 4 days, the following parameters and investigations will be obtained and / or performed:

- Safety lab parameters before trial drug administration as specified in Section 5.2.3.1
- Vital signs at time points specified in Section 5.2.5.1
- Adverse events (AEs)
- Changes in concomitant therapies

6.2.3 End of treatment and follow-up period for refractory or relapsed AML patients

6.2.3.1 EOT visit

This visit includes an evaluation for further treatment. Those patients with clinical benefit after 8 administrations and who are tolerating the infusions well may continue until PD or other criteria for withdrawal are met as noted in Section 3.3.4.1. For those patients who will receive more than 8 administrations, this visit is to be performed 7 days (± 2 days) after the 8th administration of BI 836858. For those patients who receive <8 administrations, this visit is to be performed 14 days (± 2 days) after the last administration of BI 836858.

If the patient concludes the trial within a treatment cycle not at the end of a treatment cycle, the information required to be collected at the EOT visit should be obtained immediately.

The following parameters and investigations will be obtained and /or performed:

- Safety lab parameters and urine analysis as specified in Section 5.2.3.1
- Physical examination, weight
- Vital signs at time points specified in Section 5.2.5.1
- Serum pregnancy test in women of childbearing potential.
- 12-lead ECG
- Adverse events (AEs)
- Changes in concomitant therapies
- Bone marrow aspiration.

- Eligibility for further administration may be performed up to 2 days prior to this visit.
- End of active trial treatment. This will include the reason for conclusion of trial if applicable, premature discontinuation of trial, and date of last administration of the trial drug.

6.2.3.2 Further treatment (Visit 1 and Visit 2)

These visits are only for those patients with clinical benefit after 8 administrations and who are tolerating the infusions well. Patients can receive further treatment once the result from the bone marrow assessment from EOT is available. Procedures already done at EOT (i.e., safety lab, pregnancy test) do not need to be repeated at FTE if FTE visit is within 7 days from EOT. The patients will continue to receive weekly infusions until PD or other criteria for withdrawal are met as noted in Section 3.3.4.1.

Prior to each infusion, the following parameters and investigations will be obtained and /or performed:

- Safety lab parameters before trial drug administration as specified in Section 5.2.3.1
- Physical examination every other cycle starting with cycle 5 (may be completed up to 2 days prior) and ECOG performance score.
- Vital signs at time points specified in Section 5.2.5.1
- Serum pregnancy test in women of childbearing potential (required at odd-numbered administrations e.g. 9, 11, 13 etc.)
- Adverse events (AEs)
- Changes in concomitant therapies
- Administration with BI 836858
- Eligibility for further administration may be performed up to 2 days prior to this visit.

6.2.3.3 End of further treatment

This visit is only for those patients who received administrations in further treatment and should be performed 14 days (± 2 days) after the last administration of BI 836858.

ECG, bone marrow aspiration, will be performed at EOFT only if the patient has completed at least 2 cycles (e.g. received 4 administrations) since the EOT visit.

The following parameters and investigations will be obtained and /or performed:

- Safety lab parameters and urine analysis as specified in Section 5.2.3.1
- Physical examination including weight (may be completed up to 2 days prior)

- Vital signs at time points specified in Section 5.2.5.1
- Serum pregnancy test in women of childbearing potential
- 12 lead ECG (completed only in patients who receive at least 4 administrations since EOT visit)
- Adverse events (AEs)
- Changes in concomitant therapies
- Bone marrow aspirate (completed only in patients who receive at least 4 administrations since EOT visit)

6.2.4 Treatment period for AML patients in CR

6.2.4.1 Visit 1– Day 1 of BI 836858 administration (administrations 1-3)

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

- Review of inclusion and exclusion criteria (patient eligibility), prior to the first administration only
- Safety lab parameters before trial drug administration as specified in Section 5.2.3.1. An additional safety lab will be collected on day 2 of Cycle 1 (i.e., 24 hours after the first administration of BI 836858). Other lab tests to be included: haptoglobin, direct antiglobulin test, bilirubin (direct and indirect) and free hemoglobin. Non pre-existing abnormal laboratory values (CTCAE Grade 3 or higher) will be followed up every 48 hours until these laboratory values are back to at least CTCAE Grade 1.
- Physical examination and ECOG performance score completed every second cycle beginning with cycle 1. Physical exam may be completed up to 2 days prior to administration and ECOG must be completed on the day of the administration. Height and weight (only at Day 1 of first cycle). If the first administration is completed within 3 days of the screening visit, these examinations do not need to be repeated.

- Vital signs at time points specified in Section 5.2.5.1
- Serum pregnancy test in women of childbearing potential (required at odd-numbered administrations e.g. 1, 3, 5, 7).
- 12-lead ECG (required at Visit 1 of each cycle)
- Adverse events (AEs)
- Changes in concomitant therapies
- Bone marrow aspiration (at the discretion of the Investigator).

- Peripheral blood for disease assessment. If suspicion of relapse, bone marrow aspiration (or biopsy) for disease assessment is to be performed.

- Administration of BI 836858 after final confirmation of dose tier
- Eligibility for further administration may be performed up to 2 days prior to this visit (at administration 2 and beyond).

6.2.4.2 Further treatment

These visits are only for those patients who have received 3 infusions and are tolerating the infusions well. Patients can receive further treatment every second cycle (i.e., Cycle 5 Day 1, Cycle 7 Day 1, etc.). The patients will continue to receive monthly infusions for overall up to one year of treatment or until PD or other criteria for withdrawal are met (as noted in Section 3.3.4.1).

Prior to each infusion, the following parameters and investigations will be obtained and /or performed:

- Safety lab parameters before trial drug administration as specified in Section 5.2.3.1
- Physical examination every other cycle starting with cycle 5 (may be completed up to 2 days prior)
- Vital signs at time points specified in Section 5.2.5.1
- 12-lead ECG (required at Visit 1 of each cycle)
- Serum pregnancy test in women of childbearing potential (required at odd-numbered administrations e.g. 5, 7, 9 etc.)
- Adverse events (AEs)
- Changes in concomitant therapies
- Peripheral blood for disease assessment. If suspicion of relapse, bone marrow aspiration (or biopsy) for disease assessment is to be performed.
- Administration with BI 836858
- Eligibility for further administration may be performed up to 2 days prior to this visit.

6.2.4.3 End of Treatment (EOT) visit

The EOT visit will be performed as soon as possible but no later than one week (7 days) after permanent discontinuation of trial medication for any reason, or when the Investigator decides with the patient to permanently discontinue the trial medication.

If the patient concludes the trial within a treatment cycle not at the end of a treatment cycle, the information required to be collected at the EOT visit should be obtained immediately.

The following parameters and investigations will be obtained and /or performed:

- Safety lab parameters and urine analysis as specified in Section 5.2.3.1
- Physical examination, weight
- Vital signs at time points specified in Section 5.2.5.1
- Serum pregnancy test in women of childbearing potential.
- 12-lead ECG
- Adverse events (AEs)
- Changes in concomitant therapies
- Bone marrow aspiration.

- Peripheral blood for disease assessment. If suspicion of relapse, bone marrow aspiration (or biopsy) for disease assessment is to be performed.

- End of active trial treatment. This will include the reason for conclusion of trial if applicable, premature discontinuation of trial, and date of last administration of the trial drug.
- In case the patient receives further anti-cancer treatment: regimen, drug name and start and stop dates

6.2.4.4 End of Residual Effect Period visit (EoR)

The REP is defined in Section 5.2.2.2. The End of REP (EoR) visit should not be performed earlier than 30 days after permanent discontinuation of the trial medication. The information collected at this visit should include all new reportable AEs that occurred after EOT and a follow-up of adverse events ongoing at EOT.

