Boehringer Ingelheim

CLINICAL TRIAL PROTOCOL

	Document Number:	**c03377067-08**
EudraCT No.:	2015-002892-30	
BI Trial No.:	1315.2	
BI Investigational Product:	BI 836858	
Title:	An open-label, Phase I/II trial to determine the maximum tolerated dose and investigate safety, pharmacokinetics and efficacy of BI 836858 in combination with decitabine in patients with acute myeloid leukemia	
Brief Title:	A trial to find and investigate a safe dose of BI 836858 in combination with decitabine for patients with acute myeloid leukemia (AML)	
Clinical Phase:	Phase I/II	
Trial Clinical Monitor:	[redacted] Phone: Fax: E-mail: [redacted]	
Coordinating Investigator:	[redacted] Phone: Fax: E-mail: [redacted]	
Status:	Final Protocol (revised Protocol; based on global amendment 6)	
Version and Date:	**Version:**	**Date:**
	7.0	**21 Aug 2019**

CLINICAL TRIAL PROTOCOL SYNOPSIS

Name of company:		**Boehringer Ingelheim**	
Name of finished product:		n.a.	
Name of active ingredient:		BI 836858	
Protocol date: 19 Oct 2015	**Trial number:** 1315.2		**Revision date:** **21 Aug 2019**

Title of trial:	An open-label, Phase I/II trial to determine the maximum tolerated dose and investigate safety, pharmacokinetics and efficacy of BI 836858 in combination with decitabine in patients with acute myeloid leukemia
Coordinating Investigator:	[redacted] Phone: [redacted] Fax: E-mail:
Trial site(s):	Multi-centre trial
Clinical phase:	Phase I/II
Objective(s):	Phase I Dose Escalation: To determine the maximum tolerated dose (MTD) and the recommended dose for Phase I Extension (RExP1D) and to investigate the safety, pharmacokinetics and efficacy of BI 836858 in combination with decitabine in patients ≥ 65 years of age with previously untreated acute myeloid leukemia (AML) and considered ineligible for standard intensive therapy, or patients ≥ 18 years of age with refractory or relapsed AML. Phase I Extension: To collect additional data on safety, pharmacokinetics and efficacy and to decide if the RExP1D will become the Recommended Phase II Dose (RP2D) of BI 836858 in

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	combination with decitabine in patients ≥ 65 years of age with previously untreated AML and considered ineligible for standard intensive therapy, or if additional patients need to be enrolled in existing or additional dose escalation cohorts. Phase II: To investigate efficacy, safety and pharmacokinetics of BI 836858 in combination with decitabine compared to decitabine monotherapy in patients ≥ 65 years of age with previously untreated AML and considered ineligible for standard intensive therapy.
Methodology:	Phase I Dose Escalation: Open-label, single-arm, dose escalation (i.e. consecutive cohorts of escalating doses of BI 836858 plus intensive decitabine treatment schedule), Bayesian logistic regression model (BLRM) with overdose control. Phase I Extension: Open-label, two consecutive groups (i.e. Cohort A treated with BI 836858 plus intensive decitabine treatment schedule, followed by Cohort B treated with BI 836858 plus standard decitabine treatment schedule). If deemed necessary by the Sponsor and the SMC (Safety Monitoring Committee): Option to open further Phase I Dose Escalation cohort(s) to determine the RP2D, based on additional biomarker, PK/PD and safety data with either the intensive or the standard decitabine schedule, as specified for each cohort separately prior to starting enrollment. Phase II: Open-label, two-arm randomized, BI 836858 plus decitabine *versus* decitabine monotherapy.
No. of patients:	Approximately 160-170 patients

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total entered:	Phase I Dose Escalation: **16** patients Phase I Extension: **33** patients **After completion of recruitment to Phase I Extension Cohort A and Cohort B, the recruitment to this trial is discontinued.** Phase I option for additional dose tiers: option to add further Dose Escalation cohort(s) with at least 3 patients each (based on SMC recommendation) Phase II: approx. 100 (2 x 50) patients
each treatment:	All patients participating in any part of this trial will receive decitabine. Phase I Dose Escalation, Extension, and potential additional dose tiers: All patients (approx. 60-70) will receive the combination treatment of BI 836858 and decitabine. Phase II: 50% of patients (approx. 50 patients) will receive the combination treatment of BI 836858 and decitabine, and 50% of patients (approx. 50 patients) will receive decitabine monotherapy.
Diagnosis :	Phase I Dose Escalation: Patients ≥ 65 years of age with previously untreated AML, who are considered ineligible for standard intensive therapy, or patients ≥ 18 years of age with relapsed or refractory AML. Phase I Extension, Phase II and potential additional dose tiers: Patients ≥ 65 years of age with previously untreated AML who are considered ineligible for standard intensive therapy

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Main criteria for inclusion:	• Phase I Dose Escalation only: Patients ≥ 65 years of age with previously untreated AML, or patients ≥ 18 years of age with relapsed or refractory AML • Phase I Extension and Phase II only: Patients ≥ 65 years of age with previously untreated AML • Histologically or cytologically confirmed AML according to the WHO classification • Patients eligible for treatment with decitabine
Test product:	BI 836858
dose:	The Phase I starting dose of BI 836858 is 20 mg. The Recommended Phase II Dose (RP2D) is based on the MTD determined in Phase I.
mode of administration:	Intravenous (i.v.) infusion
Combination treatment:	Decitabine (standard of care)
dose:	20 mg/m² (daily)
mode of administration:	Intravenous (i.v.) infusion
Duration of treatment:	Patients will be treated in repeated cycles until disease progression or relapse in the absence of other withdrawal criteria, and as long as neither patient nor investigator request treatment discontinuation.
Endpoints for efficacy and pharmacokinetics:	**Primary endpoint (Phase II):** • Number of patients with objective response combining - Complete Remission (CR) - CR with incomplete blood count recovery (CRi) **Secondary endpoint (Phase I):**

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	• Number of patients with objective response (CR+CRi) **Secondary endpoints (Phase II):** • Event-free survival (EFS) • Relapse-free survival (RFS) • Remission duration • Time to remission
Safety criteria:	**Primary endpoints (Phase I):** • Maximum tolerated dose (MTD) of BI 836858 in combination with decitabine. • Number of patients with Dose Limiting Toxicity (DLT) for BI 836858 in combination with decitabine during Cycle 1.
Statistical methods:	Descriptive statistics and exploratory data analysis. Dose escalation is guided by a Bayesian logistic regression model (BLRM) with overdose control that will be fitted to binary toxicity outcomes. The estimate of parameters will be updated as data are accumulated using the BLRM. At the end of Phase I Dose Escalation, the toxicity probability at each dose level will be calculated to determine an estimate of the MTD.

FLOW CHART

Trial period	**Screening**		**Treatment***																	
	Screening		**Cycle 1[1]**										**Cycles 2 - 3[1]**							
Visit	**SCR**		**1**						**2**	**3**		**4 or End of Cycle**	**1**					**2**	**3**	**4 or End of Cycle**
Day(s) in respective treatment cycle)**	**1 to 14 days before C1_V1**	**Randomization/ Dose assignment**	**1**	**2-5**	**6-7**	**8*** **	**9*** **	**10*** **	**16**	**23**	**24**	**29±3**** **	**1**	**2-5**	**6-7**	**8**	**9-10**	**15**	**22**	**29±3**** **
Informed consent (including biomarkers & pharmacogenetics)	x																			
Informed consent for DNA-biobanking (optional)	x																			
Demographics and baseline conditions [2]	x																			
Medical history	x																			
Review of in-/exclusion criteria[2]	x	x																		
Documentation of planned hospitalisations	x	x																		
Dose assignment (Phase I Dose Escalation and Extension)		x																		
Randomization (Phase II)		x																		
LABS/SAFETY ASSESSMENTS																				
Physical examination [3]	x		x										x[3]							
ECOG performance status[4]	x		x[4]										x[4]							
Vital signs (for details on BI 836858 infusion days see Section 5.3.5)	x		x			x	x	x	x	x		x	x			x	x	x	x	x
Weight and height (height only measured once at screening)	x		x										x							
Coagulation parameters[6]	x		x									x	x							x
Hematology[6]	x		x			x	x	x[7]	x	x		x	x			x		x	x	x
Biochemistry[6]	x		x			x	x	x[7]	x	x		x	x			x		x	x	x
Urinalysis[8]	x																			
Serum pregnancy test[9]	x		x										x							
12-lead ECG	x		x										x							
Number and type of transfusions			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
DLT Assessment						x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Patient status (progression or relapse, death, lost to follow-up)																				

Trial period	**Screening**		**Treatment***																		
	Screening		**Cycle 1[1]**										**Cycles 2 - 3[1]**								
Visit	**SCR**		**1**						**2**	**3**		**4 or End of Cycle**	**1**					**2**	**3**	**4 or End of Cycle**	
Day(s) in respective treatment cycle)**	**1 to 14 days before C1_V1**	**Randomization/ Dose assignment**	**1**	**2-5**	**6-7**	**8*** **	**9*** **	**10*** **	**16**	**23**	**24**	**29±3**** **	**1**	**2-5**	**6-7**	**8**	**9-10**	**15**	**22**	**29±3**** **	
DISEASE ASSESSMENT																					
Disease assessment with peripheral blood and clinical assessment	x											x								x	
Disease assessment with bone marrow (BM) aspirate (and biopsy if indicated); Separate portion of BM samples for biomarkers[11] (see Table 3 and Table 4)	x[11]								x[11]			x[11]								x[12]	
Cytogenetics and molecular genetics[14]	x[14]																				
[redacted]																					
[redacted]			▮																		
[redacted]						▮	▮	▮	▮	▮	▮	▮	▮	▮		▮		▮	▮		
[redacted]						▮	▮		▮	▮		▮	▮			▮		▮	▮		
[redacted]	▮		▮			▮	▮	▮	▮			▮									
[redacted]	▮		▮	▮	▮	▮	▮	▮	▮	▮	▮	▮	▮	▮	▮	▮	▮	▮	▮	▮	
[redacted]	▮		▮	▮	▮	▮	▮	▮	▮	▮	▮	▮	▮	▮	▮	▮	▮	▮	▮	▮	
[redacted]																					
TRIAL MEDICATION																					
Administration of decitabine intensive treatment *(starting in Cycle 1 with treatment on 10 consecutive days)*			x	x	x	x	x	x					x	x	x[16]	x	x[16]				
Administration of decitabine standard treatment *(starting in Cycle 1 with treatment on 5 consecutive days)*			x	x									x	x							
Administration of premedication[17]						x***	x***		x	x			x			x		x	x		
Administration of BI 836858[17,18] (for details on BI 836858 administration refer to Table 4.1.3.1: 2 and 4.1.3.2: 1)						x***	x***		x	x			x			x		x	x		
Eligibility check for (further) drug administration of BI 836858						x	x		x	x		x	x			x		x	x	x	

*) The planned duration of a treatment cycle is 28 days. Day 1 of each cycle is defined as the day when the first dose of decitabine in that cycle is administered. The start of the next cycle must not be earlier than Day 29 of the previous cycle.There will be a maximum of 4 administrations of BI 836858 in one treatment cycle (with the exception of treatment Cycle 1, where there is a maximum of 3 administrations of BI 836858). All assessments should be performed prior to dose administration on dosing days, unless otherwise specified.

**) Days are calculated as calendar days. Please refer to Section 6.2 for details on time windows for visits and individual study procedures or assessments.

***) In case treatment with BI 836858 cannot be started on Day 8 of Cycle 1 (due to documented medical or administrative reasons), the first dose of BI 836858 may be administered on Day 9 of Cycle 1 (at the latest). All procedures described in this Flow Chart for Day 8, Day 9 and Day 10 (especially blood sampling for PK and biomarkers as per Table 1 and Table 3) should be shifted accordingly.

****) Day 29 (Visit 4) can be the same day as Day 1 (Visit 1) of the next treatment cycle if the patient is eligible to receive further treatment without delay. In that case Day 29 becomes Day 1 of next cycle, and all procedures and assessments as indicated for EOC and Day 1 of the next cycle have to be performed.
In case a patient does not continue immediately with the next cycle for any reason (and not moving to EoT), additional visits are recommended to be performed on a weekly basis, at investigator's discretion, in the period until the next cycle starts. These additional (unscheduled) visits should be documented in eCRF.

*****) For patients treated in Phase I only two FU visits are scheduled; the first FU visit will be at approximately 3 months after the EOT visit and the second FU visit will be at approximately 6 months after the EOT visits. For patients treated in Phase II, FU visits are scheduled approximately every 3 months until death or lost to follow-up. In case patients do not visit the site, the FU visit can be conducted by phone.

1) Due to intensive PK sampling schedule during Cycle 1 and Cycle 2 it is strongly recommended to follow the proposed visit days and sampling time points as outlined in Table 1 and Table 2. The permitted visit windows (as per Section 6.2) should only be used if medically indicated. For exact time points please refer to Table 1 and Table 2.
2) For each patient entering this trial the investigator will document in detail in the source document and in the eCRF the medical reason(s) why the patient is considered ineligible for standard intensive therapy (see Section 5.6.1)
3) Physical examination only every second cycle (i.e. before cycle 1, 3, 5, 7 etc.) Physical examination may be completed up to 2 days prior to Day 1 of next planned treatment cycle.
4) Eastern Cooperative Oncology Group (ECOG) performance status only every second cycle (i.e. before cycle 1, 3, 5, 7 etc.). If the first administration of decitabine occurs within 3 days of the screening visit, this examination does not need to be repeated on Day 1 of Cycle 1.
5) Vital signs at FU visits only when patient is visiting the site
6) For details refer to Section 5.3.6.1. Safety lab assessments will be performed at the Investigator's local lab. Time points for TLS monitoring (selected hematology and biochemistry parameters) sample collection as per Table 1. All other safety lab assessments may be completed up to 2 days prior to the next scheduled administration of BI 836858.
7) An additional safety lab will be collected on Day 10 (i.e. 24 hours after start of the first administration of BI 836858). Other lab test to be included on that day (i.e. in addition to standard panel) are: haptoglobin and direct antiglobulin test. 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.
8) Urinalysis (dipstick; reported as semiquantitative measurements) at screening, after completion of Cycle 4 and at EOT.
9) For women of childbearing potential only. Serum pregnancy test completed at Screening, Visit 1 of each Cycle and EOT.
10) Only needed in case safety lab values were outside normal range or ECG was abnormal at EOT with findings not present at baseline.
11) Separate portion of BM aspirate required at screening and in Cycle 1 at Day 29 (±3 days) and at EOT for central lab assessment for biomarkers (refer to Table 3 and Table 4). In Cycle 1 at Day 16 (± 2 days) the BM aspirate is required for central lab assessment for biomarkers only, i.e. no mandatory local disease assessment on that day.
12) BM aspirate (and biopsy if indicated) to assess efficacy at end of Cycle 1, at end of Cycle 2 and then every other cycle thereafter. The BM sample collection at the end of Cycle 2 is not a mandatory trial procedure in patients with ≥ 5% blasts in peripheral blood. From Cycle 2 onwards, BM samples can be taken up to 7 days before the scheduled visit 4 (EOC), i.e. between Day 22 and Day 29, unless the patient has achieved CR in which case further bone marrow aspiration/biopsies are not required unless clinically indicated; earlier response assessments can be performed based on count recovery. If progressive disease or relapse is diagnosed, perform EOT visit.
13) BM aspirate (only in patients who did not end treatment due to PD or relapse and who did not have a BM aspirate within the past four weeks, or if PD is suspected but not cytologically confirmed)
14) In Phase I no mandatory separate BM sampling and/or local testing for cytogenetics and molecular genetics is required; cytogenetic and molecular genetic data from initial diagnosis/clinical routine can be used for eCRF completion, if available (see Section 5.3.6.2).
In Phase II BM sampling and shipment to central lab for cytogenetics and molecular genetic testing is mandatory.
15) Follow-up of AEs not recovered at EoR. Concomitant therapy at EoR visit collected only if indicated for treatment of adverse event.
16) Individually customized decitabine treatment schedule for Cycles ≥ 2 depending on WBC at the end of previous cycle. For details refer to Table 4.1.3.1:1 for patients treated in Phase I Dose Escalation and Table 4.1.3.2:1 for patients treated in Phase I Extension and Phase II. No trial-specific visits need to be performed (irrespective of "x" in this Flow Chart) when treatment with decitabine was already stopped in that cycle.
17) For time windows of drug administration days of BI 836858 refer to Section 4.1.4.
18) The treatment schedule with BI 836858 will be individually customized for cycles ≥ 2 based on the response to the treatment. Depending on the time point when the response was observed and the type of response (CR or CRi), the weekly infusions with BI 836858 may be reduced to monthly infusions (maintenance treatment). For details refer to Table 4.1.3.1:2 for patients treated in Phase I Dose Escalation and to Table 4.1.3.2:1 for patients treated in Phase I Extension and Phase II

Trial period									**Residual Effect Period (REP)**		**Extended Follow-up (FU)**
	Cycles ≥ 4							**Cycles >7**	**REP**		**Follow-up**
	1			**2**	**3**	**4 or End of Cycle**		**1**	**End of Treatment (EOT)**	**End of REP (EoR)**	**FU*******
Day(s) in respective treatment cycle)**	**1**	**2-5**	**8**	**15**	**22**	**29±3******		**1**	**As soon as possible but not later than one week after permanent discontinuation of trial medication(s)**	**Not earlier than 30 days after last infusion with trial medication(s)**	**every 12 weeks ± 2 weeks***** (No FU visits after implementation of CTP version 7.0)**
Informed consent (including biomarkers & pharmacogenetics)											
Informed consent for DNA-biobanking (optional)											
Demographics and baseline conditions [2]											
Medical history											
Review of in-/exclusion criteria											
Documentation of planned hospitalisations											
Dose assignment (Phase I Dose Escalation and Extension)											
Randomization (Phase II)											
LABS/SAFETY ASSESSMENTS											
Physical examination [3]	x[3]							X[19]	x[19]		
ECOG performance status[4]	x[4]							X[19]	x[19]		
Vital signs (for details on BI 836858 infusion days see Section 5.3.5)	x		x	x	x		x	X[20]	x[19]	x[19]	x[5]
Weight and height (height only measured once at screening)	x							X	x[19]		
Coagulation parameters[6]	x						x	X[19]	x[19]	x[10, 19]	
Hematology[6]	x		x	x	x		x	X[19]	x[19]	x[10, 19]	
Biochemistry[6]	x		x	x	x		x	X[19]	x[19]	x[10, 19]	
Urinalysis[8]							x[8]	X[19]	x[19]	x[10, 19]	
Serum pregnancy test[9]	x							X[19]	x[19]		
12-lead ECG	x							X[19]	x[19]	x[10, 19]	
Number and type of transfusions	x	x	x	x	x		x	X[19]	x[19]	x[19]	
DLT Assessment	x	x	x	x	x		x	X	x[19]	x[19]	
Patient status (progression or relapse, death, lost to follow-up)											x

Trial period								**Residual Effect Period (REP)**		**Extended Follow-up**
	Cycles ≥ 4						**Cycles >7**	**REP**		**Follow-up**
Visit	**1**			**2**	**3**	**4 or End of Cycle**	**1**	**End of Treatment**	**End of REP**	**FU*****
Day(s) in respective treatment cycle)**	**1**	**2-5**	**8**	**15**	**22**	**29±3******	**1**	**As soon as possible but not later than one week after permanent discontinuation of trial medication(s)**	**Not earlier than 30 days after last infusion with trial medication(s)**	**every 12 weeks ± 2 weeks***** **(No FU visits after approval of CTP version 7.0)**
DISEASE ASSESSMENT										
Disease assessment with peripheral blood and clinical assessment						x	X[19]	X[19]		
Disease assessment with BM aspirate (and biopsy if indicated) Separate portion of BM samples for biomarkers[11] (see Table 3 and Table 4)						x[12]	X[19]	X[11, 13, 19]		
Cytogenetics and molecular genetics[14]										
[redacted]										
[redacted]										
[redacted]										
[redacted]										
[redacted]										
[redacted]										
[redacted]										
[redacted]										
[redacted]										
TRIAL MEDICATION										
Administration of **decitabine intensive treatment** *(starting in Cycle 1 with treatment on 10 consecutive days)*	x	x								
Administration of **decitabine standard treatment** *(starting in Cycle 1 with treatment on 5 consecutive days)*	x	x					X			
Administration of premedication[17]	x		x	x	x		X			
Administration of BI 836858 [17, 18] (for details on BI 836858 administration refer to Table 4.1.3.1:2 and 4.1.3.2:1)	x		x	x	x		X			
Eligibility check for (further) drug administration of BI 836858	x		x		x	x	X			

*) The planned duration of a treatment cycle is 28 days. Day 1 of each cycle is defined as the day when the first dose of decitabine in that cycle is administered. The start of the next cycle must not be earlier than Day 29 of the previous cycle.There will be a maximum of 4 administrations of BI 836858 in one treatment cycle (with the exception of treatment Cycle 1, where there is a maximum of 3 administrations of BI 836858). All assessments should be performed prior to dose administration on dosing days, unless otherwise specified.