The following parameters and investigations will be obtained and / or performed:

- Date and type of contact
- Vital Signs
- Safety laboratory parameters only if not within normal range at EOT
- 12-lead ECG only if abnormal at EOT and pathological findings were not present at baseline

- Follow-up of adverse events in case they were not yet recovered at EoT visit
- Documentation of concomitant medications only if indicated for treatment of adverse events
- In case the patient receives further anti-cancer treatment: regimen, drug name and start and stop dates

6.2.5 Follow up

Follow up (FU) visits will be performed for both patient populations. These visits will occur after the patient has completed treatment according to protocol or is not eligible for further treatment cycles. These follow-up visits will begin 4 weeks after the last infusion with BI 836858. In patients with AML in CR, follow-up visit 1 (FU1) is the same as EoR. Follow up will end in case the patient is lost to follow-up or in case the Investigator and Sponsor agree not to pursue further follow up visits. Follow up visits should be performed at 4 week intervals or earlier if appropriate as determined by the Investigator.

Follow-up visits should be completed at the investigational site but may be performed by telephone interview in case the patient is unable to visit the Investigator. Follow-up visits should be performed for 6 months after the last infusion with BI 836858. At the last follow-up visit, and end of trial assessment will be performed and documented in the eCRF. For follow-up of patients with adverse events which have not recovered at the last planned follow-up visit please refer to Section 5.2.2.2.

The following will be obtained and / or performed:

- Safety laboratory (hematology, biochemistry including serum immunoglobulin levels and direct antiglobulin test, coagulation, urine; for details please refer to Section 5.2.3.1)
- Physical examination, vital signs.
- AEs since last visit in case they occurred during the observational period (42 days after the last trial drug administration in refractory or relapsed AML patients) or residual effect period (REP, 30 days after the last trial drug administration) or are considered drug-related (see Section 5.2.2.1)
- Concomitant therapy indicated for treatment of an AE
- Follow-up of AEs in case they were not yet recovered at EOT
- Bone marrow aspirate, if indicated
- Treatment with any other anti-leukemia drug (report date of treatment and drug)
- Vital status evaluated at each follow up visit

6.2.6 End of the whole trial

The clinical trial will be analysed and reported after the last patient has completed 4 treatment cycles or stopped treatment prior to completion of cycle 4. In case the trial is ended by the

Sponsor when patients are still being treated with BI 836858 when the final report of the trial is being prepared, the patients will either be included in a follow-up trial or alternatively kept on treatment in this trial. Those patients will then be reported in a revised report and it will be noted in the original report that such a revised report will be written.

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 STATISTICAL DESIGN - MODEL

This trial will be performed as an open-label study. The primary objective of the trial is to determine the MTD of BI 836858 for both patient populations separately. To determine the MTD, patients are entered sequentially into escalating dose tiers using the 3+3 design (see Section 3.1). After the MTD has been determined, up to 12 patients for each patient population are additionally entered at this dose level to better characterize the safety of BI 836858.

7.2 NULL AND ALTERNATIVE HYPOTHESES

The analyses in this trial are descriptive and exploratory. No formal statistical tests will be performed.

7.3 PLANNED ANALYSES

For the determination of the MTD, only MTD evaluable (i.e. non-replaced patients) will be considered.

For the analysis of secondary all patients in the treated set (i.e. patients treated with at least one dose of BI 836858) will be included in the analysis, including the patients who have been replaced for any reason (see Section 3.3.4.1).

7.3.1 Primary analyses

The primary objective for this study is to identify the MTD (for both patient populations separately) and to investigate the safety profile of BI 836858. MTD is defined in Section 3.1, and will be identified by the occurrence of DLT in the dose escalation scheme. In order to identify the MTD, the number of patients with a DLT during the first two cycles at each dose level will be presented. Patients who discontinue during the first two treatment cycles for reasons other than DLT will be excluded from the determination of MTD.

However, for those patients who receive more than two cycles of BI 836858, all AEs that constitute a DLT will be taken into consideration for the purpose of determining the recommended dose for the expansion cohort or the recommended dose for subsequent phase II trial(s).

DLT is defined in Section 5.2.1.1. For the analysis of the tolerability and safety, please refer to Section 7.3.3.

The primary analysis will take place when all patients from the dose escalation and dose expansion cohorts have had a minimum of 4 cycles or have discontinued from the trial prior to reaching end of cycle 4 due to meeting the criteria for withdrawal as outlined in Section 3.3.4.1.

In case patients are still being treated at the time of the primary analysis, a revised clinical trial report (CTR) will be created when the last patient has completed his/her last visit, including all primary and secondary analyses.

7.3.2 Secondary analyses

This section outlines the analyses for the secondary as defined in Section 5.1.1.

7.3.2.3 Best overall response

Each patient will be assigned to one of the response categories described in Section 5.1.2.3. Each patient's best overall response will be used as a primary measure. To describe response over time, the proportion of patients in each response category will be tabulated at specified time intervals. The number of patients with objective response (best response of CR, CRi, or PR) will be summarized. Patients will be followed up for assessment of response and progression until they progress, receive any other anti-leukemia 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. Frequency distribution and other descriptive statistical measures will be used to examine these variables.

7.3.2.4 Progression free survival, time to treatment failure

These time-to-event variables will be analyzed with the Kaplan-Meier method.

In case there is no occurrence of death, progression or treatment failure 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. Details of censoring rules will be provided in the statistical analysis plan.

The cause of death will be summarized, along with whether death was plausible related to disease progression.

7.3.3 Safety analyses

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary. Standard BI summary tables and listings will be produced. All adverse events with an onset between start of treatment and end of the residual effect period (REP), a period of 30 days after the last dose of trial medication, will be assigned to the treatment period for evaluation.

All treated patients will be included in the safety analysis. In general, safety analyses will be descriptive in nature and will be based on BI standards. No hypothesis testing is planned.

Statistical analysis and reporting of adverse events will concentrate on treatment-emergent adverse events. To this end, all adverse events occurring between start of treatment and end of the residual effect period will be considered 'treatment-emergent'. The residual effect period is defined as a period of 30 days after the last dose of trial. Adverse events that start before first drug intake and deteriorate under treatment will also be considered as 'treatment-emergent'.

Frequency, severity, and causal relationship of adverse events will be tabulated by system organ class and preferred term after coding according to the current version of the Medical Dictionary for Drug Regulatory Activities (MedDRA).

Laboratory data will be analysed both quantitatively as well as qualitatively. The latter will be done via comparison of laboratory data to their reference ranges. Values outside the reference range as well as values defined as clinically relevant will be highlighted in the listings. Treatment groups will be compared descriptively with regard to distribution parameters as well as with regard to frequency and percentage of patients with abnormal values or clinically relevant abnormal values.

Vital signs, physical examinations, or other safety-relevant data observed at screening, baseline, during the course of the trial and at the end-of-trial evaluation will be assessed with regard to possible changes compared to findings before start of treatment.

7.3.4 Interim analyses

The sponsor will continuously monitor safety. The dose escalation design foresees that regular safety evaluations are performed. These evaluations will be un-blinded to dose.

No formal interim analysis of efficacy data is foreseen, although efficacy data when available may be considered as part of the safety evaluations.