**) Days are calculated as calendar days. Please refer to Section 6.2 for details on time windows for visits and individual study procedures or assessments.

***) In case treatment with BI 836858 cannot be started on Day 8 of Cycle 1 (due to documented medical or administrative reasons), the first dose of BI 836858 may be administered on Day 9 of Cycle 1 (at the latest). All procedures described in this Flow Chart for Day 8, Day 9 and Day 10 (especially blood sampling for PK and biomarkers as per Table 1 and Table 3) should be shifted accordingly.

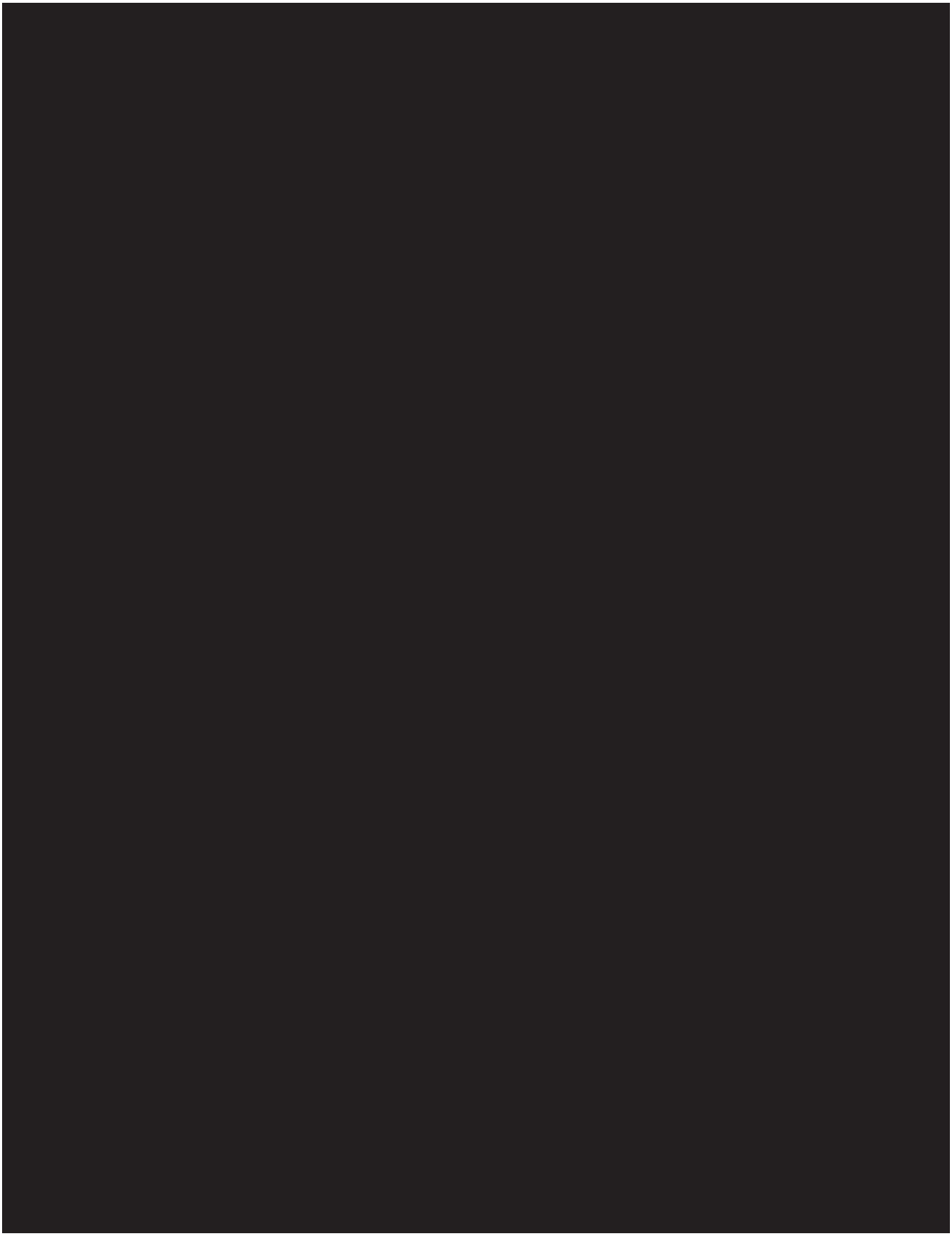
****) Day 29 (Visit 4) can be the same day as Day 1 (Visit 1) of the next treatment cycle if the patient is eligible to receive further treatment without delay. In that case Day 29 becomes Day 1 of next cycle, and all procedures and assessments as indicated for EOC and Day 1 of the next cycle have to be performed.. In case a patient does not continue immediately with the next cycle for any reason (and not moving to EoT), additional visits are recommended to be performed on a weekly basis, at investigator's discretion, in the period until the next cycle starts. These additional (unscheduled) visits should be documented in eCRF.

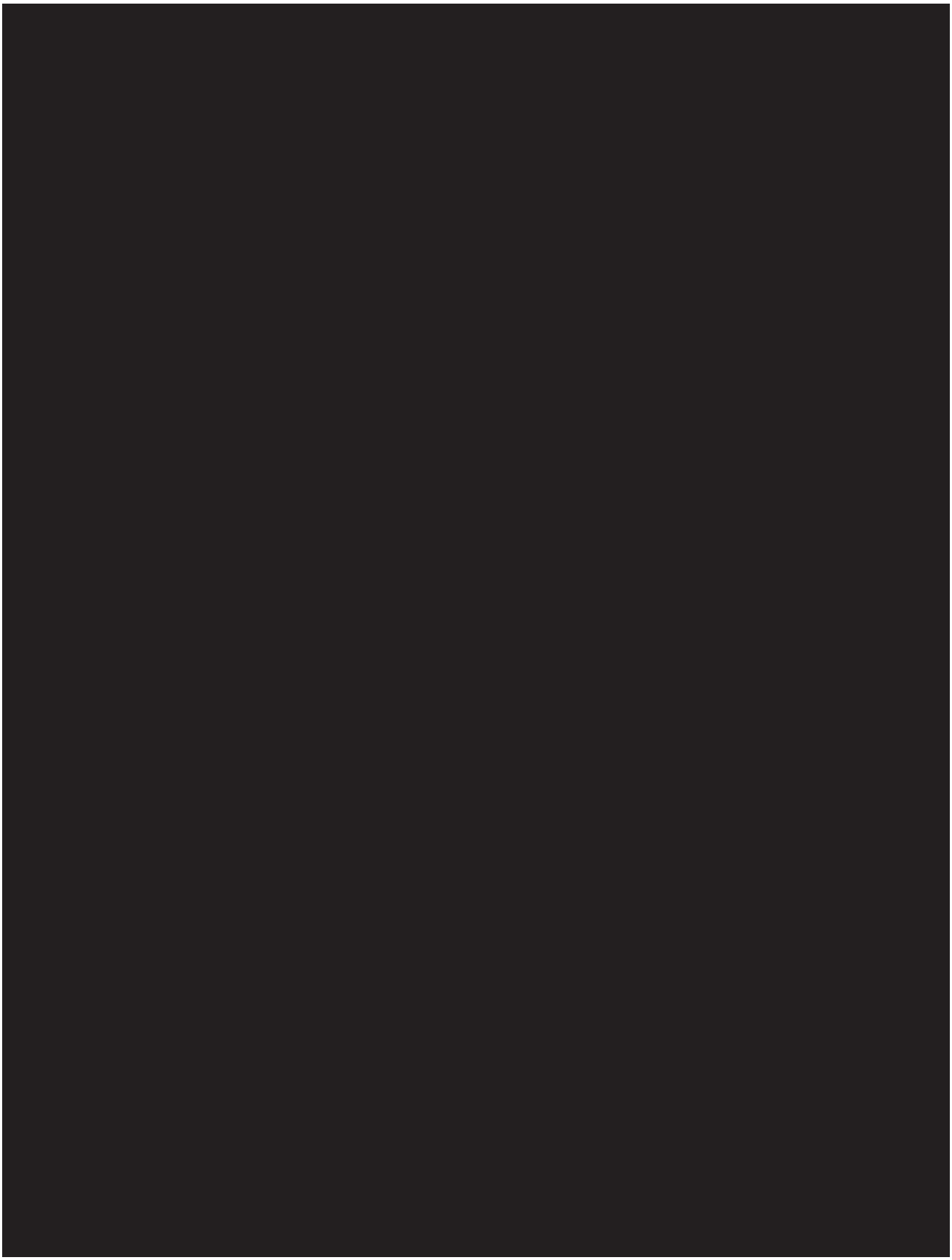
*****) For patients treated in Phase I only two FU visits are scheduled; the first FU visit will be at approximately 3 months after the EOT visit and the second FU visit will be at approximately 6 months after the EOT visits. For patients treated in Phase II, FU visits are scheduled approximately every 3 months until death or lost to follow-up. In case patients do not visit the site, the FU visit can be conducted by phone. **After approval of Protocol version 7.0, no Follow-up visits.**

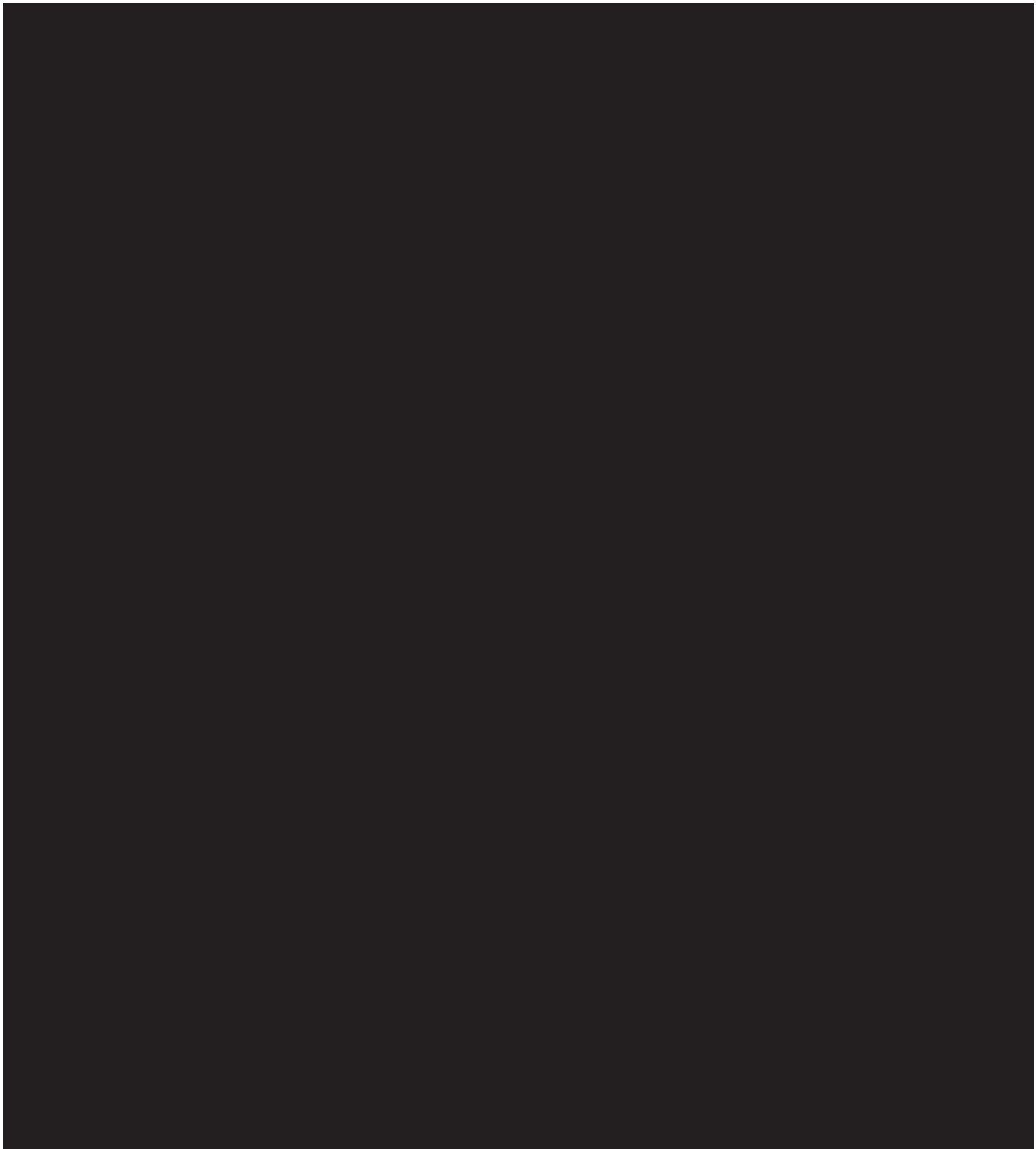
1) Due to intensive PK sampling schedule during Cycle 1 and Cycle 2 it is strongly recommended to follow the proposed visit days and sampling time points as outlined in Table 1 and Table 2. The permitted visit windows (as per Section 6.2) should only be used if medically indicated. For exact time points please refer to Table 1 and Table 2.
2) For each patient entering this trial the investigator will document in detail in the source document and in the eCRF the medical reason(s) why the patient is considered ineligible for standard intensive therapy (see Section 5.6.1)
3) Physical examination only every second cycle (i.e. before cycle 1, 3, 5, 7 etc.) Physical examination may be completed up to 2 days prior to Day 1 of next planned treatment cycle.
4) Eastern Cooperative Oncology Group (ECOG) performance status only every second cycle (i.e. before cycle 1, 3, 5, 7 etc.). If the first administration of decitabine occurs within 3 days of the screening visit, this examination does not need to be repeated on Day 1 of Cycle 1.
5) Vital signs at FU visits only when patient is visiting the site
6) For details refer to Section 5.3.6.1. Safety lab assessments will be performed at the Investigator's local laboratory. Time points for TLS monitoring (selected hematology and biochemistry parameters) sample collection as per Table 1. All other safety lab assessments may be completed up to 2 days prior to the next scheduled administration of BI 836858.
7) An additional safety lab will be collected on Day 10 (i.e. 24 hours after start of the first administration of BI 836858). Other lab test to be included on that day (i.e. in addition to standard panel) are: haptoglobin and direct antiglobulin test. 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.
8) Urinalysis (dipstick; reported as semiquantitative measurements) at screening, after completion of Cycle 4 and at EOT.
9) For women of childbearing potential only. Serum pregnancy test completed at Screening, Visit 1 of each Cycle and EOT.
10) Only needed in case safety lab values were outside normal range or ECG was abnormal at EOT with findings not present at baseline.
11) Separate portion of BM aspirate required at screening and in Cycle 1 at Day 29 (±3 days) and at EOT for central lab assessment for biomarkers (refer to Table 3 and Table 4). In Cycle 1 at Day 16 (± 2 days) the BM aspirate is required for central lab assessment for biomarkers only, i.e. no mandatory local disease assessment on that day. **After the approval of Protocol version 7.0, bone marrow sampling for response assessment is no longer mandatory at defined visits but is performed at the investigator's discretion; BM samples are evaluated at the trial site only, and shipping samples to the biomarker lab is stopped.**
12) BM aspirate (and biopsy if indicated) to assess efficacy at end of Cycle 1, at end of Cycle 2 and then every other cycle thereafter. The BM sample collection at the end of Cycle 2 is not a mandatory trial procedure in patients with ≥ 5% blasts in peripheral blood. From Cycle 2 onwards, BM samples can be taken up to 7 days before the scheduled visit 4 (EOC), i.e. between Day 22 and Day 29, unless the patient has achieved CR in which case further bone marrow aspiration/biopsies are not required unless clinically indicated; earlier response assessments can be performed based on peripheral blood count recovery. If progressive disease or relapse is diagnosed, perform EOT visit. **After the approval of Protocol version 7.0, bone marrow sampling for response assessment is no longer mandatory at defined visits but is performed at the investigator's discretion and BM samples are evaluated at the trial site only (no shipment of samples to central biomarker lab).**
13) BM aspirate (only in patients who did not end treatment due to PD or relapse and who did not have a BM aspirate within the past four weeks, or if PD is suspected but not cytologically confirmed): **After the approval of Protocol version 7.0, bone marrow sampling for response assessment is no longer mandatory at defined visits but is performed at the investigator's discretion and BM samples are evaluated at the trial site only (no shipment of samples to central biomarker lab).**
14) In Phase I no mandatory separate BM sampling and/or local testing for cytogenetics and molecular genetics is required; cytogenetic and molecular genetic data from initial diagnosis/clinical routine can be used for eCRF completion, if available (see Section 5.3.6.2). In Phase II BM sampling and shipment to central lab for cytogenetics and molecular genetic testing is mandatory.
15) Follow-up of AEs not recovered at EoR. Concomitant therapy at EoR visit collected only if indicated for treatment of adverse event.
16) Individually customized decitabine treatment schedule for Cycles ≥ 2 depending on WBC at the end of previous cycle. For details refer to Table 4.1.3.1:1 for patients treated in Phase I Dose Escalation and Table 4.1.3.2:1 for patients treated in Phase I Extension and Phase II. No trial-specific visits need to be performed (irrespective of "x" in this Flow Chart) when treatment with decitabine was already

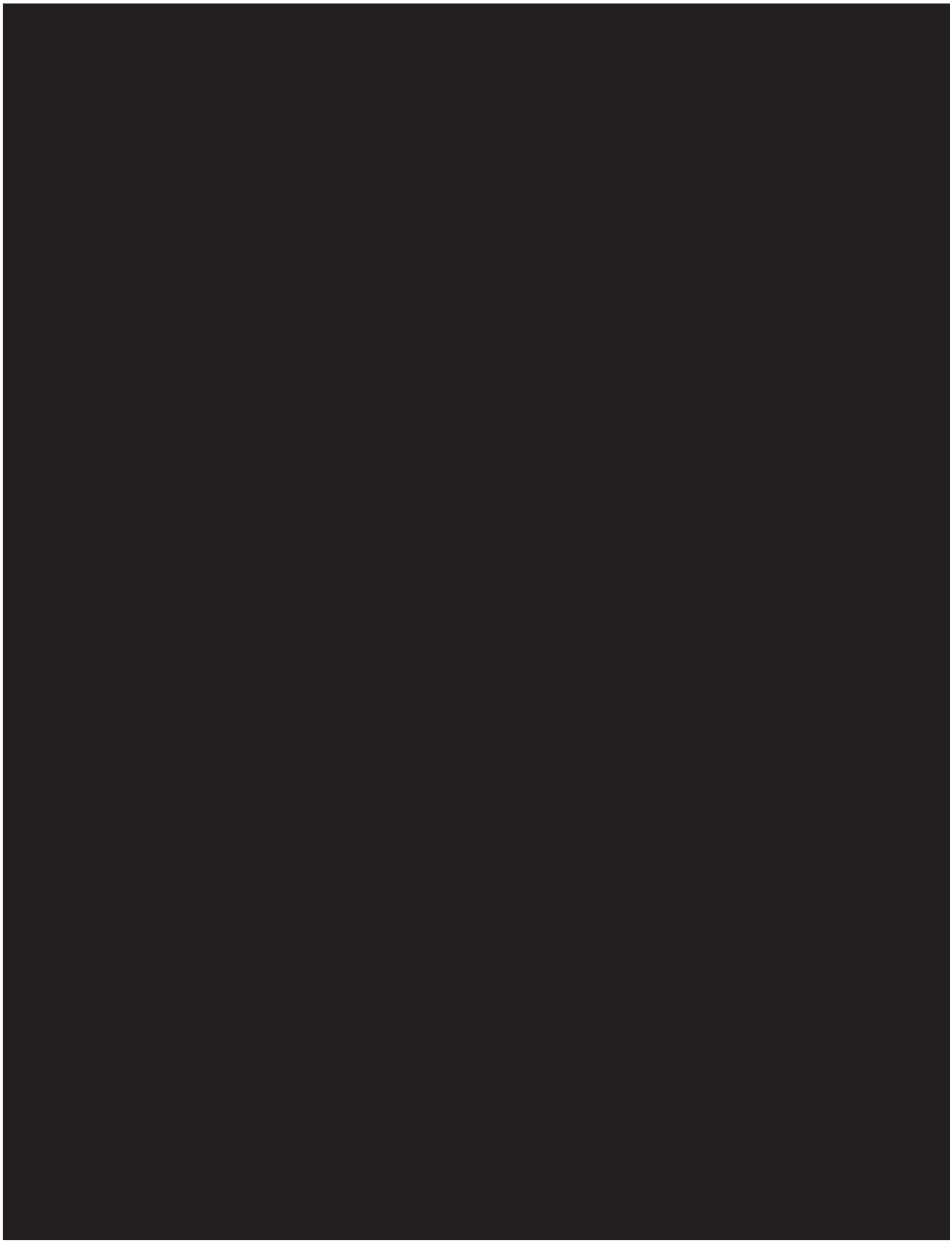
stopped in that cycle.

17) For time windows of drug administration days of BI 836858 refer to Section 4.1.4.
18) The treatment schedule with BI 836858 will be individually customized for cycles ≥ 2 based on the response to the treatment. Depending on the time point when the response was observed and the type of response (CR or CRi), the weekly infusions with BI 836858 may be reduced to monthly infusions (maintenance treatment). For details refer to Table 4.1.3.1:2 for patients treated in Phase I Dose Escalation and to Table 4.1.3.2:1 for patients treated in Phase I Extension and Phase II.
19) Procedures/assessments not mandatory after approval of CTP version 7.0, but assessments (e.g. laboratory tests, bone marrow aspirates) should be performed at the investigator's discretion, based on standard medical care. Findings are documented in the eCRF only if qualifying for (S)AE.
20) Results on Vital signs during and after trial drug infusion to be documented in the eCRF only if qualifying for (S)AE.
21) Documentation of Concomitant Therapy information in the eCRF only if the indication is treatment for (S)AE.









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ABBREVIATIONS

ADA	Anti-drug antibody
ADCC	Antibody dependent cellular cytotoxicity
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine Amino Transferase
AML	Acute Myeloid Leukemia
ANC	Absolute Neutrophil Count
ASCT	Allogeneic Stem Cell Transplantation
AST	Aspartate Amino Transferase
[redacted]	[redacted]
BI	Boehringer Ingelheim
[redacted]	[redacted]
BLRM	Bayesian logistic regression model
BM	Bone marrow
BSA	Body Surface Area
CCDS	Company Core Data Sheet
[redacted]	[redacted]
CML	Local Clinical Monitor
CR	Complete Remission
CRA	Clinical Research Associate
CRF	Case Report Form
CRi	CR with incomplete blood count recovery
CRO	Contract Research Organization
CTCAE	Common Terminology Criteria for Adverse Events
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
DILI	Drug Induced Liver Injury
DLT	Dose Limiting Toxicity
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic Acid
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EFS	Event-free survival
EOC	End of Cycle
EoR	End of Residual Effect Period
EOT	End of Treatment
EudraCT	European Clinical Trials Database
EWOC	Escalation with Overdose Control
FAB	French-American-British
FACS	Fluorescence-activated cell sorting
[redacted]	[redacted]

FDA	Food and Drug Administration
GCP	Good Clinical Practice
i.v.	intravenous
IB	Investigator's Brochure
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IRR	Infusion-related reaction
IRT	Interactive Response Technology
ISF	Investigator Site File
LDAC	Low-Dose Cytarabine
LPDD	Last Patient Drug Discontinuation
mAb	Monoclonal antibody
MDS	Myelodysplastic Syndrome
MedDRA	Medical Dictionary for Drug Regulatory Activities
MTD	Maximum Tolerated Dose
NC	Not calculated
NCCN	National Comprehensive Cancer Network
NOA	Not analyzed
NOR	No valid result
NOS	No sample
NYHA	New York Heart Association
OS	Overall Survival
p.o.	per os (oral)
PD	Disease Progression (Progressive Disease)
PK	Pharmacokinetics
PR	Partial Remission
RDC	Remote Data Capture (BI system that enables sites to enter data into eCRF)
REP	Residual Effect Period; after the last dose of medication with measureable drug levels or pharmacodynamic effects still likely to be present
RExP1D	Recommended Extension Phase I Dose (recommended dose of BI 836858 for Phase I Extension)
RFS	Relapse-free survival
RP2D	Recommended Phase II Dose
SAE	Serious Adverse Event
SD	Stable Disease
SMC	Safety Monitoring Committee
SOP	Standard Operating Procedure
SPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reactions
[redacted]	[redacted]
TCM	Trial Clinical Monitor
TDMAP	Trial Data Management and Analysis Plan
TLS	Tumor Lysis Syndrome
[redacted]	[redacted]
TMF	Trial Master File

TMW	Trial Medical Writer
TNF	Tumor Necrosis Factor
TSAP	Trial Statistical Analysis Plan
[redacted]	[redacted]
WBC	White Blood Cell count

1. INTRODUCTION

1.1 ACUTE MYELOID LEUKEMIA

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 favourable, intermediate, and unfavourable risk. Other factors with impact on prognosis are age, performance score, white blood cell count, blood chemistry disturbances and *de novo versus* secondary AML.

Intensive treatment approaches for AML with curative intention include two phases. The first, induction treatment, most commonly cytarabine and an anthracycline, is aiming to reach a complete remission (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 to 75 % 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 are 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 median overall survival (OS), for patients, not achieving a CR is < 1 year, even with best palliative treatment. 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.

Beside treatment in clinical trials, re-induction followed by allogeneic stem cell transplantation (ASCT) 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.

Even for patients who have received induction and consolidation treatment the overall survival and cure rate are poor: over 60% will die due to their disease within 5 years. ASCT is only indicated for young patients and is an option for < 10% of all patients diagnosed with AML.

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

1.1.1 Acute myeloid leukemia in patients ≥ 65 years of age

Patients of ≥ 65 years of age with AML are biologically and clinically distinct from younger patients. Although the prognosis of AML worsens with increasing age, older patients are generally considered as age 60 years or older. They are more likely to die early and to exhibit therapeutic resistance (R07-2772, R10-2948). Increasing age is associated with factors predictive of early death, such as poor performance status or various comorbidities, and of treatment resistance (e.g. adverse cytogenetics, secondary AML or the multidrug resistant phenotype (R10-5308). A recent analysis suggested that while intensive chemotherapy can be delivered to older patients (≥ 70 years) with AML, it may not be beneficial to most, and could be harmful to some. Indeed, this analysis showed that the prognosis of most patients (72%) aged ≥ 70 years with AML is poor with intensive chemotherapy, with an 8-week mortality of 36% and a median survival < 6 months (R10-5306). Therefore, a substantial number of older AML patients are not considered eligible for intensive treatment; available data indicate that about 70% of patients aged 65 to 74 and less than 30% of patients aged ≥ 74 years receive intensive therapy at initial diagnosis of AML. Alternatives to standard dose intensive treatment are sought for these patients (R10-1398, R10-2947). Although substantial numbers of AML patients are considered as ineligible for intensive treatment, no validated criteria are defined to judge a patient's eligibility for intensive treatment (R07-2771). The assessment of eligibility for intensive treatment is regularly done for every single patient based on the specialized physician's clinical experience and the comprehensive review of factors like patient’s age, AML cytogenetics/molecular genetics, performance score, organ dysfunctions and co-morbidities, as well as the patient's informed decision. In current practice, the final decision to treat intensively or not is made by the treating haematologist on a case by case basis. This approach is reflected in current practice guidelines (e.g. European Leukemia Net recommendations (R10-2947), NCCN (National Comprehensive Cancer Network) guideline (R15-5032)).

Based on data showing a significant benefit in survival for AML patients ≥ 65 years of age treated with cytarabine compared with hydroxyurea, low-dose cytarabine (LDAC) is an established treatment option although the outlook for patients who receive LDAC remains unsatisfactory (R07-2771). In a Phase III trial in patients with previously untreated AML, decitabine has shown a similar safety profile compared to LDAC and demonstrated higher response rates and a trend for overall survival advantage (R12-3309). According to guidelines for AML patients ≥ 65 years of age considered ineligible to receive intensive treatment, investigational treatment is widely regarded as the preferred therapeutic option beside LDAC and decitabine (R07-2768, R07-2772, R10-2947).

1.2 DRUG PROFILE

1.2.1 BI 836858

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 (MDS) (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).

[redacted]

[redacted]

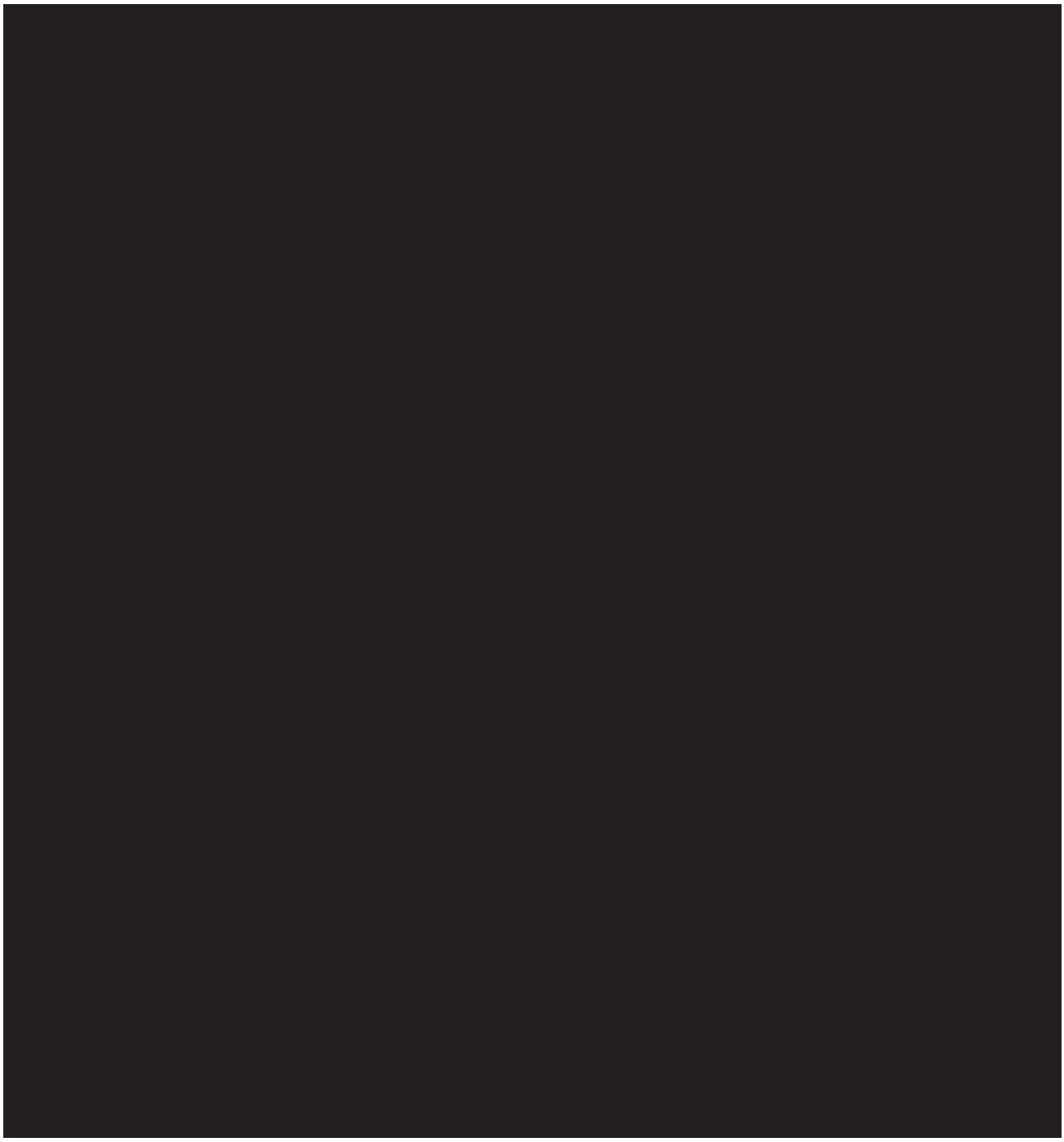
[redacted]

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 that has been in clinical development for AML (R11-1471).

[redacted]

[redacted]

[redacted]



For a more detailed description of the drug profile refer to the current Investigator's Brochure (c02324887-03) which is included in the Investigator Site File (ISF).

1.2.2 Decitabine

Decitabine is a marketed product. In 2006, decitabine was approved by the Food and Drug Administration (FDA) for the treatment of MDS including previously treated and untreated, *de novo* and secondary MDS of all French-American-British (FAB) subtypes. In 2012, decitabine was approved in Europe for the treatment of adult patients (≥ 65 years) with newly

diagnosed *de novo* or secondary AML, who are not candidates for standard induction chemotherapy.

Decitabine is a hypomethylating agent that hypomethylates DNA by inhibiting the DNA methyltransferase. Decitabine is believed to exert its antineoplastic effects after phosphorylation and direct incorporation into the DNA and inhibition of the DNA methyltransferase, which causes hypomethylation of DNA and cellular differentiation or apoptosis. Decitabine inhibits DNA methylation *in vitro*, which is achieved at concentrations that do not cause major suppression of DNA synthesis. Decitabine-induced hypomethylation in neoplastic cells may restore normal function to genes that are critical for the control of cellular differentiation and proliferation. In rapidly dividing cells, the cytotoxicity of decitabine may also be attributed to the formation of covalent adducts between DNA methyltransferase and decitabine incorporated into DNA. Non-proliferating cells are relatively insensitive to decitabine (R11-1093).

Decitabine has been shown to induce hypomethylation both *in vitro* and *in vivo*. Pharmacokinetics of decitabine following i.v. infusion have been evaluated in patients with hematologic malignancies (R15-3858, R15-3859, R15-3860). Plasma concentration time profiles after discontinuation of infusion showed a bi-exponential decline. Decitabine disappears rapidly from plasma and its high volume of distribution suggests extensive tissue distribution. The terminal half-life ($t_{1/2}$) was about 35 min. Upon repeated doses there was no systemic accumulation of decitabine or any changes in PK parameters.

Decitabine has been studied in the treatment of previously treated and untreated young adult and elderly patients (≥ 65 years) with AML (R11-1089, R11-1105, R11-1099, R11-2725, R11-2726, R11-2727).
One of the recommended treatment regimens for decitabine is continuous i.v. infusion over 1 h repeated daily for 5 days, but more intensive treatment regimen starting with repeated i.v. infusions daily for 10 days for the first few cycles, followed by individually customized therapy in subsequent cycles is also widely used. The intention of this more intensive, but individually customized treatment based on response and toxicity, is to improve tolerability and response.
Repeated cycles of decitabine are given every 4 weeks, irrespective of the duration of the decitabine administration (i.e. consecutive Days 1-5 or Days 1-10 of each cycle), in order to allow efficient incorporation of drug into the newly synthesized DNA of myeloid blast. Most common adverse reactions of decitabine (> 50%) are neutropenia, thrombocytopenia, anaemia, and pyrexia. Other common adverse events include nausea, vomiting, diarrhoea, constipation, fever, oedema, hyperglycemia, hypomagnesemia, hypokalemia, arthralgias, back pain, cough, headache, insomnia, rash, petechiae, and pallor (R11-1101, R11-1104). For detailed efficacy, safety, and pharmacology profile information of decitabine, refer to the EU Summary of Product Characteristics (SPC) for decitabine (R15-4802). Detailed information on this medicinal product is available on the website of the European Medicines Agency (EMA) website.ema.europa.eu.

Also, in patients ≥ 65 years of age with previously untreated AML, who were ineligible for intensive therapy, decitabine has been investigated. Recently, the trial results from a Phase III

trial, the largest to date in patients ≥ 65 years of age with AML, have been released (R12-3309). In this Phase III trial, patients ≥ 65 years of age with newly diagnosed *de novo* or secondary AML and poor- or intermediate-risk cytogenetics were randomized into two treatment groups: decitabine 20 mg/m^2 once daily 1 h i.v. for 5 consecutive days, every 4 weeks; or either treatment choice of supportive care or 20 mg/m^2 low-dose cytarabine (LDAC) subcutaneously once daily for 10 consecutive days, every 4 weeks. Of 485 enrolled patients, 242 were randomized to receive decitabine and 243 to treatment choice of supportive care (N=28) or LDAC (N=215). In the decitabine group, 25.6% achieved objective response rate (CR+CRi); the median duration of treatment was 4.4 months and the median survival was 7.7 months. In the supportive care or LDAC group, 10.7% of patients achieved objective response (CR+CRi); the median duration of treatment was 2.4 months and the median survival was 5.0 months. Decitabine compared to LDAC has demonstrated a trend for overall survival advantage and higher objective response rates without major differences in safety.

Also widely used, especially at academic sites, is a decitabine treatment regimen with repeated i.v. infusions daily for 10 days. This intensified regimen of decitabine (20 mg/m^2 daily for 10 days) was applied to 53 patients (median age 74 years) who were unsuitable for standard chemotherapy. Most of the patients received one or two cycles of 10 day decitabine followed by cycles with the standard regimen of 5 days decitabine. The CR rate was 47% and CRi was 17%, with 30- and 60-day mortality rates of 2% and 15%, respectively. Median OS and disease-free survival durations were 55 and 46 weeks, respectively. Responses were present in all subgroups regardless of age, cytogenetics, leukocyte count, and antecedent myelodysplasia. The data from this small single-arm trial are encouraging (R12-3308).

In patients with relapsed or refractory AML, decitabine has been used for salvage chemotherapy. Medical records of 79 patients who received decitabine-based salvage therapy have been reviewed from September 2006 through July 2009 at Weill Cornell Medical College (R11-1105). Patients with relapsed or refractory AML were given salvage chemotherapy with decitabine 20 mg/m^2 daily for 10 days or decitabine 20 mg/m^2 x 5 days with gemtuzumab ozogamicin. Overall, 16% of patients achieved a CR and 5% CRi (platelets < 100,000). Patients receiving decitabine alone had a median OS of 209 days and those receiving decitabine/gemtuzumab ozogamicin had a median OS of 177 days but the difference was not statistically significant. These study results suggested that decitabine-based treatment for relapsed and refractory AML is a low intensity alternative that has activity rivalling more intensive regimens. However, further investigation of decitabine-based salvage is warranted as a second retrospective trial of decitabine for the treatment of relapsed or refractory AML observed a lack of response in a heavily pre-treated population.

1.2.3 Combination Treatment of BI 836858 and Decitabine

This trial will investigate tolerability, safety, pharmacokinetics and efficacy of BI 836858 in combination with decitabine in patients with AML for the first time in the clinical setting. Therefore, no data on tolerability, safety, pharmacokinetics or efficacy on this combination in humans are available to date.

Combination experiments were performed to evaluate potential effects of clinically relevant combination partners on the ADCC of BI 836858. [redacted] These findings provide a rationale for clinical investigation of BI 836858 in combination with decitabine in AML.

2. RATIONALE, OBJECTIVES, AND BENEFIT - RISK ASSESSMENT

2.1 RATIONALE FOR PERFORMING THE TRIAL

Treatment for relapsed or refractory adult patients with AML independent of age and previously untreated AML patients ≥ 65 years of age, who are considered ineligible for intensive treatment, remains a major challenge. While progress has been made in treating younger adults, challenges still remain in treating the elderly population. Patients who are aged ≥ 65 years, particularly those with non-favourable cytogenetics, aged ≥ 75 years, or those with significant co-morbidities are considered ineligible for standard intensive chemotherapy. Therefore, there is an urgent need for discovering innovative treatments.

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). The clinical experience with lintuzumab supports the assumption that targeting CD33 with an IgG1-type antibody may translate into clinical response in patients with AML with an acceptable side effect profile. Preclinical data demonstrating an enhanced ADCC of BI 836858 over lintuzumab support the development of BI 836858 in patients with AML (see Section 1.2).

Recent studies have demonstrated clinical activity of decitabine in AML (R12-3309). The result suggested that decitabine as monotherapy may have at least activity similar to LDAC. Therefore, besides LDAC, decitabine provides another established treatment option for patients with previously untreated AML that are considered ineligible to receive standard intensive therapy.

Especially in a proliferative disease like AML, where number and functionality of effector cells may be limited, antibodies like BI 836858 need a combination partner to enhance their efficacy.

Preclinical data (see Section 1.2.3) showing that treatment with decitabine can enhance the ADCC activity of BI 836858 supports the clinical investigation of this drug combination.

The trial is aimed to investigate BI 836858 in combination with decitabine in patients with AML with regard to safety and efficacy.

2.2 TRIAL OBJECTIVES

The objective of the present trial is to investigate BI 836858 in combination with decitabine. If justified by safety and efficacy data of BI 836858 in combination with decitabine, late phase development of BI 836858 in combination with decitabine may be considered in the future.

The trial will be performed in two parts: a Phase I part consisting of a dose escalation and an extension part, as well as a randomized Phase II part (see also Figures 3.1.1 and 3.1.2).

The objectives of the Phase I Dose Escalation part of the trial are to determine the MTD and to investigate safety, pharmacokinetics and efficacy of BI 836858 in combination with decitabine in previously untreated patients ≥ 65 years of age and considered ineligible for standard intensive therapy, or patients ≥ 18 years of age with relapsed or refractory AML. In case the MTD would not be reached because of preliminary signals of activity or due to tolerability issues in repeated treatment cycles at doses below the MTD, the dose to be used for further development of BI 836858 in combination with decitabine in adult patients with AML would be determined (also see Section 3.1). Within the context of this trial that dose will be referred to as the Recommended Extension Phase I Dose (RExP1D).

The objectives of the Phase I Extension cohorts are to collect additional data on safety, pharmacokinetics and efficacy and to decide if the RExP1D will become the Recommended Phase II Dose (RP2D) of BI 836858 in combination with decitabine in patients ≥ 65 years of age, or if additional patients need to be enrolled in existing or additional dose escalation cohorts. Furthermore, based on the totality of efficacy and safety data, the treatment duration of decitabine in the combination treatment with BI 836858 will be assessed for the subsequent use in the Phase II part.