As patients with refractory or relapsed AML are known to have low monocyte counts and functional abnormalities of NK cells, both of which are required for the mode of action of BI 836858 (see Section 2.1), detailed evaluations will be performed to ensure a positive benefit-risk assessment in this patient population. If considered unjustifiable, treatment of patients with refractory or relapsed AML may be terminated based on these interim evaluations.

Results of this evaluation of patients with refractory or relapsed AML will be documented and stored. If applicable, the format and the detailed content of the analysis will be defined in the statistical analysis plan.

If considered necessary, a preliminary safety evaluation may also be performed in AML patients in CR. This analysis will have no impact on the further conduct of the trial but can become necessary for internal project purposes. Results of this evaluation will be documented and stored. If applicable the format and the detailed content of such a preliminary analysis will be defined in the statistical analysis plan.

7.4 HANDLING OF MISSING DATA

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

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

The occurrence of missing data should be minimized 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.

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

7.5 RANDOMISATION

This is a non-randomized Phase I trial. All the patients will receive BI 836858.

7.6 DETERMINATION OF SAMPLE SIZE

Patients with refractory or relapsed AML:

Assuming 4 cohorts of 3 patients (i.e. no patients with DLT at given level) and 2 cohorts of 6 patients (i.e. 1 DLT witnessed in first 3 patients so further 3 patients exposed with no DLTs), 24 evaluable patients will be necessary for the dose escalation part.

Together with an assumed number of 12 additional patients for the expansion cohort this leads to an expected sample size of 36 evaluable patients.

AML patients in CR:

Assuming 1 cohort of 3 patients (i.e. no patients with DLT at given level) and 2 cohorts of 6 patients (i.e. 1 DLT witnessed in first 3 patients so further 3 patients exposed with no DLTs), 15 evaluable patients will be necessary for the dose escalation part in this patient population.

Together with an assumed number of 12 additional patients for the expansion cohort this leads to an expected sample size of 27 evaluable AML patients in CR.

Note that in general, the sample size is induced by the 3+3 design and is subject to different random factors.

8. INFORMED CONSENT, DATA PROTECTION, TRIAL RECORDS

The trial will be carried out in compliance with the protocol, the principles laid down in the Declaration of Helsinki, in accordance with the ICH Harmonised Tripartite Guideline for Good Clinical Practice (GCP) and relevant BI Standard Operating Procedures (SOPs). Standard medical care (prophylactic, diagnostic and therapeutic procedures) remains in the responsibility of the treating physician of the patient.

The Investigator should inform the Sponsor immediately of any urgent safety measures taken to protect the study subjects against any immediate hazard, and also of any serious breaches of the protocol/ICH GCP.

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.

8.1 STUDY APPROVAL, PATIENT INFORMATION, AND INFORMED CONSENT

This trial will be initiated only after all required legal documentation has been reviewed and approved by the respective Institutional Review Board (IRB) / Independent Ethics Committee (IEC) and competent authority (CA) according to national and international regulations. The same applies for the implementation of changes introduced by amendments.

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 authorized CML/Clinical Research Associate (CRA) or Clinical Quality Assurance auditors appointed by Boehringer Ingelheim, by appropriate IEC members, and by inspectors from regulatory authorities.

8.2 DATA QUALITY ASSURANCE

The trial will be conducted in compliance with the protocol, the principles laid down in the Declaration of Helsinki (please, refer to Section 8), local law and according to the principles of GCP and the company SOPs. To inform all Investigators about the trial drugs and the

procedures of the trial, either an Investigator meeting will be performed prior to start of the trial, or each Investigator will be visited individually by the Clinical Monitor and the 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 8.3.1.

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 Clinical Trial Master File (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.

A quality assurance audit/inspection of this trial may be conducted by the Sponsor or Sponsor's designees or by IRBs/IECs or by regulatory authorities. 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.

8.3 RECORDS

Case Report Forms (CRFs) for individual patients will be provided by the Sponsor via remote data capture. For drug accountability, refer to Section 4.1.8.

8.3.1 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 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.

8.3.2 Direct access to source data and 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 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 8.3.1.

8.4 LISTEDNESS AND EXPEDITED REPORTING OF ADVERSE EVENTS

8.4.1 Listedness

To fulfil the regulatory requirements for expedited safety reporting, the Sponsor evaluates whether a particular adverse event is "listed", i.e. is a known side effect of the drug or not. Therefore a unique reference document for the evaluation of listedness needs to be provided. For BI 836858 this is the current version of the IB (c02324887-03). The current versions of these reference documents are provided in the ISF.

8.4.2 Expedited reporting to health authorities and IECs/IRBs

Expedited reporting of SAEs, e.g. suspected unexpected serious adverse reactions (SUSARs) to health authorities and IECs/IRBs, will be done according to local regulatory requirements. Further details regarding this reporting procedure are provided in the ISF.

8.5 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 authority.

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10. APPENDICES

10.1 PUBLICATION POLICIES

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).

The present trial will be published in a clinical trial registry indicating the trial dates and indication as well as the number of sites and location.

10.2 EASTERN COOPERATIVE ONCOLOGY GROUP (ECOG) PERFORMANCE STATUS

ECOG PERFORMANCE STATUS (R01-0787)

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

10.3 CLINICAL EVALUATION OF LIVER DISEASE

10.3.1 Introduction

Alterations of liver laboratory parameters, as described in Section 5.2.2.1 (Protocol-Specified Significant Events), are to be further evaluated using the following procedures:

10.3.2 Procedures

Repeat the following lab tests: ALT, AST, and bilirubin (total and direct) - within 48 to 72 hours. If ALT and/or AST >3-fold ULN combined with an elevation of total bilirubin >2-fold ULN are confirmed, results of the laboratory parameters described below must be made available to the Investigator and to BI as soon as possible.

In addition,

- obtain a detailed history of current symptoms and concurrent diagnoses and medical history according to the "Drug Induced Liver Injury (DILI) checklist" provided in the ISF
- obtain history of concomitant drug use (including non-prescription medications, herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets according to the "DILI checklist" provided in the ISF;
- obtain a history of exposure to environmental chemical agents (consider home and work place exposure) according to the "DILI checklist" provided in the ISF; and report these via the CRF.

Clinical chemistry
Alkaline phosphatase, albumin, PT or INR, CK, CK-MB, coeruloplasmin, α-1 antitrypsin, transferin, amylase, lipase, fasting glucose, cholesterol, triglycerides

Serology
Hepatitis A (Anti-IgM, Anti-IgG), Hepatitis B (HbsAg, Anti-HBs, DNA), Hepatitis C (Anti-HCV, RNA if Anti-HCV positive), Hepatitis D (Anti-IgM, Anti-IgG), Hepatitis E (Anti-HEV, Anti-HEV IgM, RNA if Anti-HEV IgM positive), Anti-Smooth Muscle antibody (titer), Anti-nuclear antibody (titer), Anti-LKM (liver-kidney microsomes) antibody, Antimitochondrial antibody

Hormones, tumor marker
TSH

Haematology
Thrombocytes, eosinophils

- Provide abdominal ultrasound to rule out biliary tract, pancreatic or intrahepatic pathology, e.g. bile duct stones or neoplasm.

- Initiate close observation of subjects by repeat testing of ALT, AST, and total bilirubin (with fractionation by total and direct) at least weekly until the laboratory ALT and/or AST abnormalities stabilize or return to normal, then according to the protocol. Depending on further laboratory changes, additional parameters identified e.g. by reflex testing will be followed up based on medical judgment and Good Clinical Practice (GCP).