In the randomized Phase II part, the primary objective is to investigate the efficacy, safety and pharmacokinetics of BI 836858 in combination with decitabine compared to decitabine monotherapy in previously untreated patients with AML, who are≥ 65 years of age and considered ineligible for standard intensive therapy.

2.3 BENEFIT - RISK ASSESSMENT

The treatment of patients with AML ≥ 65 years of age has become increasingly important as the age of population increases. Patients ≥ 65 years of age with previously untreated, relapsed or refractory AML have an overall poor prognosis with very limited treatment options. If patients are unfit for standard intensive treatment, the participation in a clinical trial would be the appropriate choice as recommended by clinical practice guidelines (R15-5032).

The most relevant side effect of decitabine administration is expected to be a transient inhibition of proliferation of normal dividing cells (e.g. in bone marrow). The effects on the hematopoietic system lead to a temporary decrease of blood cells (red cells, white blood cells and platelets). 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.

As the cardinal symptom of AML patients is cytopenia, the symptoms of AML and haematological side effects of treatment with BI 836858 and decitabine are expected to overlap. For most anti-leukemia therapy, a drug-related transient worsening of cytopenia is common and inevitable. Therefore, especially the CTCAE grade and duration of cytopenia (as well as complications of cytopenia) will be important safety criteria that will be closely monitored for clinical symptoms of infections throughout this trial in order to limit the risk of the treatment with the trial drugs used in combination in this trial. The use of anti-infective prophylaxis (refer to Section 4.2.1) is strongly recommended.

The preclinical safety assessments for BI 836858 have revealed TNF-alpha and INF-gamma release, suggesting a potential for infusion-related reactions. So far only clinical data from 20 patients with refractory/relapsed AML, treated with weekly 10 and 20 mg of BI 836858 in the ongoing first in human trial, are available. Infusion-related reaction (IRR) was the most frequent drug-related adverse event (AE), reported in 7 patients (35%). Considering these data and the experience with other monoclonal antibodies in hemato-oncology indications, infusion-related reactions are likely. Prophylactic measures will be recommended for primary prevention, and supportive treatments are available (see Section 4.1.4).
In order to minimize the risk associated with the potentially additive adverse effects of the combination therapy, in both parts of the trial, a group of experts will be responsible for continuous surveillance and assessment of the trial data to ensure overall safety of the patients treated (refer to Section 3.1).

Investigators participating in the Phase I part of the trial will participate in frequent and periodic Safety Monitoring Committee (SMC) teleconference meetings to review the status of ongoing patients. In addition, during these SMC teleconference meetings, safety data to date will be summarized and reviewed with all participating Investigators, and options for dose escalations and de-escalations will be discussed.
In Phase II, the ongoing monitoring of safety data will be conducted by the Data Monitoring Committee (DMC).

Although rare, a potential for drug-induced liver injury is under constant surveillance by Sponsors and regulators. Therefore, this trial ensures timely detection, evaluation, and follow-up of laboratory alterations in selected liver laboratory parameters to protect patients' safety, see also Section 5.3.8.1.

A case of tumor lysis syndrome (TLS) with fatal outcome was reported in trial 1315.2 in AML. The patient was diagnosed with AML with extramedullary disease (skin (confirmed), abdominal and mediastinal lymph nodes (suspected)), assigned to a dose of 80 mg BI 836858 in combination with decitabine, and classified as low risk for TLS based on LDH and WBC (R18-1901). The event triggered measures for this trial to ensure patients safety including a modification of the infusion schedule (see Section 4.1.3) to mitigate the risk for rapid onset of activity and additional mandatory laboratory monitoring for early detection of TLS (see Section 5.3.6 and Table 1).

The benefits of participating in this protocol may include disease response to the trial treatment, better disease control, improvement of leukemia-related symptoms and/or improvement in quality of life, as a result of receiving BI 836858 and decitabine as a combination treatment. In addition, all patients who are taking part in the trial may derive general medical benefit from careful and close monitoring by the treating Investigator and site personnel during the trial. Safety will be ensured by monitoring of the patients for AEs, both clinically and by laboratory testing.

Given the above considerations, the benefit-risk assessment in this highly compromised AML patient population is considered favourable for this trial and the potential benefit of therapy with BI 836858 in combination with decitabine is expected to outweigh the treatment-related risks.

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

The trial will be performed according to an open-label design for both, Phase I and Phase II part. The data obtained from the Phase I part of the trial will be used to determine the MTD (or a Recommended Extension Phase I Dose (RExP1D), see Section 4.1.3 for details) of BI 836858 in combination with decitabine based on a Bayesian logistic regression model (BLRM) with overdose control.

Based on data from the Phase I Extension it will be decided if the RExP1D will become the Recommended Phase II Dose (RP2D) of BI 836858, or if additional patients need to be enrolled in existing or additional dose escalation cohorts to determine the RP2D.

In Phase II, this trial will explore efficacy and safety of BI 836858 in combination with decitabine *versus* decitabine monotherapy in a randomized manner.

In both phases of the trial, a group of experts (in Phase I a trial-internal Safety Monitoring Committee (SMC) and in Phase II a Sponsor-internal DMC) will be responsible for continuous assessment of the trial data as described in this protocol and the DMC charter (filed in the Trial Master File) to ensure overall safety of the patients treated. In Phase I, the SMC's responsibility will be the recommendation of the dose escalation and de-escalation steps and the monitoring of the quality of the data. In Phase II the DMC will provide advice about the conduct of the trial and the integrity of the data.

After having provided informed consent and after a screening period of up to 14 days, eligible patients will be allocated to treatment by Interactive Response Technology (IRT) to the respective dose cohort or treatment group. The patients will be asked to remain under the Investigator's or their staff's supervision during the duration of administration of decitabine as well as BI 836858. The patients will visit the site at regular intervals for assessment of safety and efficacy and for collection of blood for analysis of the PK of BI 836858 and decitabine. Treatment will continue until progression or relapse of the underlying AML or if patients and/or Investigators decide to discontinue therapy according to the criteria as defined in Section 3.3.4.

In Phase I patients will be followed up at regular intervals for approx. 6 months after end of treatment or until death, whichever occurs earlier. In Phase II, after the last administration of any of the two trial drugs the patients will be followed up at regular intervals for OS until death or until the end of the whole trial, whichever occurs earlier (refer to Section 6.2.3).

The results of the trial will aid in the decision-making on the further development program of BI 836858 in AML.

Phase I:
In the Phase I Dose Escalation, patients ≥ 65 years of age with previously untreated AML, who are considered ineligible for standard intensive therapy, or patients ≥ 18 years of age

with relapsed or refractory AML will be assigned to the respective dose cohort that is being investigated when the patient is entering the trial. The Phase I Dose Escalation will be guided by a Bayesian logistic regression model (BLRM) with overdose control (refer to Section 7). As new patient safety information becomes available, the BLRM estimates the MTD by updating estimates of the probability of observing a DLT in the first cycle for each dose level in the study. At any time in the trial, it will not be permitted to escalate to a dose which does not fulfil the escalation with overdose control (EWOC) criterion (refer to Section 7). Dose escalation will be restricted to a maximum of 100% from the previous dose.

At least 3 patients will be required for every dose escalation cohort, (refer to Section 7). In the case that only 2 patients are evaluable and neither has experienced a dose-limiting toxicity within Cycle 1 (patient has received at least 3 administrations of BI 836858 and reached end of Cycle 1, i.e. patient is eligible to continue trial treatment on Day 1 of Cycle 2 at the latest on Day 57 after start of Cycle 1, refer to Section 5.3.1), then dose escalation can occur based on these 2 patients.

After all patients in a cohort have either experienced a DLT or have been observed for at least one cycle without experiencing a DLT, the Bayesian logistic regression model (BLRM) will be updated with the newly accumulated data. The overdose risk will then be calculated for each dose and escalation will be permitted to all doses fulfilling the EWOC criterion and the additional 100% escalation rule. Based on the model and on additional information (e.g. PK, pharmacodynamics, AE, patient profiles), the members of the SMC will determine the next dose level and cohort size.

If DLTs are observed in the first two consecutive patients of a previously untested dose level, subsequent enrolment to that cohort will be stopped. The BLRM will be re-run to confirm that the dose level still fulfils the EWOC criterion. Based on this information, the SMC will evaluate whether the next patients will be enrolled on the same dose level, or if they will be enrolled on a lower dose level.

The SMC may recommend stopping the dose escalation phase after the criterion for MTD (refer to Sections 5.3.2 and 7.1) is fulfilled. Further patients may be included to confirm this MTD estimate. If no DLT is observed at a dose of which the efficacy is considered sufficient, the SMC may recommend to include an additional number of patients at the same dose level and to declare this dose as the RExP1D.

Based on the totality of data (PK, pharmacodynamics, biomarker and safety) the SMC may also recommend treating additional patients prior to the Phase I Extension part with the MTD (or RExP1D) or higher doses of BI 836858 in combination with the standard treatment schedule of decitabine. The number of patients to be treated and the dose of BI 836858 to be tested will be discussed and recommended by the SMC.

In the Phase I Extension part of the trial, up to 30 previously untreated patients with AML who are ≥ 65 years old and considered ineligible for standard intensive therapy, will be allocated subsequently into two cohorts. Up to 15 patients will be allocated to Cohort A, i.e. treatment with BI 836858 and decitabine 20 mg/m² for 10 consecutive days (decitabine

intensive treatment schedule) and up to 15 patients will be allocated to Cohort B, i.e. treatment with BI 836858 and decitabine 20 mg/m² for 5 consecutive days (decitabine standard treatment schedule).

If deemed necessary by the Sponsor and the SMC, based on a comprehensive review of available clinical trial data, biomarker results (including CD33 receptor saturation) and PK-results, additional patients may be enrolled after the extension cohorts into pre-existing or new dose escalation cohorts to further optimize the BI 836858 dose and determine the RP2D. Dose escalation steps for additional dose cohorts will be defined according to the rules as outlined for the phase I dose escalation part of this protocol.
The decitabine schedule to be used for each cohort will be determined by the Sponsor in agreement with the SMC and documented in the SMC meeting minutes.

A final recommendation on the RP2D dose of BI 836858 and on the duration of treatment with decitabine will be given after Phase I safety data of both, the dose escalation part as well as the extension part, will have been summarized and reviewed by the SMC.

Prior to the initiation of Phase II, safety and preliminary PK results will be analyzed and documented in a safety analysis report or lean interim Clinical Trial Report (CTR). This Phase I safety analysis report or lean interim CTR will be sent to competent authorities/ethic committees. A summary of safety and efficacy endpoints and determination of the RP2D will be included in this report.

The RP2D of BI 836858 with either the standard 5 day treatment schedule or the intensive 10 day treatment schedule of decitabine will be used in the combination treatment Arm 1 of the Phase II of the trial.

After completion of recruitment to Phase I Extension Cohort A and Cohort B, the recruitment to this trial is discontinued.

Phase II:
In Phase II, previously untreated patients with AML, who are ≥ 65 years old and considered ineligible for standard intensive therapy will be randomized in a 1:1 manner to investigate efficacy and safety of BI 836858 at RP2D in combination with decitabine *versus* decitabine monotherapy. The screening phase may be up to 14 days; therefore, the first dose of trial treatment should occur no more than 15 days after the informed consent is signed. The type of AML (*de novo*, secondary AML) is an important prognostic factor (R07-2768); therefore, patients will be stratified by type of AML to ensure a balanced distribution of this prognostic factor between treatment groups. A total of approx. 100 patients, 50 in each arm, will be enrolled in Phase II.

Patients will be enrolled in the trial once they have signed the informed consent form and entered into the trial once they have been confirmed to meet the inclusion and exclusion criteria.

Patients will be treated within the assigned cohort or treatment arm until progression/relapse or until patients and/or Investigators decide to discontinue therapy (refer to Section 3.3.4.). No patients will be allowed to continue trial treatment and switch or be entered into another part of this trial.

The overall structure of the trial is described in Figures 3.1: 1. (Phase I) and 3.1: 2 (Phase II)

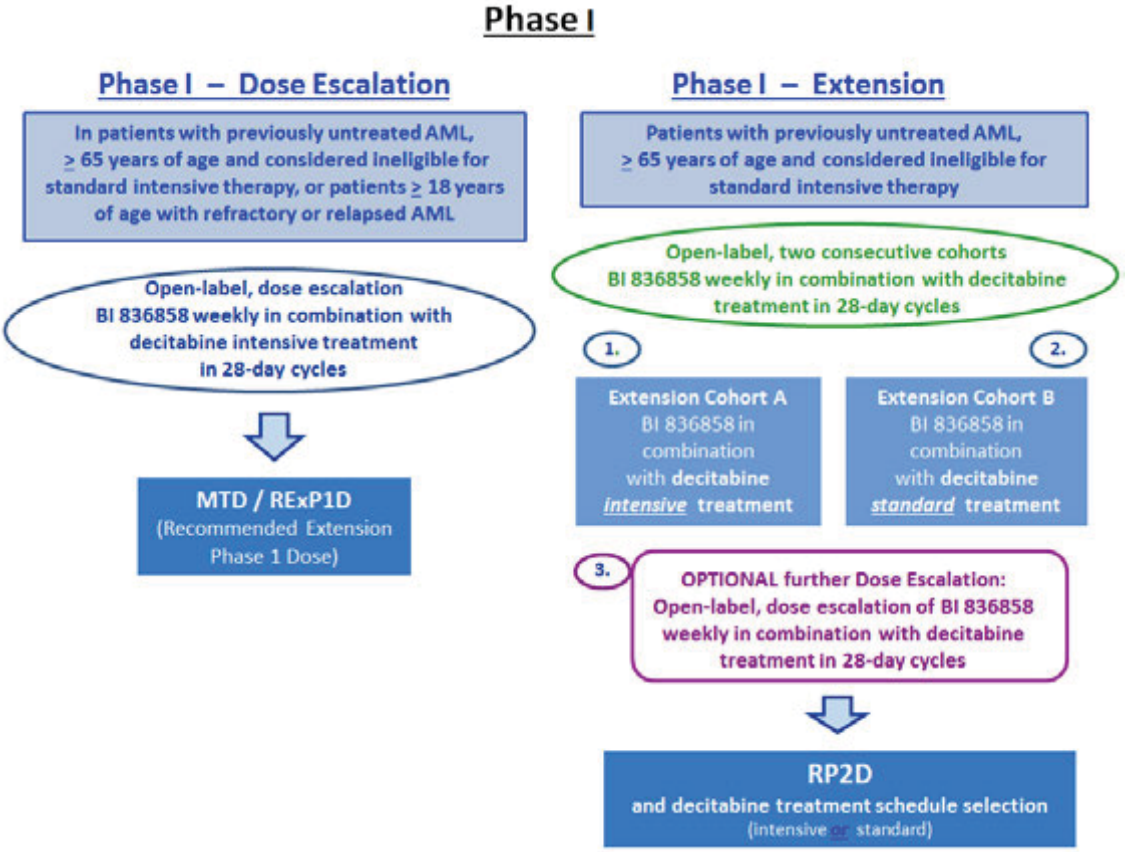


Figure 3.1: 1 Overall structure of the trial Phase I

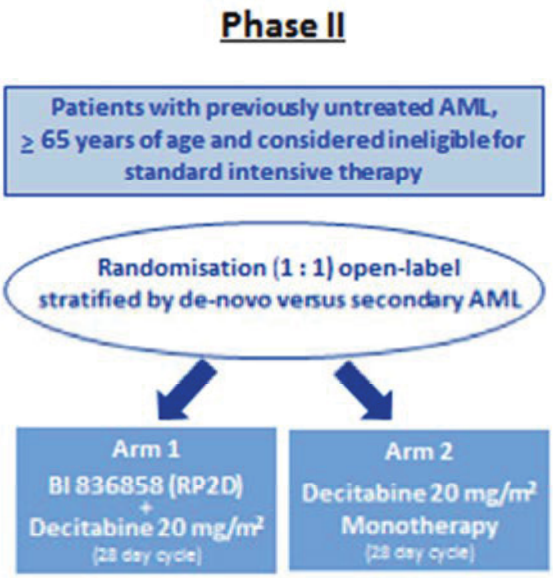


Figure 3.1: 2 Overall structure of the trial Phase II

3.1.1 Administrative structure of the trial

Boehringer Ingelheim (BI) is the Sponsor of this trial.

The Coordinating Investigator will be appointed by BI and shall be experienced in treatment of patients with AML and also experienced in performance of Phase I and other clinical trials in this patient population. The Coordinating Investigator will be responsible for the coordination of Investigators at different centres participating in this multicentre trial. The tasks and responsibilities of the Coordinating Investigator will be defined in a contract.

Participating Investigators will be physicians experienced and specialized in the treatment of AML and in the conduct of Phase I/II trials. Relevant documentation on the participating (Principal) Investigators and other important participants, including their *curricula vitae*, will be filed in the ISF.

Tasks and functions assigned in order to organise, manage, and evaluate the trial will be defined according to BI Standard Operating Procedures (SOPs). A list of responsible persons and relevant local information can be found in the ISF. On-site monitoring will be performed by BI or a Clinical Research Organizations (CRO) appointed by BI.

Boehringer Ingelheim will appoint CROs for special services such as IRT for patient enrolment, entry and trial medication logistics.

All trial relevant documentation will be stored in the trial master file (TMF) at BI. In addition each site will have an Investigator Site File (ISF) containing all trial documents relevant for the site.

The safety laboratory investigations (hematological, biochemical, coagulation, and urine; for details see Section 5.3.6) will be performed at local laboratories associated with the sites, i.e. no central laboratory will be used for this purpose.

Local and/or central laboratories will be used for assessment of biomarkers, pharmacokinetics, cytogenetics, molecular genetics and pharmacogenomics analyses. For details on analyses of BI 836858 and decitabine concentrations in plasma please refer to Section 5.4.

Both parts of the trial will be overseen by a group of experts (in Phase I by SMC, in Phase II by DMC) to ensure patient safety.

For Phase I, the SMC will consist of the Phase I Investigators and experts of the Sponsor, namely the following functions will be represented: Team Member Medicine (TMM), Trial Clinical Monitor (TCM), Project Statistician (PSTAT), Clinical Pharmacological Project Lead (CPPL) and TransMed Expert (TME). Additional experts may be invited as needed. The information on the overdose risk will be presented by the trial statistician to the SMC. Additional information, such as lower grade adverse events, PK, pharmacodynamics, individual patient profiles or data listings and other relevant information may also be presented. Based on this information, the members of the SMC will reach a decision on the next dose level to be investigated. This dose level may be above, below or identical to the currently investigated dose level. The SMC will also recommend the size of the next cohort. Minutes of the SMC meetings and recommendations will be documented and archived by the TCM.

In Phase II, the DMC shall be responsible for safeguarding the interests of trial participants, assessing the safety and efficacy of the interventions during the trial, and for monitoring the overall conduct of the trial. The DMC shall provide recommendations to BI on whether the study should continue, be modified or stopped for efficacy or safety concerns. Further details of the DMC members and how the DMC will operate will be described in a separate DMC Charter that will be filed in the ISF.

Boehringer Ingelheim has appointed a TCM, responsible for coordinating all required activities, in order to

- manage the trial in accordance with applicable regulations and internal SOPs,
- direct the clinical trial team in the preparation, conduct, and reporting of the trial,
- order the materials as needed for the trial,
- ensure appropriate training and information of local clinical monitors (CMLs), Clinical Research Associates (CRAs), and Investigators of participating countries.

Data Management and Statistical Evaluation will be done by BI or a CRO appointed by BI according to BI SOPs.

Tasks and functions assigned in order to organise, manage, and evaluate the trial will be defined according to BI SOPs. A list of responsible persons and relevant local information can be found in the ISF.

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

Decitabine is an established treatment option for patients with previously untreated AML who are considered ineligible to receive standard intensive therapy, and is a recommended treatment according to NCCN clinical practice guidelines (R15-5032). All patients participating in this clinical trial will be treated with decitabine. The dose and duration of treatment with decitabine in the Phase II part of the trial will be the dose and duration of the therapy regimen which has been investigated in the Phase I Extension part of this trial and was considered safe and potentially effective.

In Europe, the approved posology of decitabine is 20 mg/m² body surface area (BSA) by i.v. infusion over 1 h (as per decitabine SPC) repeated daily for 5 consecutive days in 28-day cycles. This treatment schedule will be referred to as the "decitabine standard treatment schedule". However, in clinical practice and in completed and ongoing clinical trials (e.g. EORTC (European Organisation for Research and Treatment of Cancer) 1301-LG trial, EudraCT Number 2014-001486-27, ClinicalTrials.gov Identifier NCT02172872) a dosing schedule of decitabine 20 mg/m² BSA i.v. over one hour (as per decitabine SPC) repeated daily for 10 consecutive days is also widely used. This treatment schedule will be referred to as the "decitabine intensive treatment schedule". The overall goal is to optimize the therapy of the patients with AML. A SMC will continuously supervise the safety of the patients, assess the risk-benefit profile and recommend any changes in the design in case a change of the risk-benefit profile would require a variation to the protocol.