11. DESCRIPTION OF GLOBAL AMENDMENTS

Number of global amendment		01
Date of CTP revision		13 April 2012
EudraCT number		N/A
BI Trial number		1315.1
BI Investigational Product(s)		BI 836858
Title of protocol		A Phase I, open, cohort dose escalation trial with BI 836858 in patients with refractory or relapsed acute myeloid leukemia
To be implemented only after approval of the IRB/IEC/Competent Authorities		☒
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		☐
Can be implemented without IRB/IEC/ Competent Authority approval as changes involve logistical or administrative aspects only		☐
Section to be changed		Title page
Description of change		Change of TCM and contact information; Status: "Final Protocol" has been removed and "Revised Protocol (based on Global Amendment 01)" has been added Version and Date: Version 1.0 has been replaced with Version 2.0
Rationale for change		Clarification and update
Section to be changed		Section 3.3.3 Exclusion Criteria
Description of change		The following exclusion criterion has been added: **Patients who are candidates for allogeneic stem cell transplantation.**
Rationale for change		Clarification that all eligible patients should have

Number of global amendment		01
		received all standard therapies available for AML, before participating in a first in human trial
Section to be changed		Section 4.1.3 Selection of doses in the trial and Table 4.1.3: 1 Entry of patients into trial, by cohort
Description of change		Section 4.1.3: Clarification of the cohort dose escalation phase for enrolment of patients into the first dose cohort of 10 mg Table 4.1.3: 1: Addition of footnote for clarification of cohort dose escalation phase for enrolment of patients into the first dose cohort of 10 mg
Rationale for change		Clarification

Number of global amendment		**02**
Date of CTP revision		14 Jun 2013
EudraCT number		N/A
BI Trial number		1315.1
BI Investigational Product(s)		BI 836858
Title of protocol		A Phase I, open, cohort dose escalation trial with BI 836858 in patients with refractory or relapsed acute myeloid leukemia
To be implemented only after approval of the IRB/IEC/Competent Authorities		☒
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		☐
Can be implemented without IRB/IEC/ Competent Authority approval as changes involve logistical or administrative aspects only		☐
Section to be changed		Title page
Description of change		Status: "Revised Protocol (based on Global Amendment 01)" has been updated to be "Revised Protocol (based on Global Amendments 01 and 02)" Version and Date: Version 2.0 has been replaced with Version 3.0
Rationale for change		Clarification and update
Section to be changed		Protocol Synopsis
Description of change		Objective: "refractory or relapsed" has been added Mode of admin: the time period of the infusion "over 3 hours" was deleted Duration of treatment: Language has been updated from "Those patients with partial response (PR) or complete response (CR) after 8 administrations and who are tolerating the infusions may continue until progressive disease (PD)" to read *"Those patients with clinical benefit as defined by International Working Group (IWG) objective response (partial*

Number of global amendment		**02**
		remission (PR) or complete remission (CR) or complete remission with incomplete blood recovery (CRi)) or subjective response (in the absence of objective response) after 8 administrations and who are tolerating the infusions may continue until progressive disease (PD).” Criteria for safety: The following parameters have been added: “vital signs, ECG, physical examination and”
Rationale for change		Clarification and update
Section to be changed		Flow Chart
Description of change		Trial Period: “Demographics” has been updated to “Demographics and baseline conditions”, “Adverse events” has been marked to be collected at screening, “Pharmacokinetics” and “Anti-drug antibodies” have been marked to be collected at further treatment visits, and “Vital Status” has been added. Footnotes: EOT footnote replaced “CR” with “CRi or CR” ** section has replaced “CR” with “CRi or CR” Footnote 3 has removed “footnote 1” and replaced with “footnote 2” Footnote 4 wording has been added: “An additional safety lab will be collected on day 2 *(i.e., 24 hours after the first administration of BI 836858).Other lab tests to be included: haptoglobin, direct Coombs test, and bilirubin (direct and indirect)”.* Footnote 10 has been updated to: Bone marrow aspirate to assess efficacy before 5th and 9th administrations “*(i.e., BM performed on Day 1 (+/- 1) of cycles 3 and 5 and treatment started on day 1 (up to +3) of cycles 3 and 5)”* Footnote 14 has removed “Cycle 1 Day 9, Cycle 2 Day 2, and Cycle 2 Day 9 in addition to those” and been updated to “Sampling at the time points specified in Tables 1 and 2. As noted in Tables 1 and 2 PK sampling timepoints specify visits on Cycles 1 and 2 Days 1, 2, 4, 8, 9 and 11 and EOT and on Cycle ≥ 3 Days 1 and 8 and EOT/EOFT as noted in the Flow Chart. Footnote 17 has been updated to *“After the 8th infusion, at the end of treatment visit, patients will be evaluated to determine if they have clinical*

Number of global amendment		**02**
		benefit, as defined by IWG objective response (PR, CRi or CR) or subjective response (in the absence of objective response) and are tolerating the infusions well and who would like to continue to receive infusions until PD or other criteria for withdrawal are met as noted in Section 3.3.4.1. For each infusion past the 8th administration, patients will continue to be assessed after each cycle for clinical benefit (objective or subjective response), and that they are tolerating the infusions well and would like to continue until PD or other criteria for withdrawal are met as noted in Section 3.3.4.1."
Rationale for change		Clarification and update. For footnote 4, an additional safety lab was added on day 2, 24 hours after the first administration of BI 836858. The aim is to observe elevated laboratory values earlier and, with additional parameters (e.g. liver enzymes) to better understand the cause of the laboratory values. Non pre-existing abnormal laboratory values (CTCAE Grade 3 or higher) will be followed up every 48 hours until these laboratory values are back to at least CTCAE Grade 1.
Section to be changed		Table 1 and Table 2
Description of change		Blood sampling timepoints have been updated in both tables. For Table 2, additional blood sampling timepoints have been added for cycles≥3
Rationale for change		Update

Number of global amendment		**02**
		The schedule to investigate cytokine levels at specific timepoints was adapted following the FDA guidance (Draft Guidance for Industry Immunogenicity Assessment for Therapeutic Protein Products).
Section to be changed		Abbreviations
Description of change		"ASCT Allogeneic stem cell transplantation" was added. In CRi abbreviation, "marrow" was removed and "blood" was added. "NK Natural Killer (cells)" was added.
Rationale for change		Clarification and update
Section to be changed		Section 1.1 Medical Background
Description of change		"Objective response was defined as either CR, CRi or PR" was added
Rationale for change		Clarification and update
Section to be changed		Section 2.2 Trial Objectives
Description of change		Section was revised to read as follows: The primary objective of this trial is to determine the maximum tolerated dose (MTD) of BI 836858. BI 836858 is a new biological entity (NBE) and the MTD may not be reached. ~~Even if no MTD is reached the highest dose of BI 836858 that may be tested is 800 mg.~~ To learn more about the safety and prel**i**minary effica**c**y there will be an expansion cohort either at the MTD or ~~800mg.~~ "*the highest tested dose (e.g. 320 mg).*"
Rationale for change		Clarification and Update
Section to be changed		Sections Flow Chart- EOT footnote, 2.2, 3.3.3, 3.3.4.1, 5.5.1, 5.5.2.1, 5.5.3.2, 5.6, 5.6.2, 5.6.3, 6.2.2.2, 6.2.3.1, 7.3, 7.3.2.4, 10.3
Description of change		Grammatical and spelling updates
Rationale for change		Grammatical and spelling updates
Section to be changed		Section 3.1 Overall Trial Design and Plan
Description of change		Text was revised and dose levels were modified as follows: "*The dose is planned to be escalated in cohorts at pre-defined dose levels based on a multiplication factor of* ***2.*** ~~*3 in the low dose range, and a factor of approximately 2 at doses higher than 90 mg.*~~ ***The dose levels are 10 mg, 20 mg, 40 mg, 80 mg, 160 mg, and 320 mg*** ~~*10 mg, 30 mg, 90 mg, 200 mg, 400 mg, and 800 mg*~~ *as outlined in Section 4.1.3.* ~~*However,*~~ ***I****ntermediate dose levels* ***and levels higher than 320 mg*** *may be investigated if agreed*

Number of global amendment		**02**
		upon between Investigator and Sponsor." *"In case no MTD is reached up to the highest planned dose* ***(e.g., 320 mg),*** ~~*of 800 mg,*~~ *12 additional patients will be treated with once weekly* ***highest test dose (i.e., 320 mg)*** ~~*800 mg*~~ *of BI 836858."* Clarification of treatment in the dose escalation phase of the trial as follows: *"During the dose escalation phase, each patient will receive up to 2 repeated treatment cycles. In patients who show clinical benefit as defined by IWG objective response (CR, CRi, PR), or subjective response (in the absence of objective response) as defined by the Investigator after 2 cycles, the number of cycles on the same dose level may be increased to 4 (8 administrations) upon agreement between Investigator and Sponsor. This includes Cycle three (administration of BI 836858 on Days 29 and 36) and cycle four (administration of BI 836858 on Days 43 and 50). Continuation of treatment will be discussed between Investigators and Sponsor at each cycle."* Text has been revised as follows: Patients who show "*clinical benefit",* **(**CR, *CRi,* PR, or *subjective response)* ~~clinical benefit~~ as defined by the Investigator after 4 cycles *"(each cycle individually evaluated)),"* and who are tolerating the infusions well may continue to receive additional cycles upon agreement between Investigator and Sponsor until the patient meets any of the criteria for withdrawal as outlined in Section 3.3.4.1."
Rationale for change		Clarification and Update and Safety. To mitigate the risk of dose dependent side effects, all dose levels will be based on a multiplication factor of two (x2) and the doses pre-defined i.e. 10, 20, 40, 80, 160 and 320 mg of BI 836858.

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Section to be changed		Section 3.2 DISCUSSION OF TRIAL DESIGN, INCLUDING THE CHOICE OF CONTROL GROUP
Description of change		The text was revised as follows: In case no MTD is reached up to the highest planned dose **(e.g., 320 mg),** ~~of 800mg,~~ 12 additional patients will be treated with once weekly **of the highest tested dose (e.g., 320 mg)** ~~800 mg~~ of BI 836858. "And pharmacologic/pharmacodynamic" has been removed from this section.
Rationale for change		Clarification and Update
Section to be changed		Section 3.3 Selection of trial population
Description of change		"About" was added to target of 10 patients.
Rationale for change		Clarification
Section to be changed		Section 3.3.2 Inclusion Criteria
Description of change		Inclusion criteria #2 added "per central laboratory assessment at the Ohio State University". Inclusion criteria #3 added "See Section 10.2". Inclusion criteria #4 removed ">" and replaced with "≥".
Rationale for change		Clarification
Section to be changed		Section 3.3.3 Exclusion Criteria
Description of change		Exclusion criterion #2 – text was revised: "Patients with >30,000 leukocytes/µl in the peripheral blood was changed to "Patients with >5,000 leukocytes/µl in the peripheral blood". Exclusion criterion #3- text was removed and updated for clarification: *"Anti-leukemia therapy within two weeks before first treatment with BI 836858;* ***however, parallel treatment with Hydroxyurea is allowed.*** *~~(Hydroxyurea may be given until 48 hours before the first treatment with BI 836858)~~ (See Section 4.2.2.1)"* Exclusion criterion #13 has removed "the evaluation of efficacy or safety of the trial drug and reads as follows: *"Concomitant intercurrent illness, or any condition which in the opinion of the Investigator, would compromise safe participation in the study, e.g. active severe infection, unstable angina pectoris, new onset of exacerbation of a cardiac arrhythmia"*

Number of global amendment		**02**
Rationale for change		Clarification, update and safety. To control the WBC, a treatment with hydroxyurea is allowed (as noted in Exclusion #3). The parallel use of hydroxyurea may allow patients with a proliferative disease to remain on study. This may also reduce the number of early study withdrawals, especially in the lower dose cohorts, as disease progression may be controlled.
Section to be changed		Section 3.3.4.1 Removal of individual patients
Description of change		"4 administrations (1 cycle)" has been replaced by "4 administrations (2 cycles)".
Rationale for change		Clarification and correction
Section to be changed		Section 4.1 TREATMENTS TO BE ADMINISTERED
Description of change		Text was revised to read as follows: *BI 836858 will be administered as an as a rate-controlled intravenous infusion.* Text was deleted for clarification: (Volume: 250 mL~~), Rate: see Table 4.1.1:1 below)~~
Rationale for change		Posology was revised - update
Section to be changed		Section 4.1.1 Identity of BI investigational product and comparator product
Description of change		Posology was revised from "Infusion over 3 hours" to "Rate controlled infusion". Table 4.1.1: 1 was removed and text was added as explanation for infusion rate as follows: "*The first and second infusion will be started at a rate of 10 mL/h. The infusion rate should be increased every 30 (+/-10) minutes by 10 mL/h to a maximum of 80 mL/h as long as tolerated by the patient. If considered safe by the Investigator, the stepwise increase of infusion rate during the third and subsequent infusions may be faster or steps may be omitted, but the maximum infusion rate must not exceed 120 mL/h. If symptoms of an infusion-related reaction occur, the infusion should be temporarily stopped. Upon recovery, it should be infused at 50% of the rate at which the reaction occurred and should not be dose escalated from this dose for at least 30 minutes. Lower rates may be selected if clinically indicated. Depending on the time of occurrence and the severity of the reaction, the investigator may consider administering additional*

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		supportive medication, e.g. corticosteroids. A stepwise re-increase of the infusion rate to a maximum of 80 mL/h is possible. For medical reasons, in case a patient experiences an adverse event during the infusion, the duration of the infusion may be expanded until the use-by date and use-by time indicated on the label is reached. The actual duration of the infusions and the infusion steps need to be documented in the eCRF including actual start and end time, actual time points for interruption and restart of the infusion and the actual infusion rates."
Rationale for change		Clarification and Update. The stepwise increase of the infusion rate of BI 836858 was adapted and an upper limit of 80ml/hr is defined in the protocol amendment. However, some flexibility is given in case the first four administrations of BI 836858 are well tolerated.
Section to be changed		Section 4.1.3 Selection of doses in the trial
Description of change		Text was modified as follows: "BI 836858 will be administered as a rate-controlled~~,~~ intravenous infusion ~~as noted in Table 4.1.1: 1 over 3 hours~~ every 7 days." The text referring to dose levels was modified: "The dose is planned to be escalated in cohorts at pre-defined dose levels based on a multiplication factor of **2**. ~~3 in the low dose range, and a factor of approximately 2 at doses higher than 90 mg~~. ~~The dose levels are 10 mg, 30 mg, 90 mg, 200 mg, 400 mg, and 800 mg. However,~~ **The dose levels are 10 mg, 20 mg, 40 mg, 80 mg, 160 mg, and 320 mg. I**ntermediate **dose levels and** dose levels **higher than 320 mg** may be investigated if agreed upon between Investigator and Sponsor. Clarification that enrolment into the next highest dose cohort has been corrected from "14 days" to "28 days". Text was modified: In case no MTD is reached up to the highest ~~planned~~ **tested** dose **(e.g. 320 mg),** ~~of 800 mg,~~ 12 additional patients will be treated with