In Phase I Dose Escalation of the trial, the investigational drug BI 836858 will be combined with decitabine to determine the MTD/RExP1D (Section 4.1.3) for the decitabine intensive treatment schedule. Dose escalation for BI 836858 will be conducted following a Bayesian logistic regression model (BLRM) with overdose control. An escalation with overdose control design will increase the chance of treating patients at efficacious doses while reducing the risk of overdosing. This design is based on practical experience and is an efficient method due to its ability to identify the dose with a desired toxicity rate and its allocation of a greater proportion of patients to doses at, or close to that dose (R13-4802, R13-4804, R13-4805). The use of Bayesian models for Phase I studies has also been advocated by the EMA guideline on small populations (R07-4856) and by the FDA (R13-4881).

Once a RExP1D has been defined, patients will be treated at the RExP1D in two consecutive extension cohorts (Section 4.1.3) using the two different decitabine treatment schedules as described above (also refer to Figure 3.1: 1). Based on efficacy and safety data, the treatment duration of decitabine in the combination treatment with BI 836858, which will be used in Phase II part, will be determined.

If deemed necessary by the Sponsor and the SMC, based on a comprehensive review of available clinical trial data, biomarker results (including CD33 receptor saturation) and PK-

results, additional patients may be enrolled after the extension cohorts into pre-existing or new dose escalation cohorts to further optimize the BI 836858 dose and determine the RP2D. In Phase II of the trial, patients ≥ 65 years of age with previously untreated AML considered ineligible to receive standard intensive therapy will be randomized to either receive decitabine in combination with BI 836858 at RP2D or decitabine alone. To avoid potential bias at inclusion, in the Phase II part the patients will be randomly allocated to the treatment arms (stratified by type of AML; refer to Section 3.1). In both treatment arms decitabine will be administered according to the same treatment schedule as determined at the end of Phase I. Due to the fact that the study drug is administered intravenously and additional placebo infusions should be avoided, this part of the trial is also performed open-label (Section 4.1.5).The conduct of this part of the trial, including patient safety and integrity of the trial data as per the DMC charter, will be overseen by the DMC.

BI 836858 will be investigated in combination with the established compound decitabine throughout this trial, with the exception of the control arm in Phase II, where patients will be treated with decitabine monotherapy. This control arm is needed to allow a clear comparison of the combination treatment effect *versus* the monotherapy treatment.

3.3 SELECTION OF TRIAL POPULATION

In order to enter approximately 150 evaluable patients to the trial, it is anticipated that about 200 patients will need to be screened (i.e. screening of approximately 30 patients for the Phase I Dose Escalation part of the trial, 40 patients for the Phase I Extension part and 130 patients for the Phase II part of the trial). During the Phase I Dose Escalation part of the trial, approximately 2 patients are expected to be entered every month; approximately 5-10 patients are expected to be entered every month in the Phase I Extension and the Phase II part of the trial.

A log of all patients enrolled into the trial (i.e. who have signed informed consent) will be maintained in the ISF at the investigational site irrespective of whether they have been treated with investigational drug or not.

The Phase I Dose Escalation of the trial will be conducted at approximately 6-8 sites preferably in Germany and the USA; possibly further countries will also participate. The Phase I Extension and the Phase II part of the trial will be performed at approximately 15-25 sites in the USA, Germany and approx. 5 other countries.

Screening of patients for this trial is competitive; screening for the trial will be terminated once the number of screened patients is considered sufficient to achieve the required number of entered and randomized patients, respectively. Investigators will be notified about the end of screening (for both Phase I and Phase II) and will not be allowed to recruit additional patients for this trial beyond the definite date. Patients who have signed the informed consent for the Phase I Extension cohort or Phase II prior to notification of the termination of recruitment will be allowed to continue in the trial, if they meet all entry criteria.

The Investigators are trained to assess a patient's eligibility for standard intensive AML therapy based on their special medical experience. The criteria impacting the decision to

assess a patient's eligibility will be documented to allow continuous monitoring and to enable reporting of the rationale to enter patients into the trial.

3.3.1 Main diagnosis for trial entry

Phase I Dose Escalation: Patients ≥ 18 years of age with relapsed or refractory AML (defined as persisting AML after at least two induction cycles) or patients ≥ 65 years of age with previously untreated AML, who are considered ineligible for standard intensive therapy.

Phase I Extension and Phase II: Patients ≥ 65 years of age with previously untreated AML who are considered ineligible for standard intensive therapy.

Please refer to Section 8.3.1 (Source Documents) for the documentation requirements pertaining to the in- and exclusion criteria. The investigator's decision to consider a patient as ineligible for standard intensive therapy must be based on documented medical reasons (e.g. disease characteristics like AML genetics, type of AML (*de novo* or secondary), and patient characteristics like performance score, concomitant diagnoses, organ dysfunctions).

3.3.2 Inclusion criteria

1) **Phase I Dose Escalation**:

   a. Male or female patients ≥ 18 years of age with relapsed or refractory AML (defined as persisting AML after at least two induction cycles) and no anti-leukemia therapy within 2 weeks before first treatment with decitabine.

   b. Male or female patients ≥ 65 years of age with previously untreated AML ineligible for receiving standard intensive therapy based on documented medical reasons as defined in Section 5.6.1.

   Phase I Extension and Phase II:

   Male or female patients ≥ 65 years of age with previously untreated AML ineligible for receiving standard intensive therapy based on documented medical reasons as defined in Section 5.6.1.

2) Histologically or cytologically confirmed AML according to the WHO classification (R09-2581).

3) Patients must be eligible for treatment with decitabine.

4) Eastern co-operative oncology group (ECOG) performance score ≤ 2 at screening

5) Signed and dated written informed consent (including consent for biomarker and genetic testing; refer to Section 8.1) by the start date of the Screening Visit in accordance with GCP and local legislation.

Please note that prior therapy for MDS is allowed for all patients participating in Phase I and Phase II of this trial (with the exception of hypomethylating agents such as decitabine and azazitidine).

Prior treatment with hydroxyurea in order to reduce high WBC and treatment with hydroxyurea to control the WBC count during the first treatment cycle is allowed (refer to Section 4.2.2.1).

3.3.3 Exclusion criteria

1) Acute promyelocytic leukemia (FAB subtype M3), according to WHO classification (R09-2581).

2) Patients who are candidates for allogeneic stem cell transplantation.

3) Active chronic graft versus host disease requiring immunosuppressive treatment.

4) Prior treatment with a hypomethylating agent (this also includes prior MDS treatment with decitabine or azazitidine).

5) Prior treatment with CD33 antibody.

6) Second malignancy currently requiring active therapy (except for hormonal/anti-hormonal treatment, e.g. in prostate or breast cancer).

7) Current clinical central nervous system symptoms deemed by the Investigator to be related to leukemic CNS involvement (no lumbar puncture required, clinical assessment per Investigator's judgment is sufficient).

8) Aspartate amino transferase (AST) or alanine amino transferase (ALT) greater than 2.5 x the upper limit of normal (ULN) or AST or ALT greater than 5 times the ULN for those with Gilbert syndrome.

9) Prothrombin time > 1.5 x ULN.

10) Total bilirubin ≥ 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 ≥ 2.0 mg/dL.

12) Presence of concomitant intercurrent illness, or any condition which in the opinion of the Investigator, would compromise safe participation in the trial, e.g. active severe infection, unstable angina pectoris, new onset of exacerbation of a cardiac arrhythmia.

13) Psychiatric illness or social situation which in the opinion of the Investigator would limit compliance with trial requirements.

14) 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.

15) Pregnant or breast feeding patients.

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 a minimum of 6 months after completion of trial treatment [i.e. combination of two forms of effective contraception (hormonal contraception, intrauterine device, transdermal patch, implantable or injectable contraceptive, bilateral tubal occlusion, etc.)].

    Women of childbearing potential are defined as females who
    a) have experienced menarche and
    b) are not postmenopausal (12 months with no menses without an alternative medical cause) and
    c) are not permanently sterilised (e.g. hysterectomy, bilateral oophorectomy or bilateral salpingectomy)

17) Male patients with partners of childbearing potential who are unwilling to use condoms in combination with a second medically acceptable method of contraception during the trial and for a minimum of 6 months after completion of trial treatment.

18) Treatment with another investigational agent under the following conditions:
    a) Within 2 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.

19) Known hypersensitivity to the trial drugs.

20) Patients 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 trial treatment, i.e. treatment with any trial medication, if:

- The patient withdraws consent. Patients are free to withdraw consent for trial treatment only or both, trial treatment and trial participation, without the need to justify the decision.
- Patients who are assigned to the combination treatment (any of the Phase I parts, or Arm 1 in the Phase II part) and who decide to withdraw consent for further administration of only one of the trial drugs, i.e. BI 836858 or decitabine, may not continue with monotherapy treatment of the other drug, but have to end the treatment phase. In that case the patient will be asked to have the EOT and EoR visits performed and will be followed up as per protocol.
- The patient needs to take concomitant drugs that interfere with the investigational product or other trial medication (please refer to Section 4.2.2)
- Start of subsequent treatment cycle needs to be delayed by longer than 8 weeks due to a drug-related event (e.g. delay in recovery of blood counts or awaiting resolution of toxicity; please refer to Section 4.1.4.2).
- The patient can no longer be treated with trial medication 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.
- For patients in Phase I only: The patient is not eligible for treatment with BI 836858 on Day 8 (or Day 9 at the latest) of Cycle 1. The patient will be asked to have the EOT and EoR visit performed and will be followed up as per protocol (i.e. the patient will be withdrawn from the trial treatment and may be treated with decitabine monotherapy according to local standard of care).

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. As soon as a patient is withdrawn from the trial treatment, the End of Treatment (EOT) visit and the End of Residual Effect Period (REP) visit (EoR visit) have to 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 documented full consent withdrawal (i.e. withdrawal from both, trial treatment and trial participation), no further visits will be completed and no further trial data will be collected. However, if

information about survival status is publicly available, then the Investigator is requested to report this information in the eCRF.

A patient has to discontinue trial drug administration, i.e. both BI 836858 and decitabine, in case:

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

Patients who have not completed at least 3 administrations of BI 836858 during cycle 1 due to BI 836858-related toxicity will not be replaced; this will be considered as a DLT. However, patients who have not completed at least 3 administrations (1 cycle) of BI 836858 for reasons other than BI 836858-related toxicity will be replaced.

Patients who experienced DLT but have subsequently recovered and are able to resume trial treatment will be allowed to continue on trial treatment, as long as criteria for further treatment are met (Section 4.1.4.1).

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) Failure to meet expected enrolment goals overall or at a particular trial site.
2) Emergence of any efficacy/safety information invalidating the earlier positive benefit-risk-assessment that could significantly affect the continuation of the trial.
3) Violation of GCP, the CTP, or the contract disturbing the appropriate conduct of the trial.
4) Recommendation by the SMC/DMC to discontinue the trial.

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

After completion of recruitment to Phase I Extension Cohort A and Cohort B, the recruitment to this trial is discontinued.

4. TREATMENTS

4.1 TREATMENTS TO BE ADMINISTERED

The investigational product BI 836858 will be administered in the defined treatment regimen in Phase 1 and Phase 2 (refer to Sections 4.1.3.1, 4.1.3.2 and 4.1.3.3). All patients participating in this trial will receive decitabine as standard of care treatment, which is backbone chemotherapy (R15-5032).

BI 836858 will be administered as rate-controlled intravenous infusion for up to 8 h. The actual duration of the infusion needs to be documented in the eCRF including actual start and end time, actual time points for interruption and restart of the infusion, as well as reason for interruption and the actual infusion rates.

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

4.1.1 Identity of Investigational Medicinal Product and combination treatment

Table 4.1.1: 1 BI 836858 (Investigational Medicinal Product):

Substance:	BI 836858
Pharmaceutical formulation:	Concentrate for solution for infusion
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Unit strength:	10 mg/mL (vials with 10 mL)
Posology	Rate controlled infusion (volume: 250 mL)
Route of administration:	Intravenous

Table 4.1.1: 2 Decitabine (standard of care/backbone chemotherapy treatment):

Substance:	Decitabine
Pharmaceutical formulation:	Powder for concentrate for solution for infusion
Source:	Commercially available decitabine may be locally supplied to sites according to local regulations in participating countries. Complete guidelines for preparation, storage and administration of decitabine can be found in the country package insert. Details about the options for reimbursement by the Sponsor will be stated in the Investigator or pharmacy contract, respectively.
Unit strength:	50 mg/vial
Posology	Infusion according to manufacturer's instruction
Route of administration:	Intravenous

4.1.2 Method of assigning patients to treatment groups

All patients will be treated with decitabine for treatment of AML.

In the Phase I Dose Escalation part of the trial, patients will be assigned in an open fashion into escalating dose cohorts of BI 836858 using IRT.

After determination of the MTD (or RExP1D) approximately 30 additional patients (2 x 15 patients per cohort) will be assigned via IRT into the Phase I Extension part. The patients will be allocated to treatment with either BI 836858 and decitabine in the intensive treatment schedule (Extension Cohort A, starting with 10 consecutive days of decitabine per treatment cycle) or with BI 836858 plus decitabine using the standard treatment schedule (Extension Cohort B, starting with 5 consecutive days of decitabine per treatment cycle). The two cohorts will be filled consecutively starting with Cohort A, followed by Cohort B.

In case there will be further Dose Escalation cohort(s) after the Phase I Extension part of the trial, this will be consecutive cohorts of escalating doses of BI 836858 plus decitabine, using the BLRM with overdose control. The number of patients and the decitabine schedule to be used for each cohort will be determined by the Sponsor in agreement with the SMC.

In Phase II of the trial, patients will be randomly allocated via IRT to treatment with BI 836858 in combination with decitabine or decitabine monotherapy. Randomization will be stratified for *de novo vs* secondary AML to ensure a balance of this prognostic factor between treatment groups.

To facilitate the use of the IRT, the Investigator will receive an IRT manual including all necessary instructions. A copy of the manual will be available in the ISF.

4.1.3 Selection of doses in the trial

Treatment with a sub-saturating dose is not warranted in this patient population [redacted] fixed dose of 20 mg BI 836858 will be used as starting dose. [redacted]

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

Decitabine will be administered in a dose of 20 mg/m² per day. If medically indicated, individual administrations of decitabine may be skipped. Any skipped dose must not be administered at a later time during that cycle. The decitabine treatment duration in the following cycle should occur as prescribed, provided the re-treatment criteria (see Section 4.1.4.2) are fulfilled.

In order to allow decitabine to take effect on white blood cell count (WBC) reduction prior to the first administration of BI 836858, the very first treatment with BI 836858 in Cycle 1 will not be initiated until Day 8 after the start of treatment with decitabine on Day 1. The very first dose of BI 836858 will be split across two consecutive days: a fixed dose of 20 mg will be administered on Day 8 (or Day 9 at the latest) and the rest of the full planned dose for that week will be administered the following day. For example a planned total dose of 80 mg will be administered as 20 mg i.v. infusion on Day 8 and 60 mg i.v. infusion on Day 9 (or 20 mg i.v. infusion on Day 9 and 60 mg i.v. infusion on Day 10 at the latest).

On treatment days when both BI 836858 and decitabine will be administered, the infusion with decitabine will be administered first, followed by the premedication (refer to Section 4.1.4) to prevent infusion-related reactions 30 min to 120 min before start of administration of BI 836858.

4.1.3.1 Treatment in the Phase I Dose Escalation part of the trial

The daily dose of decitabine will not be escalated (or reduced); however, the decitabine treatment schedule (i.e. the number of consecutive days with decitabine administration in each cycle) will be individually customized based on response and toxicity as per Table 4.1.3.1: 1.

Table 4.1.3.1: 1 Decitabine intensive treatment schedule

Cycle	**Blasts in % at end of precedent cycle**	**Decitabine i.v. treatment duration**
Cycle 1	n.a.	20 mg/m² for 10 consecutive days *(Days 1-10 of 28-day cycle)*
Cycle 2-3	No blasts in peripheral blood and BM blasts < 5%	20 mg/m² for 5 consecutive days *(Days 1-5 of 28-day cycle)*
	Blasts in peripheral blood ≥ 5% (no BM assessment required) or No blasts in peripheral blood and BM blasts ≥ 5%	20 mg/m² for 10 consecutive days *(Days 1-10 of 28-day cycle)*
Cycles 4 and further, until 'progression or toxicity'	non-PD patients*	20 mg/m² for 5 consecutive days *(Days 1-5 of 28-day cycle)*

*) Only non-PD patients (i.e. patients without disease progression or relapse) will continue treatment within the trial.

In case the initially planned treatment duration (as assigned prior to Day 1 of any new cycle) is not considered to be safe by the Investigator (e.g. due to myelotoxicity in precedent cycle), Day 4 and/or Day 5 may be omitted in the current and all subsequent cycles.

The Phase I Dose Escalation for BI 836858 will be guided by a Bayesian logistic regression model (BLRM) with overdose control.

The dose is planned to be escalated in cohorts at pre-specified provisional dose levels based on a maximum escalation of 100%. The provisional dose levels to be assigned to separate cohorts of patients are listed in Table 4.1.3.1: 2. Dose levels above 40 mg will only be explored after safety data from monotherapy studies with BI 836858 have become available and if data from PK and pharmacodynamics analysis support further dose escalation. Intermediate or lower dose levels, depending on the number of DLTs observed in the study, and dose levels higher than 320 mg, as long as they fulfil the safety criteria, may be investigated if recommended by SMC and agreed upon between Investigator and Sponsor.

Table 4.1.3.1: 2 BI 836858 dose escalation scheme

Cohort	**BI 836858 i.v. weekly** [a), b)] **in 28-day cycles**	**Decitabine i.v. in 28-day cycles**
Cohort 1	[redacted]	20 mg/m²
Cohort 2	[redacted]	20 mg/m²
Cohort 3	[redacted] [c)]	20 mg/m²
Cohort 4	[redacted] [c)]	20 mg/m²
Cohort 5[d)]	[redacted] [c)]	20 mg/m²

a) BI 836858 will be administered in weekly intervals, e.g. on Days 1, 8, 15 and 22 of 28-day treatment cycles with the exception of Cycle 1, where BI 836858 will be administered for the first time on Day 8 (or Day 9 at the latest), followed by further weekly administrations, e.g. on Days 16 and 23 of the first cycle. In case WBC on Day 8 (or Day 9) of Cycle 1 is ≥ 10 x 10^3/µL, treatment with BI 836858 will not be initiated and the patient will be withdrawn from the trial treatment and replaced within the corresponding cohort (i.e. patients may be treated with decitabine monotherapy according to local standard of care and followed up as per protocol).

b) For patients who achieve CR during any of Cycles 1 through 4, the weekly administration of BI 836858 should continue for one additional cycle and should then be reduced to monthly administration (maintenance treatment, starting on Day 1 of the next cycle).

After completion of Cycle 6 and only for patients with CR or CRi the weekly administration of BI 836858 will be reduced to monthly administration, starting on Day 1 of Cycle 7 (maintenance treatment).

c) Dose levels above 40 mg will only be explored after safety data from monotherapy studies with BI 836858 have become available and if data from PK and pharmacodynamics analysis support further dose escalation.

d) Further cohorts with intermediate or lower dose levels may be explored, depending on the number of DLTs observed in the trial, and dose levels higher than 320 mg of BI 836858 may be investigated if recommended by SMC and agreed upon between Investigators and Sponsor. Additional Phase I Dose Escalation cohorts may also be opened if deemed necessary by the Sponsor and the SMC following the Phase I Extension cohorts of the trial.

A time interval of at least 7 days must have elapsed between the 1st administration of BI 836858 and initiation of treatment with decitabine to the next patient in treatment Cohort 1.
A time interval of at least 3 days must have elapsed between the 1st administration of BI 836858 and initiation of treatment with decitabine to the next patient in treatment Cohort 2 or higher (see Table 4.1.3.1: 2).

For the optional Dose Escalation Cohorts following Extension Cohorts A and B, a time interval of at least 3 days must have elapsed between the 1st administration of BI 836858 for each new patient treated. This means that start of trial treatment with decitabine (Cycle 1_Day 1) for the next subsequent patient may occur at the earliest on Cycle 1_Day 4 of the previous patient.

For any dose escalation cohort, at least 3 patients will be required (refer to Section 7). However, in the case that only 2 patients are evaluable and neither has experienced a DLT within the Cycle 1 (i.e. patient has received at least 3 administrations of BI 836858 and reached end of Cycle 1; please refer to Section 5.3.2) then dose escalation can occur based on these 2 patients.

After all patients in a cohort have either experienced a DLT or have been observed throughout Cycle 1 (refer to Section 5.3.2) without experiencing a DLT, the Bayesian model will be updated with the newly accumulated data. The overdose risk will then be calculated for each dose, and escalation will be permitted to all doses which fulfil the EWOC criterion and the additional 100% escalation rule. Based on the model and on additional information (e.g. PK, pharmacodynamics, AE, patient profiles), the members of the Safety Monitoring Committee (SMC) will recommend the next dose level and cohort size.