Number of global amendment		**02**
		once weekly **with the highest tested dose (e.g. 320 mg)** ~~800 mg~~ of BI 836858 in the expansion cohort.
Rationale for change		Clarification and update To mitigate the risk of dose dependent site effects, all dose levels will be based on a multiplication factor of two (x2) and the doses pre-defined i.e. 10, 20, 40, 80, 160 and 320 mg of BI 836858.
Section to be changed		Section 4.1.4 Drug assignment and administration of doses for each patient
Description of change		Updated glucocorticoid i.v., equivalent to prednisolone dose from "50mg" to "100mg" Language updated to read as follows: *"If BI 836858 has been well tolerated without signs of infusion-related reactions in the first administration, glucocorticoid premedication may be reduced to a dose equivalent to* ~~*25*~~ ***50*** *mg prednisolone for the second* ***through fourth*** *administration****s, and in case this is well tolerated reduce the steroids with the 5th infusion (25 mg with 5th and 0 mg with the 6th infusion.) However, in case an administration of BI 836858 was not well tolerated the premedication with prednisolone can be re-escalated up to 100 mg."***
Rationale for change		Update. To further mitigate the risk of infusion related symptoms, the prophylaxis, given before each infusion of BI 836858, was adapted
Section to be changed		Section 4.1.4 Drug assignment and administration of doses for each patient
Description of change		Text added for clarification: 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 thrombocytopenia was preexistent prior to trial entry. "*Patients with active leukemia who go from Grade 3 neutropenia to Grade 4 neutropenia after treatment may continue on study provided there is no evidence of infection or febrile neutropenia. Patients with active leukemia who go from Grade 3 to Grade 4 thrombocytopenia after treatment may continue on study provided that post-transfusion platelet count is at least 20,000/uL before therapy is given.*"

Number of global amendment		**02**
Rationale for change		Clarification
Section to be changed		Section 4.1.7 Storage conditions
Description of change		Added "- stored in a refrigerator 36-46°F (2-8°C); do not freeze".
Rationale for change		Clarification
Section to be changed		Section 4.2.2.1 Restrictions regarding concomitant treatment
Description of change		The word "the" was removed from text Text was modified and added to allow use of Hydroxyurea as follows: "Prior anti-leukemia therapy must have been discontinued at least two weeks before the first administration of the trial drug (Hydroxyurea may be given ***during study participation)*** ~~until 48 hours before the first treatment with BI 836858)~~ and the patient must have recovered from all clinically relevant reversible toxicities as determined by the investigator. ***"For peripheral blood blast control, as this may correlate with the risk of occurrence of infusion related symptoms, hydroxyurea will be allowed (maximum dose of hydroxyurea 3gm daily) before and during study participation. Leukocyte must be ≤ 5,000/µl at start of each administration of BI 836858.*** ~~During the first two dose cohorts, if in the first cycle more than 2 patients who receive BI 836858 experience a leukocyte count over 40,000/µl indicative of disease progression, then hydroxyurea will be allowed (maximum dose of hydroxyurea 3gm daily) during the week after the first infusion of BI 836858 for all subsequent patients.~~ ~~If the change of permitting hydroxyurea is implemented and more than 2 of the next 6 patients experience the leukocytosis (40,000/µl indicative of disease progression) and discontinue the due to disease progression in the first cycle, then the eligibility criteria will be modified such that patients requiring hydroxyurea within a week of study entry to maintain WBC <30,000/ul will no longer be eligible.~~

Number of global amendment		**02**
Rationale for change		Clarification and update. To control the WBC, a treatment with hydroxyurea will be allowed. The parallel use of hydroxyurea may allow patients with a proliferative disease to remain on the study. This may also reduce the number of early study withdrawals, especially in the lower dose cohorts, as disease progression may be controlled.
Section to be changed		Section 5.1.2.3 Assessment and definition of best overall response
Description of change		Language updated for clarification to read as follows: *"Response will be assessed according to the criteria from the IWG based on laboratory data from the peripheral blood, bone marrow examination, ~~and~~ clinical examination (at the end of each cycle), ~~e.g. prior to the next dose of BI 836858,~~ at the evaluation for further treatment-visit and~~,~~ the EOT-visit.~~, and at all follow up visits~~. Bone marrow examination will be performed before the Cycle 3 and Cycle 5 (5th and 9th administration of BI 836858) (i.e., BM performed on Day 1 (+/-1) of cycles 3 and 5 and treatment started on Day 1 (up to +3) of cycles 3 and 5) and at the discretion of the Investigator, e.g. in case clinical and laboratory examinations of peripheral blood demonstrate that a CR has been achieved, or for assessment of persistent neutropenia, anemia or thrombocytopenia.*" Treatment Failure: added " Resistant disease: Patient survives ≥7 days post-course of treatment; persistent leukemia in blood or bone marrow. Aplasia: Patient survives ≥7 days post-course of treatment; death while cytopenic, with aplastic bone marrow Indeterminate cause: Patients who die < 7 days posttherapy. Patients who die > 7 days posttherapy with no peripheral blood blasts, but no bone marrow examination. Patients who do not complete the first course of therapy. Morphologic relapse: Reappearance of blasts post-CR in peripheral blood or bone marrow." Progressive Disease: removed "10%" for increase of

Number of global amendment		**02**
		blast population in bone marrow or peripheral blood and replaced with "50%".
Rationale for change		Clarification and update
Section to be changed		
Rationale for change		Updated
Section to be changed		Section 5.2.2.1 Definitions of adverse events
Description of change		Protocol-specified significant events: Updated for patients with impaired liver function at baseline "2.5" was removed and replaced with "5.0" times ULN for AST or ALT is considered a protocol-specified significant event. And "1.5" was removed and replaced with "2.0"ULN for bilirubin protocol-specified significant event. Clarification added that SAEs should be reported "(within 24 hours or the next business day whichever is shorter)". Change of spelling in the word DILI
Rationale for change		Clarification and update
Section to be changed		Section 5.2.3.1 General safety laboratory parameters
Description of change		Text added: "*An additional safety lab will be collected on day 2 of Cycle 1 (i.e., 24 hours after the first administration of BI 836858). Other lab tests to be included: haptoglobin, direct Coombs test, bilirubin (direct and indirect) and free hemoglobin. Non pre-existing abnormal laboratory values (CTCAE Grade 3 or higher) will be followed up every 48 hours until these laboratory values are back to at least CTCAE Grade 1."*
Rationale for change		Update
Section to be changed		Section 5.2.5.1 Vital signs

Number of global amendment		**02**
Description of change		Text was updated: Additional time points for blood pressure and heart rate at the day of administration of BI 836858 are: prior to the start of premedication, prior to the start of BI 836858 infusion, *and in 30 (±10) minute intervals throughout the course of the* ~~and 30 (±10), 60 (±10), 90 (±10), 120 (±10), 150 (±10) and 180 (±10) minutes after start of the~~ infusion of BI 836858 and 60 (±10) minutes after the end of the infusion, thereafter every 4-8 hours until at least 24 hours after ~~the~~ start of the infusion.
Rationale for change		Clarification and update
Section to be changed		Section 5.2.5.2 Physical examination
Description of change		Added "height" for clarification of procedures to be performed during a PE.
Rationale for change		Clarification
Section to be changed		Section 5.3.2.1 Demographics and history
Description of change		Updated to include "CRi".
Rationale for change		Clarification
Section to be changed		Section 5.4 Appropriateness of measurements
Description of change		References updated removing "R10-4429" and replacing with "R06-0452".
Rationale for change		Update
Section to be changed		Section 5.5.1

Number of global amendment		**02**
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Number of global amendment		**02**
Section to be changed		Section 6.2.1 Screening and run-in period
Description of change		Updated to be consistent with Flow Chart: "Visit 0" revised to "Visit 1" "and baseline conditions" was added to Demographics
Rationale for change		Clarification

Number of global amendment		**02**
Section to be changed		Added Section 6.2.1.1 Rescreening
Description of change		Added to include rescreening of patients for the trial
Rationale for change		Update
Section to be changed		Section 6.2.2.1 Visit 1 and Visit 3 – day of BI 836858 administration (administrations 1-8)
Description of change		Safety lab was updated as follows: "*An additional safety lab will be collected on day 2 (i.e., 24 hours after the first administration of BI 836858).Other lab tests to be included: haptoglobin, direct Coombs test, bilirubin (direct and indirect) and free hemoglobin. Non pre-existing abnormal laboratory values (CTCAE Grade 3 or higher) will be followed up every 48 hours until these laboratory values are back to at least CTCAE Grade 1."* Physical examination and ECOG text modified for clarification: Physical examination "*and ECOG performance score completed"* every second cycle beginning with cycle 1.~~(~~*Physical exam* may be completed up to 2 days prior *to administration and ECOG must be completed on the day of the administration.*~~),~~ *Height and* weight (only at Day 1 of first cycle).~~ and ECOG performance score~~. If the first administration is completed within 3 days of the screening visit, these examinations do not need to be repeated. Biomarkers updated with reference to collection time points in Table 3
Rationale for change		Clarification and update. The aim is to observe elevated laboratory values earlier and, with additional parameters (e.g. liver enzymes) to better understand the cause of the laboratory values.
Section to be changed		Section 6.2.3.1 EOT visit
Description of change		", PR or CR " deleted

Number of global amendment		**02**
Rationale for change		Update
Section to be changed		Section 6.2.3.2 Further treatment (Visit 1 and Visit 2)
Description of change		Language updated to: *"These visits are only for those patients with clinical benefit~~, PR, or CR~~ after 8 administrations and who are tolerating the infusions well. Patients can receive further treatment once the result from the bone marrow assessment from EOT is available. Procedures already done at EOT (i.e., safety lab, pregnancy test) do not need to be repeated at FTE if FTE visit is within 7 days from EOT."*
Rationale for change		Clarification and update
Section to be changed		Section 6.2.3.3 End of further treatment
Description of change		Physical examination language clarification to include "weight"
Rationale for change		Clarification
Section to be changed		Section 6.2.3.4 Follow up
Description of change		Text added: "Vital status evaluated at each follow up visit."
Rationale for change		Updated
Section to be changed		Section 7.3.2.3 Best overall response
Description of change		Updated with "or PR" for consistency and clarification
Rationale for change		Clarification
Section to be changed		Section 7.3.3 Safety analyses
Description of change		MTD determination clarification to be completed after 2 cycles
Rationale for change		Clarification
Section to be changed		
Rationale for change		Clarification
Section to be changed		Section 9.1 Published References
Description of change		Reference removed (R10-4429) and added (R01-0787)
Rationale for change		Update
Section to be changed		Section 10.2 EASTERN COOPERATIVE ONCOLOGY GROUP (ECOG) Performance

Number of global amendment		**02**
		Status
Description of change		Section/Table added for clarification
Rationale for change		Clarification

Number of global amendment		**03**
Date of CTP revision		28 April 2016
EudraCT number		N/A
BI Trial number		1315.1
BI Investigational Product(s)		BI 836858
Title of protocol		A Phase I, open label, cohort dose escalation trial with BI 836858 in patients with refractory or relapsed acute myeloid leukemia and patients with acute myeloid leukemia in complete remission with high risk to relapse
To be implemented only after approval of the IRB/IEC/Competent Authorities		☒
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		☐
Can be implemented without IRB/IEC/ Competent Authority approval as changes involve logistical or administrative aspects only		☐
Section to be changed		Title Page
Description of change		Title of trial updated
Rationale for change		Updated to include new patient population "Patients with AML in complete remission (CR) with high risk to relapse"
Section to be changed		Synopsis: title of trial, objectives, No. of patients, inclusion criteria, test product, duration of treatment, criteria for efficacy
Description of change		Protocol synopsis sections updated to include new patient population
Rationale for change		Revised to include new patient population
Section to be changed		Flow Chart
Description of change		A new Flow Chart was added for the new patient population. To differentiate them, now labelled "Flow Chart A" and "Flow Chart B" plus patient population. Footnote section in FC - A updated.
Rationale for change		Updated to include new patient population

Number of global amendment		**03**
Section to be changed		Abbreviations
Description of change		Updated with new abbreviations; abbreviation definitions revised; abbreviation deleted
Rationale for change		Update
Section to be changed		1.1 Medical Background
Description of change		New patient population information added and differentiated from refractory/relapsed patients. Deletion of language to update section.
Rationale for change		Updated to include new patient population and medical background information
Section to be changed		1.1 Medical Background
Description of change		Addition of lintuzumab paragraph
Rationale for change		To update medical background information
Section to be changed		1.2 Drug Profile
Description of change		Investigator brochure reference updated; preliminary data from current study added
Rationale for change		Updated with new information
Section to be changed		2.1 Rationale for Performing the Trial
Description of change		Section updated and preliminary data added to include new patient population
Rationale for change		Updated to support rationale of new patient population
Section to be changed		2.1 Rationale for Performing the Trial
Description of change		Addition of lintuzumab paragraph
Rationale for change		Update
Section to be changed		2.2 Trial Objectives
Description of change		Language revised since there will be more than 1 MTD
Rationale for change		clarification
Section to be changed		2.3 Benefit – Risk Assessment
Description of change		Text updated with new patient population; section updated/language deleted; new clinical data added
Rationale for change		Updated to support addition of new patient population
Section to be changed		3.1 Overall Trial Design and Plan
Description of change		Text added/deleted and updated to differentiate both patient populations
Rationale for change		Updated to include new patient population

Number of global amendment		**03**
Section to be changed		3.1.1, 4.1.6, 5.2.3.2, 5.2.4, 5.2.5.2, 7.3.2.3, 7.3.6, and 10.3.2
Description of change		Grammatical and spelling updates
Rationale for change		Updates
Section to be changed		3.2 Discussion of Trial Design, Including the Choice of Control Group
Description of change		Text added/deleted and updated to differentiate both patient populations
Rationale for change		Updated to include new patient population
Section to be changed		3.3 Selection of Trial Population
Description of change		Text added/deleted to differentiate both patient populations; number of patients screened and entered updated
Rationale for change		Updated to include new patient population
Section to be changed		3.3.1 Main Diagnosis for Study Entry
Description of change		Text added to differentiate both patient populations; text deleted
Rationale for change		Updated to include new patient population
Section to be changed		3.3.2 Inclusion criteria
Description of change		Text added to differentiate both patient populations
Rationale for change		Updated to include new patient population
Section to be changed		3.3.3 Exclusion criteria
Description of change		Text added/deleted and updated in exclusions # 1, # 2, # 3, and # 5 to differentiate both patient populations
Rationale for change		Updated to include new patient population
Section to be changed		3.3.3 Exclusion criteria
Description of change		Text updated in exclusions # 4 and #19 for clarification
Rationale for change		Clarification and update
Section to be changed		3.3.4.1 Removal of individual patients
Description of change		Text added/updated to differentiate expectations in both patient populations
Rationale for change		Updated to include new patient population
Section to be changed		3.3.4.1 Removal of individual patients
Description of change		Vital status collection added for clarification
Rationale for change		Clarification
Section to be changed		4.1.1 Identity of BI investigational product and comparator product
Description of change		Text added to clarify days when drug administered
Rationale for change		Updated as per new patient population