If DLTs are observed in the first two consecutive patients of a previously untested dose level, subsequent enrolment to that cohort will be stopped. The Bayesian logistic regression model (BLRM) will be re-run to confirm that the dose level still fulfils the EWOC criterion. Based on this information, the SMC will evaluate whether the next patients will be enrolled on the same dose level, or if they will be enrolled to a lower dose level.

The MTD may be considered reached if the following criteria are fulfilled:

1) The posterior probability of the true DLT rate in the target interval [0.16, 0.33) of the MTD is above 0.50, OR
2) At least 15 patients have been treated in the study, of which at least 6 were treated at the MTD.

If no DLT is observed at a dose of which the efficacy is considered sufficient, the SMC may decide to include additional patients at this dose level and to declare this dose as the RExP1D.

4.1.3.2 Phase I Extension

Patients enrolled into the Phase I Extension part of the trial will be assigned via IRT in an open fashion into one of two treatment groups, Cohort A and Cohort B:

- In the first opened Cohort A patients will be treated with BI 836858 at the dose determined during the dose escalation part of the trial in combination with decitabine in the intensive treatment schedule (see Table 4.1.3.2: 1)
- After completion of enrolment into Cohort A, patients will be enrolled into Cohort B and treated with BI 836858 at the determined dose in combination with decitabine in the standard treatment schedule (see Table 4.1.3.2: 1).

During treatment in the extension cohorts, new patients may be enrolled at any time.

If deemed necessary by the Sponsor and the SMC, there will be an option to open further Dose Escalation cohort(s) following the extension cohorts to optimize or confirm the RP2D, based on additional biomarker, PK/PD and safety data. For further details on dose escalation procedures refer to Section 4.1.3.1.

Table 4.1.3.2: 1 Phase I Extension treatment Cohorts A and B

	Extension Cohort A "decitabine intensive treatment schedule" plus BI 836858 i.v. weekly [a), b)] in 28-day cycles		**Extension Cohort B "decitabine standard treatment schedule" plus BI 836858 i.v. weekly [a), b)] in 28-day cycles**	
Cycle	**Blasts in % at end of <u>precedent</u> cycle**	**Decitabine i.v. treatment duration**)**	**Clinical disease status**	**Decitabine i.v. treatment duration**)**
Cycle 1	n.a.	20 mg/m² for *10 consecutive days*	n.a.	20 mg/m² for *5 consecutive days*
Cycle 2-3	No blasts in peripheral blood <u>and</u> BM blasts < 5%	20 mg/m² for *5 consecutive days*	non-PD patients	20 mg/m² for *5 consecutive days*
	Blasts in peripheral blood ≥ 5% (no BM assessment required) <u>or</u> No blasts in peripheral blood and BM blasts ≥ 5%	20 mg/m² for *10 consecutive days*		
Cycles 4 and further, until 'progression or toxicity'	non-PD patients*	20 mg/m² for *5 consecutive days*	non-PD patients	20 mg/m² for *5 consecutive days*

*) Only non-PD patients (i.e. patients without disease progression or relapse) will continue treatment within the trial.

**) In case the initially planned treatment duration (as assigned prior to Day 1 of any new cycle) is not considered to be safe by the Investigator (e.g. due to myelotoxicity in precedent cycle), Day 4 and/or Day 5 may be omitted in the current and all subsequent cycles.

a) BI 836858 will be administered in weekly intervals, e.g. on Days 1, 8, 15 and 22 of 28-day treatment cycles with the exception of Cycle 1, where BI 836858 will be administered for the first time on Day 8 (or Day 9 at the latest), followed by further weekly administrations, e.g. on Days 16 and 23 of the first cycle. In case WBC on Day 8 (or Day 9) of Cycle 1 is ≥ 10 x 10^3/µL, treatment with BI 836858 will not be initiated and the patient will be withdrawn from the trial treatment and replaced within the corresponding cohort (i.e. patients may be treated with decitabine monotherapy according to local standard of care and followed up as per protocol).

b) For patients who achieve CR during any of Cycles 1 through 4, the weekly administration of BI 836858 should continue for one additional cycle and should then be reduced to monthly administration (maintenance treatment, starting on Day 1of the next cycle).

After completion of Cycle 6 and only for patients with CR or CRi the weekly administration of BI 836858 will be reduced to monthly administration, starting on Day 1 of Cycle 7 (maintenance treatment).

The RP2D dose of BI 836858 will be defined after all patients have been treated in the Phase I Extension part and optional additional dose escalation cohorts of the trial and received more than 1 administration of BI 836858 and have completed Cycle 1. The RP2D

dose will be either BI 836858 in combination with decitabine intensive treatment or BI 836858 in combination with decitabine standard treatment.

4.1.3.3 Phase II

In the Phase II part of this trial, patients will receive the RP2D of BI 836858 in combination with decitabine (standard or intensive decitabine treatment schedule) as defined after the Phase I Extension part.

Patients will be randomized 1:1 via IRT in an open fashion into one of two treatments, Arm 1 or Arm 2:

- In Arm 1 patients will be treated with BI 836858 in combination with decitabine
- BI 836858 will be administered in weekly intervals, e.g. on Days 1, 8, 15 and 22 of 28-day treatment cycles with the exception of Cycle 1, where BI 836858 will be administered for the first time on Day 8 (or Day 9 at the latest), followed by further weekly administrations, e.g. on Days 16 and 23. In case WBC on Day 8 (or Day 9) of Cycle 1 is ≥ 10 x 10^3/µL, treatment with BI 836858 will not be initiated at a later time point. Instead, the patient will continue treatment within this trial with decitabine monotherapy.
- In Arm 2 patients will receive decitabine monotherapy.

In both treatment arms the decitabine treatment schedule will follow Table 4.1.3.2: 1 for the defined RP2D of BI 836858.

4.1.4 Drug assignment and administration of doses for each patient

BI 836858 and decitabine will be prepared according to the instructions provided in the ISF and administered as an intravenous infusion under the supervision of the Investigator or designated personnel.

Decitabine will be administered according to Sections 4.1.3.1 and 4.1.3.2 depending on the phase and part of the trial in which the patient is being treated.

BI 836858 will be administered as weekly i.v. infusions in 28-day cycles in combination with daily infusion of decitabine 20 mg/m^2 as per the defined decitabine treatment schedule (with the exception of treatment Arm 2 in Phase II where patients will be treated with decitabine monotherapy). BI 836858 will be administered on Days 1, 8, 15 and 22 from Cycle 2 onwards. In Cycle 1 BI 836858 will be administered on Day 8 and Day 9, Day 16 and Day 23 if WBC is < 10 x 10^3/µL on Day 8. In case WBC is ≥ 10 x 10^3/µL on Day 8 (or Day 9 at the latest) of Cycle 1, the patient will not be treated with BI 836858. WBC from blood sample collected one day prior to the planned start of treatment with BI 836858 is acceptable in order to allow sufficient time for treatment decision, IRT and pharmacy logistics, as well as for preparation and delivery of the infusion. In case the platelet count prior to the 1st planned infusion with BI 836858 on Day 8 (or Day 9 at the latest) is not ≥ 25,000/µL, the patient must be transfused to at least 25,000 platelets/µL.

Whenever possible, BI 836858 should be administered in weekly intervals, i.e. two consecutive infusions should be 7 days apart. Should any unanticipated circumstances arise that might require more flexibility in the treatment schedule in order to ensure patient safety and allow patients to continue treatment within the trial, the following exceptions are acceptable and won't be classified as protocol violations: The minimum duration between two administrations of BI 836858 is 5 days and the maximum duration is 10 days. Should the need arise to deviate from the weekly administration schedule, every attempt should be made to bring the patient back to the initial schedule in order to align with the 28-day decitabine administration cycles. It is not acceptable to have more than 4 administrations of BI 836858 within any treatment cycle.

After treatment with BI 836858 was administered on Day 1 of any specific cycle, in case any one of the further weekly administrations of BI 836858 of that specific cycle cannot be administered within the acceptable time period as defined above (due to medical or administrative reasons), that week's dose will be considered as "missed" and the visit registered as "visit with no BI 836858 assigned" into the IRT system.

For patients who achieve complete remission (CR) during Cycles 1 through 4, the weekly administration of BI 836858 should continue for one additional cycle and will then be reduced to monthly administration as maintenance treatment. The treatment schedule of decitabine will remain unchanged in that case.

After completion of Cycle 6 and only for patients with CR or CRi, the weekly administration of BI 836858 will be reduced to monthly administration as maintenance treatment, starting on Day 1 of Cycle 7.

The first (Cycle 1 Day 8 and 9) and second (Cycle 1 Day 16) infusion of BI 836858 will be started at a rate of 10 mL/h. The infusion rate should be increased every 30 (+/-10) min by 10 mL/h to a maximum of 80 mL/h as long as tolerated by the patient. The duration of the infusion should not exceed a total of 8 h. 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 the infusion rate should not be escalated from this rate for at least 30 min. 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, but never longer than a maximum total of 8 h.

BI 836858 may be administered at any time during the day, but never prior to the administration of decitabine. However, to facilitate blood sampling for PK and pharmacodynamic analyses, it is recommended to start the infusion during the morning hours.

4.1.4.1 Premedication

Premedication to prevent infusion-related reactions is obligatory 30 min (up to 120 min before start of administration of BI 836858 is permissible) prior to the first administrations of BI 836858 (Cycle 1, Day 8 and 9), unless a contraindication for premedication exists, and should include all of the following:

- 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

If no IRR is associated with BI 836858 in the first administration (Day 8 and 9), glucocorticoid premedication should be reduced to a dose equivalent of 50 mg prednisolone for the 2nd (Day 16) administration. In case no IRRs grade 2 or higher are observed with the 2nd administration of BI 836858, omit the glucocorticoid for subsequent infusions. However, in case an administration of BI 836858 is associated with an IRR grade 2 or higher, premedication should be re-escalated to 100 mg prednisolone equivalent.

4.1.4.2 Re-treatment criteria

Patients will be treated in repeat cycles in the absence of permanent treatment discontinuation criteria according to Section 3.3.4.1.

Before the start of a subsequent cycle, adverse events and safety laboratory will be assessed. To continue treatment with further administrations of any of the two trial drugs, all of the following criteria must be met (depending on the disease status only criterion 1 or 2 is applicable):

1) **For patients with circulating blasts or persistent marrow disease (≥ 5% BM blasts; evidence of active leukemia):** Treatment shall proceed as per the initially allocated treatment group regardless of pre-treatment neutrophils.
    a. Patients with active leukemia with grade 4 thrombocytopenia (platelets < 25,000/µL) may continue on trial treatment as allocated provided that there is no evidence of bleeding and post-transfusion platelet count is at least 25,000/µL.
    b. Patients with pre-existing (prior to study entry) grade 3 or 4 neutropenia or grade 3 or 4 thrombocytopenia will continue with therapy in the absence of fever (≥ 38.5°C) and/or uncontrolled infection as prescribed. However, patients allocated to the intensive decitabine treatment schedule (10 consecutive days) with pre-existing grade 2 (or better) neutropenia or thrombocytopenia who have grade 4 neutropenia or thrombocytopenia shall be cut to the standard decitabine treatment schedule (5 consecutive days) for future cycles (EXCEPT for patients with absolute blasts count > 5000/µL who may be eligible to continue with the intensive decitabine treatment (10 consecutive days) and should be discussed with the TCM and/or the Coordinating Investigator).

2) **For patients with no evidence of disease in blood or marrow (< 5% BM blasts):** After completion of the first on-trial treatment cycle, the initially allocated treatment shall proceed regardless of neutropenia or thrombocytopenia. However, patients must be transfused to ≥ 25,000/µL platelets prior to administration of next treatment (including weekly administrations of BI 836858 therapy, if applicable).
    a. For subsequent cycles, patients with pre-existing grade 4 neutropenia shall proceed with treatment in the absence of ongoing fever or uncontrolled infection. However, patients with pre-existing grade 2 (or better) neutropenia who have grade 4 neutropenia (neutrophils < 500/µL) should have all treatment(s) held for 2 weeks and then discussed with the TCM and/or the Coordinating Investigator if grade 4 neutropenia persists. Patients without evidence of fever or uncontrolled infection may be eligible to continue with treatment as allocated.
    b. Patients with grade 4 thrombocytopenia may continue on allocated trial treatment provided that post-transfusion platelet count is at least 25,000/µL, but patients with pre-existing grade 2 (or better) thrombocytopenia should have treatment held for 2 weeks and then discussed with the TCM and/or the Coordinating Investigator if grade 4 thrombocytopenia persists. Patients without evidence of bleeding may be eligible to continue therapy provided the patient can be transfused to ≥ 25,000/µL.
3) Acceptable tolerability (in case of a drug related 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). 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.

In case criterion 1 and 3 (or criterion 2 and 3) are not fulfilled, blood counts and/or the adverse events should be re-evaluated at least weekly.
Subsequent cycles can be delayed up to 2 weeks to meet the above criteria. Longer delays should be discussed with the Coordinating Investigator. Patients with delays longer than 8 weeks due to a drug-related event (e.g. delay in recovery of blood counts or awaiting resolution of toxicity) will be withdrawn from study.

All of the above re-treatment criteria apply when a subsequent cycle is started, i.e. this is applicable for combination treatment in both parts of Phase I, for combination treatment in Arm 1 of the Phase II part, and also for the start of a new cycle with decitabine monotherapy in Arm 2 of Phase II.

Furthermore, the re-treatment criteria absence of fever (≥ 38.5°C) and/or uncontrolled infection and platelets ≥ 25,000/µL apply for the weekly administrations of BI 836858 after Day 1 of any given cycle, (i.e. Day 16 and Day 23 of Cycle 1 and Day 8, Day 15 and Day 22 of any further cycle).

4.1.4.3 BI 836858 dose reduction and dose escalation criteria

Administration of the trial drugs (i.e. both, decitabine and BI 836858 for patients receiving the combination treatment) has to be stopped temporarily in case of a DLT (see Section 5.3.1). 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. No dose levels for the new dose of BI 836858 have been pre-defined; any new dose outside of the currently tested dose level/cohort 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 with BI 836858 has to be permanently discontinued. Likewise, treatment with BI 836858 has to be discontinued in case the DLT is not reversible. In Phase I such patients will need to be withdrawn from study treatment, perform EOT and EoR visits and followed-up as per protocol. Patients in Arm 1 of Phase II however may continue on decitabine monotherapy at the discretion of the investigator.

Intra-patient dose escalation
Intra-patient dose escalation may be considered in agreement between the Investigator and Sponsor for selected patients. It is restricted to patients who have received at least 4 administrations of BI 836858 and tolerated the treatment well up to 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 SMC. 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 h after the end of the infusion, including safety laboratory 24 h after the first administration of the escalated dose of BI 836858.

Patients eligible for a subsequent treatment cycle will not start treatment before 28 days after the start of the previous cycle. If the criteria above (Section 4.1.4.2) are not met on Day 29, the subsequent cycle must be delayed. The period of delay is limited to a maximum of 8 weeks. Re-treatment should be initiated as soon as the criteria are met, unless other criteria for discontinuation or withdrawal apply, according to Sections 3.3.4 and 4.1.4.2. Any delay of more than three weeks between the end of the previous and the start of the next treatment cycle should be communicated to the clinical monitor of BI prior to re-treatment.

4.1.5 Blinding and procedures for unblinding

4.1.5.1 Blinding

This is an open-label study (see Section 3.2 for justification). Blinding is not applicable on individual patient level. However, to reduce bias, the BI study team will be blinded for the aggregated Phase II part data at the treatment level until the trial database lock.

4.1.5.2 Unblinding and breaking the code

Not applicable.

4.1.6 Packaging, labelling, and re-supply of BI 836858

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.

Re-supply of BI 836858 will be managed by IRT.

4.1.7 Storage conditions

Trial drug supplies will be kept in their original packaging and in a secure limited access storage area according to the recommended storage conditions on the medication label.
A temperature log must be maintained for documentation.

If the storage conditions are found to be outside the specified range, the local clinical monitor (as provided in the list of contacts in the ISF) must be contacted immediately and the corresponding procedures described in the ISF need to be followed.

4.1.8 Drug accountability

The Investigator and/or Pharmacist will receive the trial drug(s) delivered by the Sponsor or a CRO appointed by the Sponsor when the following requirements are fulfilled:

- Approval of the trial protocol by the IRB / ethics committee,
- Availability of a signed and dated clinical trial contract between the Sponsor and the head of the investigational site,
- 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 clinical trial protocol

- Availability of the proof of a medical license for the principal Investigator
- Availability of Form 1572 or equivalent

The Investigator and/or Pharmacist must maintain records of the product's delivery to the trial site, the inventory at the site, the use by each patient, and the return to the Sponsor or alternative disposal of unused products.

These records will include dates, quantities, batch / serial numbers, expiry ('use- by') dates, and the unique code numbers assigned to the investigational product and trial patients. The Investigator / Pharmacist will maintain records that document adequately that the patients were provided the doses specified by the CTP and reconcile all investigational products received from the Sponsor. At the time of return to the Sponsor and/or appointed CRO and/or

prior to local destruction of any unused trial medication, the Investigator / Pharmacist must verify that all unused or partially used drug supplies have been fully accounted for on appropriate drug accountability/ drug inventory logs and that no remaining supplies are in the Investigator's possession.

The only exception to the above will be commercial decitabine that will be sourced locally by participating trial sites/pharmacies from local suppliers (if allowed by local regulations). In that case drug accountability (including details as described above) will be done on patient and site level only, without detailed records of the product's delivery to the trial site.

4.2 CONCOMITANT THERAPY, RESTRICTIONS, AND RESCUE TREATMENT

4.2.1 Rescue medication, emergency procedures, and additional treatment(s)

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 will be allowed, but growth factors should be avoided during the first four administrations of BI 836858 for better assessment of safety and response parameters.

Anti-infective prophylaxis

Based on the known myelosuppressive effect of decitabine, patients should receive anti-infective prophylaxis as follows:

- Antibiotic prophylaxis: it is mandatory that patients receive prophylaxis with antibiotics when absolute neutrophil count (ANC) counts are < 500/µL. This prophylaxis should be continued at least until the ANC counts have reached ≥ 500 cells/µL and can be prolonged if clinically appropriate. Antibiotics used for infection prophylaxis should be selected based on institutional and published guidelines (R15-3877, R15-4167) as well as on patient-specific medical considerations.
- Antimycotic prophylaxis: surveillance for mycotic infections should be maintained during therapy, mainly in patients with persistent and long-lasting neutropenia. Antimycotic prophylaxis is recommended and should be implemented at discretion of Investigator when deemed medically necessary.

Prevention and treatment of Tumor Lysis Syndrome (TLS)

Risk for TLS should be assessed as per published guidelines prior to starting treatment with BI836858 (R18-1901). All patients should receive adequate hydration prior to start of each administration of BI 836858 in Cycle 1. Prophylactic administration of anti-hyperuricaemic agents (e.g. allopurinol, rasburicase) should be considered according to individual patient risk. Laboratory monitoring for TLS is mandatory as outlined in Table 1 and Section 5.3.6.1. In patients developing laboratory or clinical signs of a tumor lysis syndrome (e.g. hyperkalemia, hyperphosphatemia, hyperuricemia and hyperuricosuria, hypocalcemia, and acute renal failure), accepted treatments standards as per published recommendations must be applied (R18-1901, R10-4517).

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.

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

In patients with relapsed or refractory AML, prior anti-leukemia therapy must have been discontinued at least two weeks before first treatment with decitabine and the patient must have recovered from all clinically relevant reversible toxicities as determined by the Investigator. A time interval of at least two weeks (four weeks for biologicals) must have elapsed from the last administration of any other investigational treatment for AML to the first administration of BI 836858.

For WBC control (e.g. to keep WBC < 10,000/µL), treatment with hydroxyurea will be allowed during Cycle 1 only.

No other concomitant anti-neoplastic therapy is allowed during the treatment phase of this trial.

Short term glucocorticoid medications may be used as clinically indicated to treat infusion-related reactions at any dose. 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 involvement is allowed but must be discussed and agreed upon between Investigator and Sponsor. All concomitant therapy will be recorded in the eCRF.

No formal clinical drug-drug interaction studies with BI 836858 have been conducted for decitabine. For restrictions regarding concomitant treatment with decitabine, refer to manufacturer's SPC (R15-4802).

4.2.2.2 Restrictions on diet and life style

No restrictions apply with regard to diet or life style. However, patients are required to be hospitalized for approximately 48 h after start of the first administration of BI 836858 to allow close monitoring for infusion-related reactions or other AEs. Subsequent infusions of BI 836858 may be administered in the out-patient setting depending on the Investigator's decision.

4.3 TREATMENT COMPLIANCE

BI 836858 will be administered as a single i.v. infusion under supervision of the Investigator or dedicated clinic personnel. Compliance may also be verified by PK assessment. Any discrepancies will be explained in the eCRF by the Investigators or their designee.
Decitabine will be administered as an i.v. infusion under the supervision of the Investigator or designated personnel at the investigative site according to the manufacturer's product information (available in the ISF). Administration of decitabine will also be documented in the eCRF.