Number of global amendment		**03**
Section to be changed		4.1.3 Selection of doses in the trial
Description of change		Text added/deleted to differentiate both patient populations; new IB reference # included
Rationale for change		Text added/deleted to differentiate both patient populations
Section to be changed		4.1.4 Drug assignment and administration of doses for each patient
Description of change		Text added/deleted to differentiate both patient populations; text updated in premedication and retreatment sections; text added regarding intra-patient dose escalation
Rationale for change		Updated to include new patient population and to allow intra-patient dose escalation
Section to be changed		4.1.5.1 Blinding
Description of change		Text added to differentiate both patient populations
Rationale for change		Updated to include new patient population
Section to be changed		4.1.8 Drug accountability
Description of change		Drug substance added to text for clarification
Rationale for change		Updated for clarification
Section to be changed		4.2.1 Rescue medication, emergency procedures, and additional treatments
Description of change		Text deleted for clarification
Rationale for change		Updated for clarification
Section to be changed		4.2.2.1 Restrictions regarding concomitant treatment
Description of change		Text updated for clarification
Rationale for change		Clarification
Section to be changed		5.1.1 Endpoints of efficacy
Description of change		Endpoints modified to differentiate between patient populations; endpoints deleted; secondary endpoints changed to further endpoints. Deleted supportive care endpoint and change secondary endpoints to further endpoints
Rationale for change		Updated to differentiate both patient populations and to clarify study intended endpoints
Section to be changed		5.1.1 Endpoints of efficacy
Description of change		Language on supportive care requirements was deleted to update endpoints
Rationale for change		update

Number of global amendment		**03**
Section to be changed		5.1.2.3 Assessment and definition of best overall response
Description of change		Text added for clarification and differentiation of patient populations; addition of stable disease and morphologic relapse as it was previously omitted in error
Rationale for change		Updated to differentiate both patient populations and for further clarification
Section to be changed		5.1.2.3 Assessment and definition of best overall response
Description of change		Language on Stable Disease added for update
Rationale for change		Update
Section to be changed		5.1.2.4 Progression free survival (PFS)
Description of change		Text added to clarify date of progression/relapse for clarification
Rationale for change		Updated for clarification
Section to be changed		5.1.2.5 Time to treatment failure (TTF)
Description of change		Text added/deleted to clarify date of progression/relapse
Rationale for change		Updated for clarification
Section to be changed		
Description of change		Text added for clarification
Rationale for change		Updated to clarify date of progression/relapse
Section to be changed		5.1.2.8 Supportive care requirements
Description of change		Section deleted
Rationale for change		Deleted as "supportive care requirements" is no longer an endpoint
Section to be changed		5.1.2.9 ECOG Performance status
Description of change		Section # changed from 5.1.2.9 to 5.1.2.8
Rationale for change		Revised as per deletion of the “supportive care requirements”
Section to be changed		5.2.1 Endpoints of safety
Description of change		Text added/deleted to specify primary and further safety endpoints

Number of global amendment		**03**
Rationale for change		Updated for clarification
Section to be changed		5.2.1.1 Dose Limiting Toxicity (DLT)
Description of change		Section subtitle updated with refractory/relapsed patient population; Text added/deleted for clarification
Rationale for change		Updated to reflect text relevant to refractory/ relapsed patients
Section to be changed		5.2.1.2 Dose Limiting Toxicity (DLT) for AML patients in CR
Description of change		Section added for inclusion of this patient population; text added/deleted for clarification and differentiation of each patient population
Rationale for change		Updated to include new patient population
Section to be changed		Section 5.2.2 Assessment of adverse events, 5.2.2.1, 5.2.2.2
Description of change		Sections updated as per new protocol template
Rationale for change		Update
Section to be changed		5.2.3.1 General safety laboratory parameters
Description of change		Text updated to reflect the new flow chart and change or clarification in lab test
Rationale for change		Clarification
Section to be changed		5.3.2.1 Demographics and history
Description of change		Text added/deleted to differentiate patient population
Rationale for change		Updated

Number of global amendment		**03**
Section to be changed		6. Investigational Plan sections (6.1, 6.2, 6.2.1, 6.2.2, 6.2.2.1, 6.2.2.2, 6.2.3 subtitle, 6.2.3.1, 6.2.3.2, 6.2.4, 6.2.4.1, 6.2.4.2, 6.2.4.3, 6.2.4.4, 6.2.4.5, 6.2.5 (former 6.2.3.4) and 6.2.6 (former 6.2.3.5)
Description of change		Text in these sections were added/updated to differentiate procedures to be performed with each patient population and to reflect new flow chart and tables
Rationale for change		Update and clarification
Section to be changed		7.1 statistical Design - Model
Description of change		Text added to differentiate both patient populations
Rationale for change		Update
Section to be changed		7.3 Planned Analyses
Description of change		Text updated for clarification
Rationale for change		Update
Section to be changed		7.3.1 & 7.3.2 Primary and secondary analyses
Description of change		Text updated to include both patient populations
Rationale for change		Update
Section to be changed		7.3.2.6 Supportive care requirements
Description of change		Section deleted
Rationale for change		Section deleted as "supportive care requirements" is no longer an endpoint
Section to be changed		7.3.2.7 ECOG score
Description of change		Section # changed from 7.3.2.7 to 7.3.2.6 due to deletion of previous section
Rationale for change		Update
Section to be changed		7.3.3 Safety analyses
Description of change		Text updated as per new protocol template language
Rationale for change		Update
Section to be changed		7.3.4 Interim analyses
Description of change		Text updated as per new preliminary data obtained from the refractory /relapsed patient population

Number of global amendment		**03**
Rationale for change		Update
Section to be changed		7.6 Determination of Sample Size
Description of change		Text added and updated to differentiate both patient populations
Rationale for change		Update
Section to be changed		8.4.1 Listedness
Description of change		IB reference # updated
Rationale for change		Update
Section to be changed		9.1 & 9.2 Published and Unpublished References
Description of change		References added:R10-2947, R11-4695, and c02324887-03
Rationale for change		Update
Section to be changed		10.2 ECOG
Description of change		Reference # added for clarification
Rationale for change		Update

APPROVAL / SIGNATURE PAGE

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Document Name: clinical-trial-protocol-rev3

Title: A Phase I, open, cohort dose escalation trial with BI 836858 in patients with refractory or relapsed acute myeloid leukemia

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Approval–Clinical Monitor		28 Apr 2016 22:06 CEST
Author-Trial Statistician		29 Apr 2016 11:47 CEST
Approval-Therapeutic Area		29 Apr 2016 14:19 CEST
Approval-Translational Medicine Expert		29 Apr 2016 14:37 CEST
Approval-Team Member Medicine		29 Apr 2016 17:02 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	**Signed by**	**Date Signed**