5. VARIABLES AND THEIR ASSESSMENT

5.1 TRIAL ENDPOINTS

5.1.1 Primary Endpoints

In the Phase I part of this trial, the primary endpoints to assess safety are the MTD of BI 836858 in combination with decitabine and the number of patients with DLTs during the first treatment cycle. For details on determination of MTD, please refer to Section 5.3.2 and 7.1.

In the Phase II part of the trial, the primary objective is to assess the preliminary efficacy of BI 836858 in combination with decitabine in comparison to standard therapy with decitabine alone. The primary endpoint in Phase II is objective response (CR+CRi) defined as best overall response of CR or CRi, analyzed by the number of patients with CR or CRi.
None of the endpoints listed below are assessing known safety issues.

Phase I:
- MTD of BI 836858 in combination with decitabine
- Number of patients with DLTs during the first treatment cycle (see Section 5.3.2)
- Time frame: From start of treatment until end of cycle 1 (end of REP; approximately up to 12 months).

Phase II:
- Number of patients with objective response combining
  - Complete remission (CR)
  - CR with incomplete blood count recovery (CRi)
- Time frame: From randomization until the earliest of progression, death or end of trial (approximately up to 30 months).

5.1.2 Secondary Endpoints

The secondary endpoint of the Phase I part of this trial is objective response (CR/CRi) as defined in Section 5.2.1. Secondary endpoints of the Phase II part of this trial are event-free survival (EFS), relapse-free survival (RFS), remission duration and time to remission.
None of the endpoints listed below are assessing known safety issues.

Phase I:
- Number of patients with objective response combining
  - Complete remission (CR)
  - CR with incomplete blood count recovery (CRi)
- Time frame: From start of treatment until the earliest of progression, death or end of trial (approximately up to 30 months).

Phase II:

- Event-free survival (EFS)
- Relapse-free survival (RFS)
- Remission duration
- Time to remission

Event-free survival (EFS):

- EFS is measured from the date of randomization to the date of progression, relapse, or death from any cause, whichever occurs first.
- 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, EFS will be censored at the date of last disease assessment. Patients who stopped active treatment will be followed up as described in Section 6.2.3.
- Time frame: From randomization until the earliest of progression, relapse, death or end of trial (approximately up to 30 months).

Relapse-free survival (RFS):

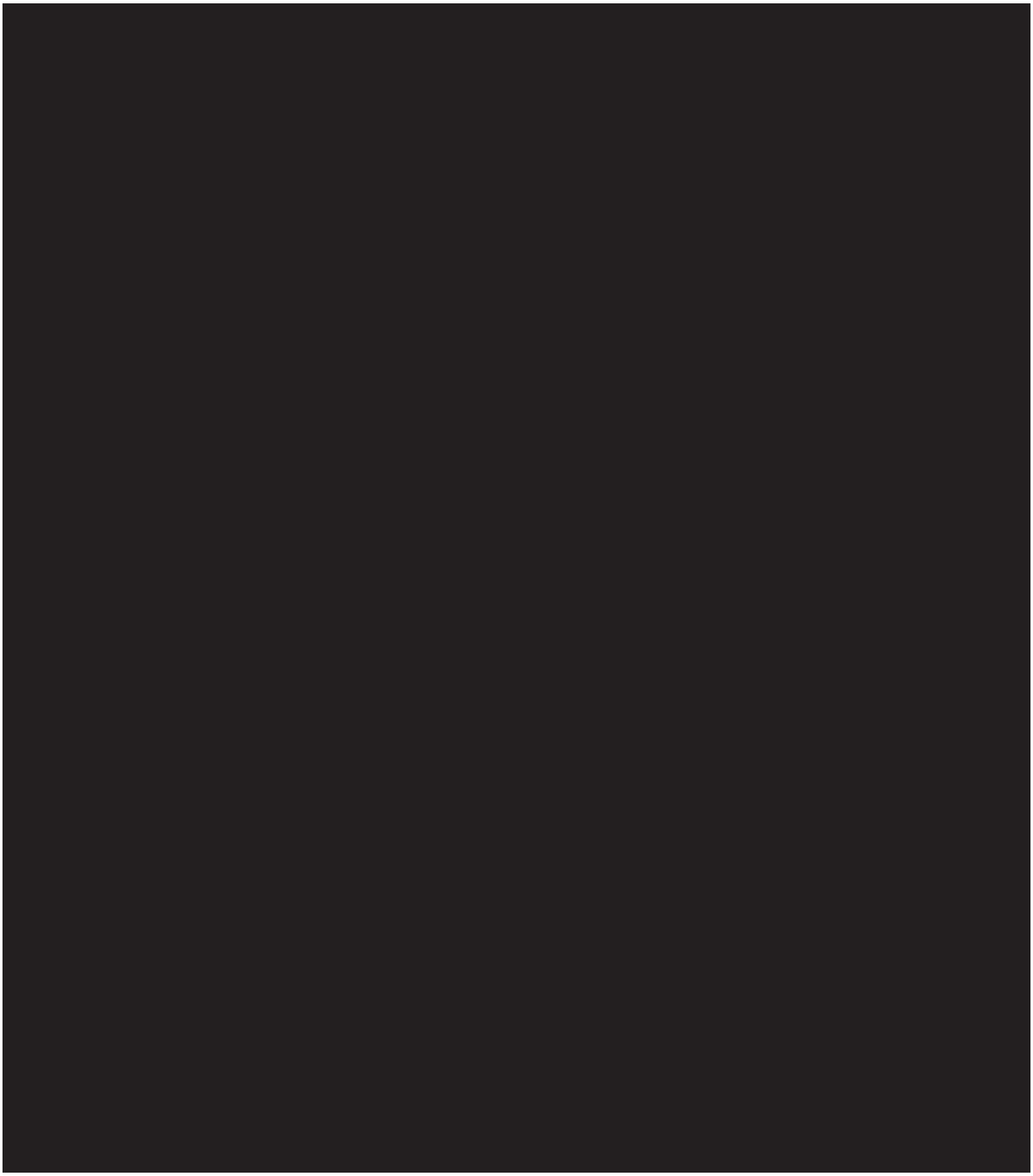
- RFS is defined only for patients who achieve a best overall response of CR or CRi and is measured from the date of first occurrence of CR or CRi until the date of relapse or death from any cause, whichever occurs first.
- The date of relapse will be the earliest of the dates of the disease assessment (blood sample, bone marrow sample, or clinical assessment) in which the relapse was observed. Patients not known to have relapsed or died at last follow-up are censored on the date they were last examined. Patients who stopped active treatment will be followed up as described in Section 6.2.3.
- Time frame: From first documented response of CR or CRi until the earliest of relapse, death or end of trial (approximately up to 30 months).

Remission duration:

- Remission duration is defined analogously to RFS only for patients with a best overall response of CR or CRi, with the exception of censoring patients who die before recurrence; i.e. remission duration is measured from the date of first occurrence of CR or CRi until the date of relapse.
- The date of relapse will be the earliest of the dates of the disease assessment (blood sample, bone marrow sample, or clinical assessment) in which the relapse was observed. For patients who die or are lost to follow-up without documented relapse, remission duration will be censored, respectively, on the date of death, regardless of cause, or on the date of last disease assessment for the patients who are alive when lost to follow-up.
- Time frame: From first documented response of CR or CRi until the earliest of relapse or end of trial (approximately up to 30 months).

Time to remission:

- Time to remission is defined only for patients who achieve a best overall response of CR or CRi; it is measured from the date of randomization until the date of first achieving CR or CRi.
- Time frame: From randomization until the first documented response of CR or CRi (approximately up to 30 months).



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5.2 ASSESSMENT OF EFFICACY

5.2.1 Overall response assessment

Response to treatment will be evaluated based on bone marrow samples (aspirations and biopsies will be collected as described in the Flow Chart) according to the following criteria (based on diagnosis and management of AML in adults: recommendations from an international expert panel, on behalf of the European Leukemia Net (R10-2947)

- Complete remission (CR)
  Bone marrow (BM) blasts < 5%; absence of blasts with Auer rods; absence of extramedullary disease; absolute neutrophil count > 1.0 x 10^9/L [1,000/µL]; platelet count > 100 x 10^9/L [100,000/µL]; independence of red blood cells transfusions (no transfusion for 1 week prior to the assessment). No minimum duration of response is required.

- Complete remission with incomplete neutrophil or platelet recovery (CRi)
  All CR criteria except for residual neutropenia (< 1.0 x 10^9/L [1,000/µL]) or thrombocytopenia (< 100 x 10^9/L [100,000/µL]).

- Partial remission (PR)
  All haematologic criteria of CR; decrease of bone marrow blast percentage to 5% to 25%; and decrease of pre-treatment bone marrow (baseline) blast percentage by at least 50%. Bone marrow samples with <5% blasts and with presence of Auer rods also represent PR.

- Stable disease (SD)
  Patient alive with no CR, CRi, PR or PD.

- Progressive disease (PD)
  Progressive disease is defined as at least one of the criteria below:
  - 50% increase in BM blast count over baseline (AML diagnosis);
  - 50% increase in peripheral blast count over baseline that is considered clinically relevant by the Investigator;
  - evidence of new extramedullary disease;

- clinically progressive disease based on the judgement of the Investigator (any attempt should be made to verify clinically diagnosed PD by a BM assessment).

- Relapse (recurrence)
  In patients with previous CR or CRi: 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.

- Death in aplasia
  Deaths occurring ≥ 7 days following completion of treatment cycle while cytopenic; with an aplastic or hypoplastic bone marrow obtained within 7 days of death, without evidence of persistent leukemia. Completion of treatment cycle is defined as reaching of Day 28 of the cycle.

- Death from indeterminate cause
  Deaths occurring before completion of a treatment cycle, or < 7 days following its completion; or deaths occurring ≥ 7 days following completion of treatment course with no blasts in the blood, but no bone marrow examination available. Completion of treatment cycle is defined as reaching Day 28 of the cycle.

5.3 ASSESSMENT OF SAFETY

After completion of recruitment to Phase I Extension Cohort A and Cohort B, the recruitment to this trial is discontinued.

With the aim to minimize the burden for trial participants, after approval of Protocol version 7.0, the mandatory protocol procedures described below in sections 5.3.4 (Physical Examination), 5.3.6 (Safety laboratory parameters), 5.3.7 (Electrocardiogram), are reduced for all patients who continue to receive trial medication in treatment cycles >7. Instead, safety assessments should be performed at the investigator's discretion, based on standard medical care. For details refer to Flow Chart.
Findings are documented in the eCRF only if qualifying for an adverse event (see sections 5.3.8 and 5.3.9, unchanged).

5.3.1 Dose limiting toxicity (DLT)

DLT is defined as any non-disease-related non-hematological AE of CTCAE grade 3 or higher.
Expected non-hematological disease-related AEs will not be regarded as a DLT. These include complications resulting from hematological AEs such as:

- 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 anaemia as defined by the Investigator

Infusion-related reactions (IRR) associated with the administration of BI 836858 should be reported as Adverse Event of Special Interest (AESI, refer to Section 5.3.8.1), 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).

Patients who do not receive at least 3 administrations of BI 836858 due to BI 836858-related toxicity are considered to have developed a DLT. If Cycle 2 is not started until 57th day from Day 1 of Cycle 1 as a result of drug-related AE, this AE is considered as DLT (i.e. treatment delay of ≥ 4 weeks of the start of Cycle 2 due to drug-related AE). Patients who do not experience a DLT but do not receive all 3 planned administrations of BI 836858 during Cycle 1 for reasons other than toxicity or tolerability will not be evaluable for DLT and cannot be used to establish the MTD.

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.
Since patients with refractory leukemia have infections and bleeding complications from myelosuppression, these events will not be considered as DLT unless they occur in the setting of prolonged myelosuppression from the combination treatment. Prolonged myelosuppression is defined as ANC < 1000/µL and PLT < 100,000/µL by day 56 of Cycle 1 in the setting of bone marrow showing < 5% blasts, without evidence of persistent cytogenetic abnormalities or minimal residual disease by flow cytometry. In case persistent cytogenetic abnormalities or immunophenotypic evidence of leukemia is present, myelosuppression would be considered secondary to leukemia even if morphology shows < 5% blasts.

All DLTs, occurring during the first or repeated treatment cycle will be reported as Adverse Event of Special Interest (AESI, see Sections 5.3.8.1 for definitions and 5.3.9 for reporting requirements).

5.3.2 Maximum Tolerated Dose (MTD)

The MTD estimate after the dose escalation part of the trial will be obtained on the basis of DLTs observed during the first treatment cycle. However, for those patients who receive more than one cycle of the combination treatment, all AEs that constitute a DLT will be considered for re-estimation of the MTD based on the BLRM. To obtain this, the model will be re-run including the DLT information from all cycles. Based on both MTD estimates, the recommended dose for the extension cohort, the Phase II part and/or further development will be selected. In regular intervals, all available safety data including adverse events qualifying for DLT will be submitted to the SMC. The SMC will assess this information and provide recommendations for trial conduct and dose escalation.

The SMC may recommend stopping the dose finding part of the trial after the criterion for MTD is fulfilled (refer to Section 7.1). Further patients may be included to confirm the MTD. If no DLT is observed at a dose of which the efficacy is considered sufficient, the SMC may

decide to include additional number of patients at this dose level and to declare this dose as the RExP1D (Recommended Extension Phase I Dose), that will be used for the Phase I Extension part of the trial.

5.3.3 Recommended Phase II Dose (RP2D)

Before the conclusion of Phase I and prior to initiating the Phase II, up to 30 patients will receive the combination treatment of BI 836858 at MTD (or RExP1D if applicable) and decitabine in one of the two extension cohorts.

If deemed necessary by the Sponsor and the SMC, there will be an option to open further Dose Escalation cohort(s) following the extension cohorts to determine the RP2D, based on additional biomarker, PK/PD and safety data.

Based on the overall Phase I data, the SMC will make a final determination of the RP2D, which must not exceed the MTD. The Phase I safety analysis report or lean interim CTR, including the rationale of RP2D determination will be sent to competent authorities/ethic committees and made available to all participating Investigators prior to the initiation of Phase II.

5.3.4 Physical examination

A physical examination including height (only measured once at screening visit), weight and ECOG performance score will be performed at screening and at the time points specified in the Flow Chart. During the physical examination, the patient should be assessed for possible AEs and/or baseline conditions (at screening). The physical examination should preferably be performed by the same member of the trial team at the sites.

5.3.5 Vital Signs

Vital signs (blood pressure and heart rate) will be recorded at screening, during the treatment phase (including the EOT visit and EoR visit) and follow-up as specified in the FlowChart.

Additional time points for blood pressure and heart rate at the day of the first administration of BI 836858 are: prior to the start of premedication, prior to the start of BI 836858 infusion, and in 30 (±10) min intervals throughout the course of the infusion of BI 836858 and 60 (±10) min after the end of the infusion, thereafter every 4-8 h until at least 24 h 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 the 2nd infusion of BI 836858, blood pressure and heart rate will be assessed at the same time points as during the 1st infusion and until 60 (±10) min after end of infusion. **After implementation of Protocol version 7.0 the vital sign results will be documented in the eCRF only if qualifying for an adverse event (see sections 5.3.8 and 5.3.9, unchanged).**

5.3.6 Safety laboratory parameters

5.3.6.1 General safety laboratory parameters

Blood samples and urine have to be collected at the time points specified in the Flow Chart. All safety laboratory examinations will be performed at the Investigator's local laboratory and include hematology, biochemistry, coagulation and qualitative urine analysis:

Hematology	Hemoglobin, white blood cell count (WBC) with differential count, platelets Reticulocytes have to be measured only at Visit 1 of every second cycle, EOT and EoR visit
Biochemistry	Glucose, sodium, potassium, calcium, inorganic phosphate, creatinine, aspartate amino transferase (AST), alanine amino transferase (ALT), alkaline phosphatase (AP), lactate dehydrogenase, total bilirubin, urea (preferred) or BUN, total protein, albumin, uric acid, C-reactive protein (CRP). Serum immunoglobulin levels (IgG, IgM, IgA) and direct antiglobulin test have to be measured only every other cycle (starting on Day 1 of Cycle 1) and at the EOT visit.
Coagulation	Activated partial thromboplastin time, prothrombin time, international normalized ratio where indicated (e.g. treatment with vitamin K antagonists)
Urine	pH, glucose, erythrocytes, leukocytes, protein, nitrite will be analyzed by dipstick and reported as semiquantitative measurements at screening, completion of Cycle 4 and at EOT visit . 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.

Monitoring for laboratory evidence of tumor lysis syndrome

Tumor lysis syndrome (TLS) is characterized by a group of metabolic derangements caused by the massive and abrupt release of cellular components into the blood after rapid lysis of malignant cells, potentially leading to hyperuricemia, hyperkalemia, hyperphosphatemia, hypocalcemia, and uremia (R10-4517). To allow for early treatment in case TLS develops, vigilant monitoring is mandatory.
Parameters for TLS screening are included in the routine safety labs. Additional blood samples for TLS monitoring have to be obtained at the time points in Cycle 1 indicated in Table 1, further samples may be obtained as clinically indicated. Sampling for TLS in course

2 and subsequent courses should be performed as clinically indicated. The actual date and time of the blood samples should be recorded in the electronic Case Report Form.

Blood sampling to screen for laboratory evidence of TLS should include:

Haematology:	haemoglobin, white blood cell count (WBC) with differential and blast count, platelets (PLT)
Biochemistry:	uric acid, potassium, calcium, inorganic phosphate, lactate dehydrogenase (LDH), creatinine, urea

An additional safety laboratory will be collected on Day 10 of Cycle 1 (i.e. approximately 24 h after start of the first administration of BI 836858). Other laboratory tests to be included: haptoglobin and direct antiglobulin test. Non pre-existing abnormal laboratory values (CTCAE grade 3 or higher) will be followed up every 48 h 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.

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5.3.7 Electrocardiogram (ECG)

A 12-lead resting ECG will be performed in all patients according to the schedule in the Flow Chart. 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.

5.3.8 Assessment of adverse events

5.3.8.1 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,
- 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 jeopardize the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions.
  Every new occurrence of cancer of new histology must be reported as a serious event (for the reporting periods please refer to Section 5.3.9).

Life-threatening in this context 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.

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”
In accordance with the European Medicines Agency initiative on Important Medical Events, Boehringer Ingelheim has set up a list of 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 portal. A copy of the latest list of "Always Serious AEs" will be provided to the Investigators/sites upon request. These events should always be reported as SAEs as described in Section 5.3.9.

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, see Section 5.3.9.

The following are considered as protocol-specified AESIs:

- Infusion-related reactions (CTCAE grade 3 or higher)
- Tumor Lysis Syndrome (any CTCAE grade)
- Any event that qualifies for DLT
- Drug Induced Liver Injury (DILI)

  A hepatic injury (DILI) is defined by the following alterations of hepatic laboratory parameters:
  - an elevation of AST and/or ALT ≥ 3-fold ULN combined with an elevation of total bilirubin ≥ 2-fold ULN measured in the same blood draw sample, and/or
  - marked peak aminotransferase (ALT, and/or AST) elevations ≥ 10-fold ULN

  These laboratory findings constitute a hepatic injury alert and the patients showing these laboratory 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 laboratory results (ALT, AST, total bilirubin) available, the Investigator should make sure these parameters are analyzed, 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.

Severity of AEs
The severity of adverse events should be classified and recorded in the eCRF according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 (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.

Indicators of a reasonable causal relationship are:
- 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 trial drug treatment continues or remains unchanged.

5.3.9 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 eCRF by the Investigator:
- From signing the informed consent onwards until the end of treatment (including the Residual Effect Period (REP)):

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

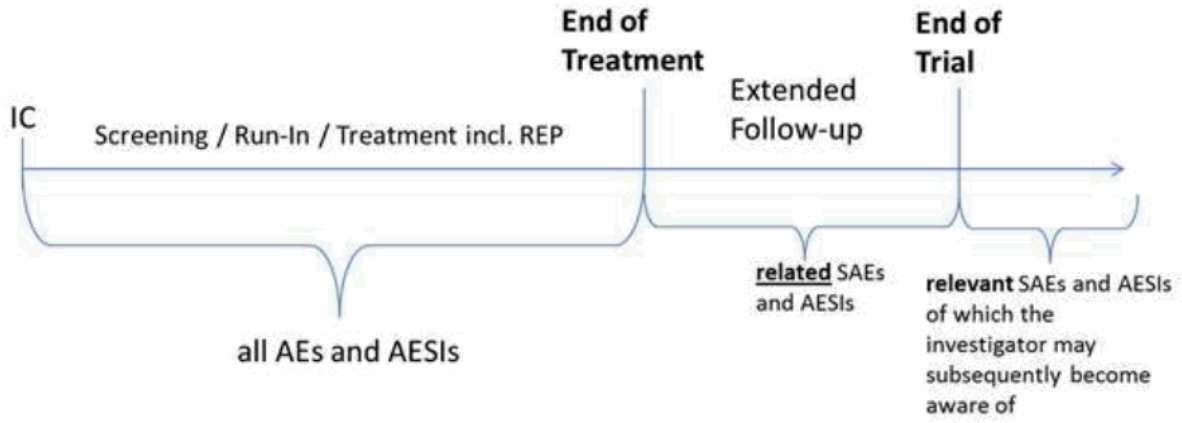
- After the end of treatment (including the REP) until the individual patient's end of trial (i.e. during extended Follow-up; for details refer to Section 6.2.3):

  All related SAEs and all related AESIs.

- After the individual patient's end of the 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, but only for Phase II part.



The Residual Effect Period (REP) is defined as 30 days after the last trial medication application (BI 836858 or decitabine, whichever is last). All AEs which occurred through the treatment phase and throughout the REP will be considered as "on treatment", refer to Section 7.3.4. 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 h) 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 eCRF pages and the BI SAE form, e.g. onset, end date, severity, treatment required, outcome, seriousness, and action taken with the investigational drug(s). The Investigator should determine the causal relationship to the trial medication.

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

- Worsening of the underlying disease or of other pre-existing conditions (for exemptions see below in paragraph "Exemptions to (S)AE Reporting")
- 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 characterized, 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 has to be reported as SAE in the Phase I part. However, disease progression is an endpoint for analysis of efficacy in the Phase II part of the trial and as such is exempted from reporting as an (S)AE. 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.

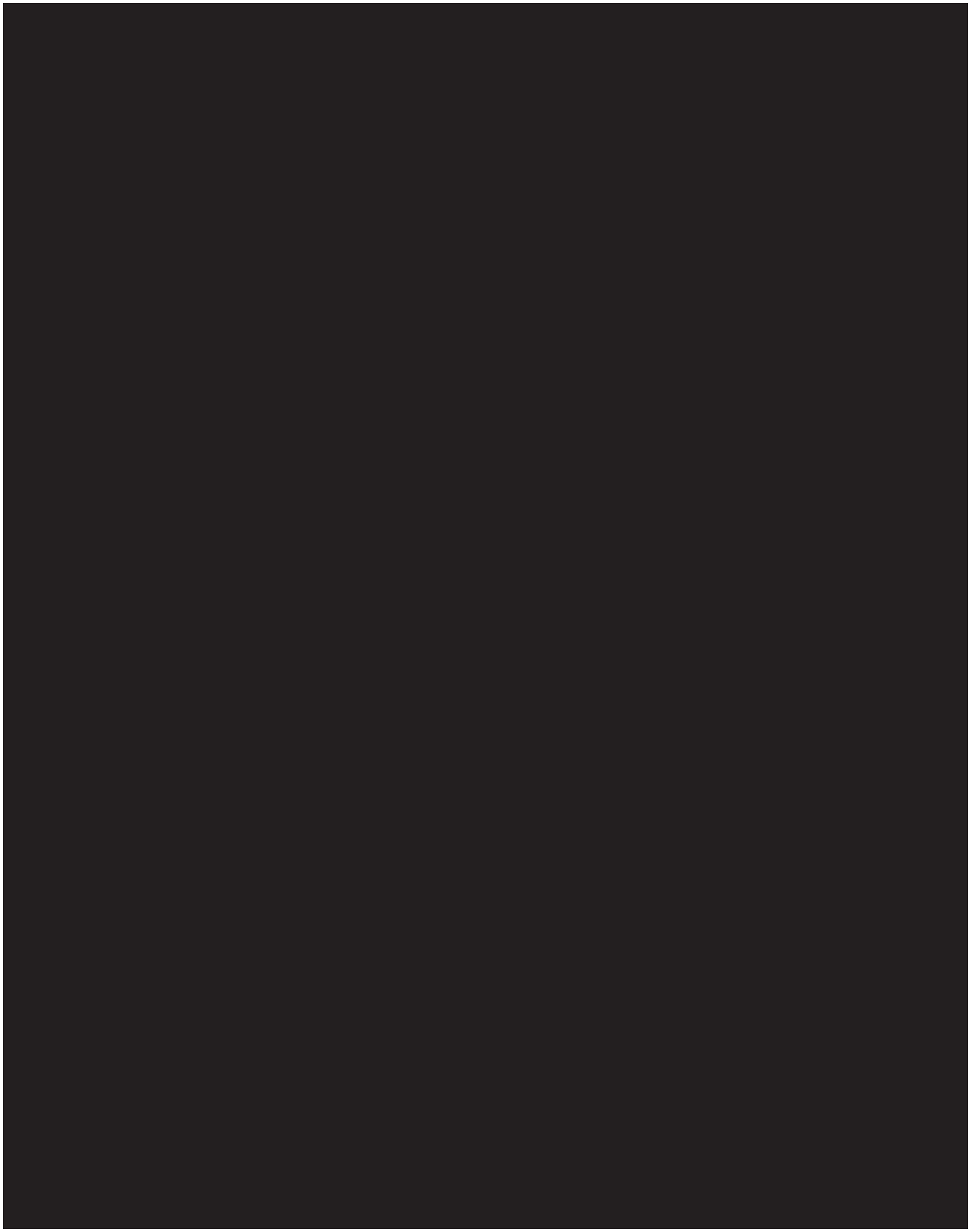
Examples of exempted events of PD may be:

- 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(s) and the progression of the underlying malignancy, the event must be reported as an (S)AE on the SAE Form and on the eCRF.

Exempted events are monitored at appropriate intervals by the applicable independent committees (i.e. SMC or DMC).

Reporting of related Adverse Events associated with any other BI drug
The Investigator is encouraged to report all adverse events related to any marketed BI product according to the local regulatory requirements for spontaneous AE reporting at the Investigator's discretion by using the locally established routes and AE report forms. The term AE includes drug exposure during pregnancy, and, regardless of whether an AE occurred or not, any abuse, off-label use, misuse, medication error, occupational exposure, lack of effect, and unexpected benefit.



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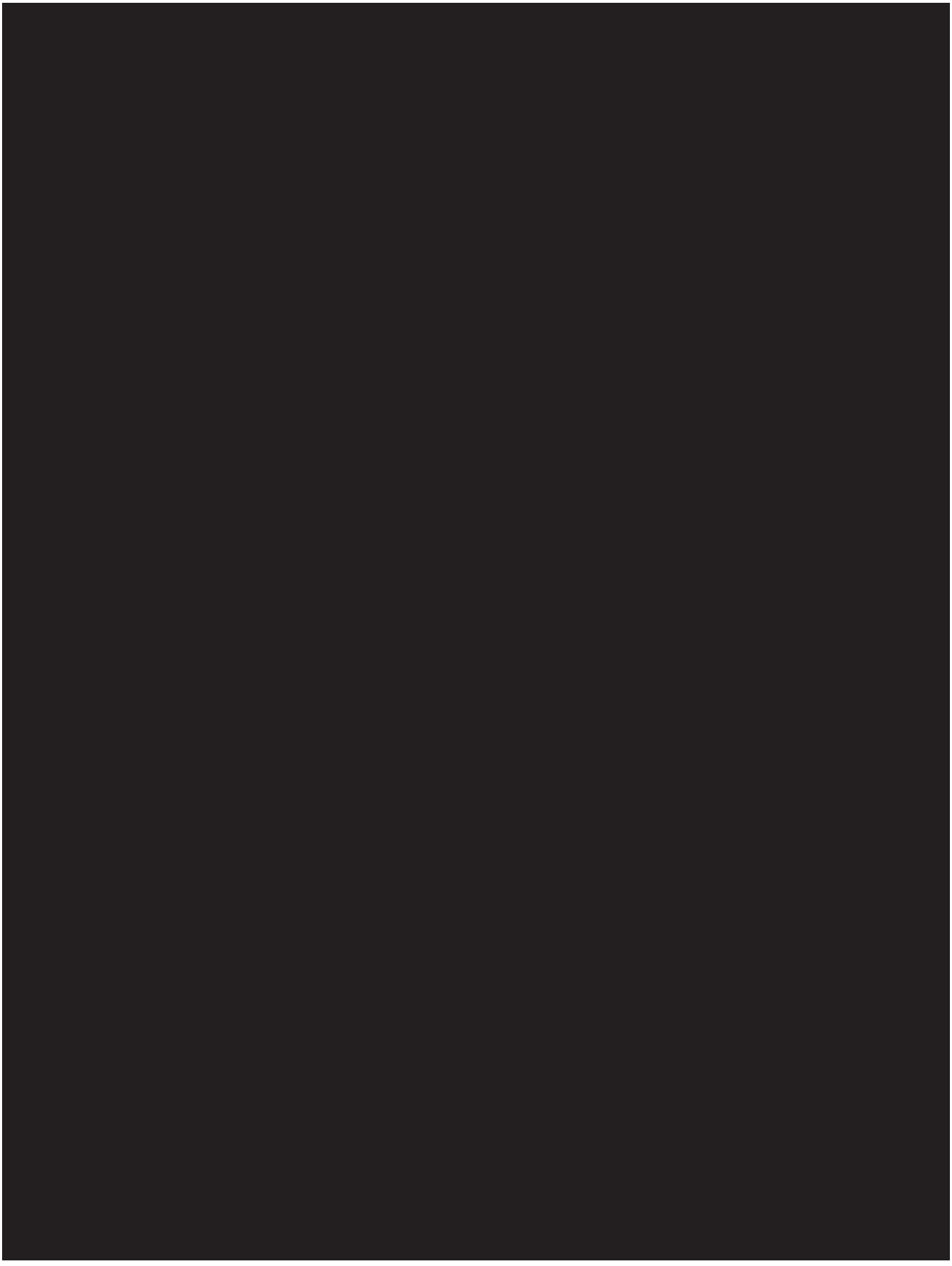

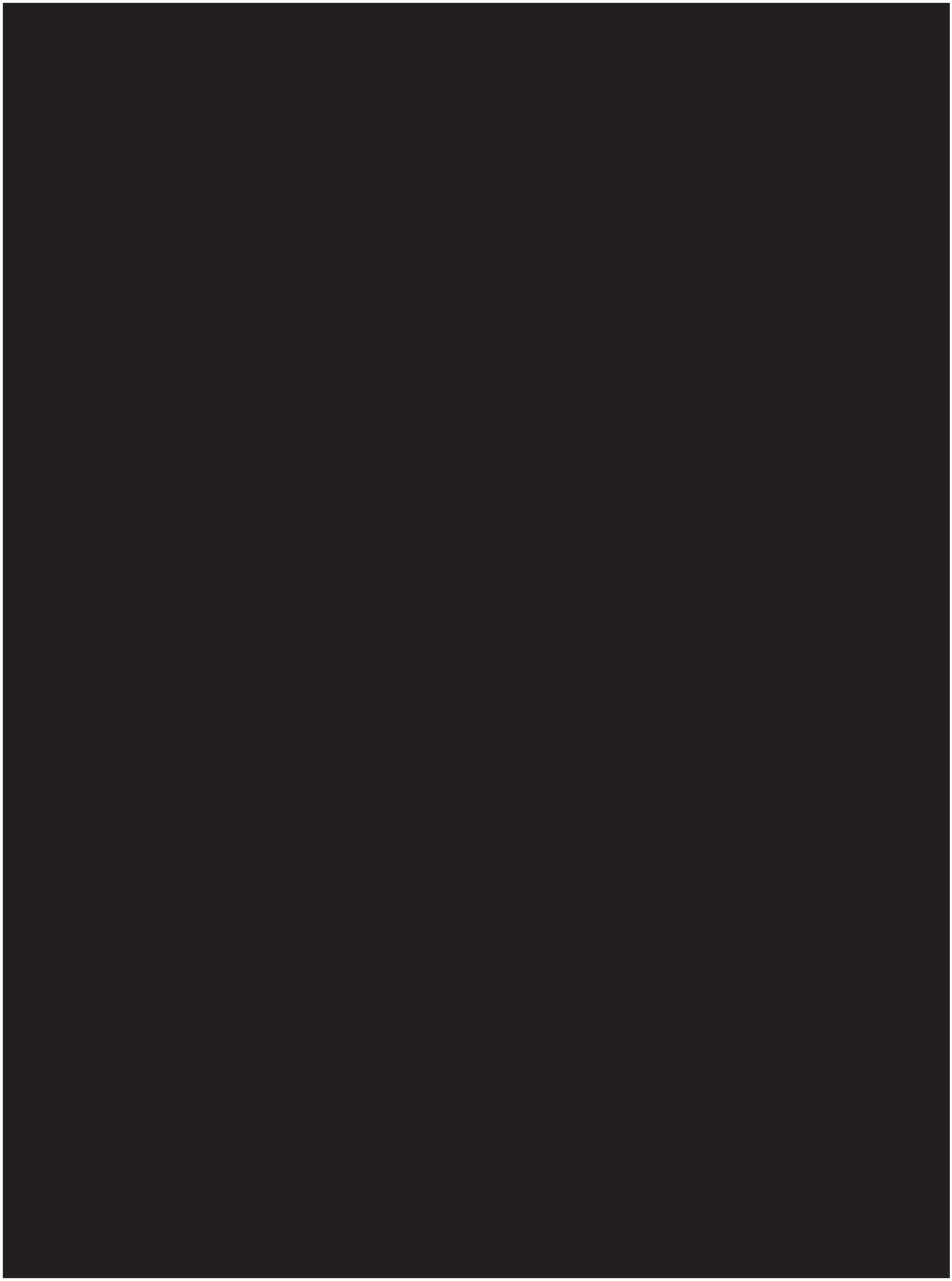

5.7 APPROPRIATENESS OF MEASUREMENTS

Determination of MTD is based on toxicities graded according to CTCAE version 4.03 (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 (R10-2947) are well established and scientifically accepted.

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

Patients must satisfy all inclusion and exclusion criteria prior to treatment administration (see Section 3.3). Details of any patient who is screened for the trial but is found ineligible must be entered in an enrolment log (see ISF) and documented in the eCRF.

All patients are to adhere to the visit schedule and the allowed visit windows as specified in the Flow Chart.

Patients are required to be hospitalized under close surveillance with access to intensive care for at least 24 h after start of 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 comorbidities 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 and the patient reports to the Investigator between the missed and the next scheduled visit, the delayed visit should be done and the actual date and the reason should be given for the delayed visit. Subsequent visits should follow the original visit schedule.

Additional unscheduled clinic visit(s) might be arranged at the discretion of the Investigator. For unscheduled visit, it is sufficient to record only the visit date, clinically relevant laboratory data and safety findings on the applicable eCRF.

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

The investigations as outlined in the Flow Chart 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 begins when the informed consent form is signed and ends just prior to the start of trial treatment on Day 1 of Cycle 1. The maximum duration of the screening period is 14 days and includes the randomization/treatment allocation. Randomization/treatment allocation should be done as close as possible to the planned start of trial medication.

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

- Informed consent (including mandatory biomarker assessments and mandatory pharmacogenetic testing)
- Informed consent for optional DNA-biobanking
- Demographics (sex, year of birth, race and ethnicity, smoking and alcohol status)

- Medical history (oncological and relevant non-oncological) including detailed history of AML, previous malignant disease and previous therapies of malignant disease/other therapies
- WHO classification of the disease, date of first cytological diagnosis (month and year) and cytogenetics of AML
- Baseline conditions
- Review of inclusion and exclusion criteria (patient eligibility)
- Safety laboratory (hematology, biochemistry, coagulation, urine; for details please refer to Section 5.3.6)
- Physical examination, height, weight, vital signs and ECOG performance score
- Serum pregnancy test in women of childbearing potential
- 12-lead ECG
- Bone marrow aspiration for disease assessment and biomarker. In case of *punctia sicca* disease assessment should be done via bone marrow biopsy.
- Molecular genetics and cytogenetics of AML (please refer to Sections 5.5.1.1 and 5.5.1.2; available data from local analysis should be entered in eCRF; analysis at central laboratory will only be performed for patients in Phase II)
- Peripheral blood for disease assessment and biomarkers as per Table 3
- Documentation of adverse events (AEs) since signing the Informed Consent Form.
- Documentation of concomitant medications (including transfusions and anti-infectives) at trial entry and / or during screening
- Documentation of planned hospitalisations (only in source documents, not recorded in eCRF)
- Phase I Dose Escalation and Extension: Dose assignment via IRT (before the first administration of the trial drug and after informed consent and review of in- and exclusion criteria)
- Phase II: Randomization via IRT

Re-Screening
Sites will be allowed to re-screen patients after 1 week from when they initially screen failed. Re-screened patients will keep their initial patient number. Any re-screening does require renewed signature of informed consent.

6.2.2 Treatment period

The first trial drug administration should occur as soon as possible after the randomization / treatment allocation. A treatment cycle is defined as 28 days. If initiation of a subsequent cycle is delayed due to medical reasons, visits beyond Day 28 may be necessary. Additional unscheduled visits may be performed at the Investigator's discretion if medically indicated, but at least weekly; these unscheduled visits should also be reported in the eCRF.

An End of Cycle (EOC) visit will be performed at the end of each treatment cycle, i.e. on Day 29 (±3 days). A subsequent treatment cycle should not start earlier than on the 29th day of the precedent cycle (if e.g. the previous cycle started on a Tuesday the next cycle will start earliest on a Tuesday 4 weeks later).

Day 29 (Visit 4, EOC) can be the same day as Day 1 (Visit 1) of the next treatment cycle if the patient is eligible to receive further treatment without delay. In that case Day 29 becomes Day 1 of next cycle and all procedures and assessments as indicated for Day 29 and Day 1 of the next cycle should be performed.

During Phase I and Phase II the decitabine treatment schedule for Cycles ≥ 2 will be individually customized depending on the blast count at the end of previous cycle. For details on the treatment schedules refer to Table 4.1.3.1: 1 for patients treated in the Phase I Dose Escalation and to Table 4.1.3.2: 1 for patients treated in the Phase I Extension and Phase II.

Refer to Section 4.1.4.2 for treatment delay and resuming subsequent cycle of treatment.

With the aim to minimize the burden for trial participants, after approval of Protocol version 7.0, the mandatory protocol procedures are reduced for all patients who continue to receive trial medication in treatment cycles >7. Refer to **updated** Flow Chart for specific requirements during treatment period.

During the treatment phase, patients will receive trial drug administration in cycles of 28 days. Day 1 of each cycle is defined as the start day of decitabine administration of that cycle. Patients will receive administration with BI 836858 once weekly, i.e. every 7 days usually on Day 1, 8, 15 and 22 of each cycle. However, independent of the trial phase, the very first administration of BI 836858 for each patient receiving the combination treatment will take place on Day 8 (or Day 9 at the latest) of Cycle 1, and then onwards in weekly intervals. Whenever possible the weekly intervals between two administrations of BI 836858 and the 4-weekly intervals between the start dates of decitabine treatment on Day 1 of two subsequent cycles should be respected. For further details on the administration schedule of BI 836858 please refer to Section 4.1.4.

[redacted] Bone marrow aspirations (and biopsies if medically indicated) for local response assessment are also required at the end of Cycle 1 (Day 29 ± 3), at the end of Cycle 2 and every other cycle thereafter (**after approval of Protocol version 7.0, BM assessments will be done at investigator´s discretion only).** The BM sample collection at the end of Cycle 2 is not a mandatory trial procedure in patients with ≥ 5% blasts in peripheral blood. From Cycle 2 onwards, BM samples can be taken up to 7 days before the scheduled visit 4 (EOC), i.e. between Day 22 and 29 of the treatment cycle) unless the patient has achieved CR in which case further bone marrow aspiration/biopsies are not required unless clinically indicated; earlier response assessments can be performed based on peripheral blood count recovery.

For patients with CR who receive maintenance treatment (patients who were switched from weekly to monthly infusions with BI 836858 and have completed one treatment cycle of maintenance treatment) and for patients with CR in Phase II treatment Arm II (receiving

decitabine monotherapy) the weekly visits on Day 8, 15 and 22 may be adjusted according to the patient's medical condition at the investigator's discretion. Weekly visits may be skipped, but it is recommended to continue with visits in bi-weekly intervals.

6.2.2.1 End of treatment visit (EOT)

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

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

- Safety laboratory parameters and urine analysis as specified in Section 5.3.6
- Physical examination including weight (may be completed up to 2 days prior) and ECOG performance score
- Vital signs at time points specified in Section 5.3.5
- Serum pregnancy test in women of childbearing potential
- 12-lead ECG
- Adverse events (AEs)
- Changes in concomitant therapies
- Number and type of transfusions, if applicable
- [redacted]
- Bone marrow aspirate and peripheral blood for disease assessment (only in patients who did not end treatment due to PD or relapse and who did not have a bone marrow aspirate within the past four weeks, or if PD is suspected but not cytologically confirmed)
- Documentation of End of 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

With the aim to minimize the burden for trial participants, after approval of Protocol version 7.0, the mandatory protocol procedures at EOT are reduced for all patients who continue to receive trial medication in treatment cycles >7. Instead, assessments should be performed at the investigator's discretion, based on standard medical care. Refer to updated Flow Chart for specific requirements during treatment period.

6.2.2.2 End of Residual Effect Period visit (EoR)

The REP is defined in Section 5.3.9. 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

With the aim to minimize the burden for trial participants, after approval of Protocol version 7.0, the mandatory protocol procedures at EoR visit are reduced for all patients who continue to receive trial medication in treatment cycles >7. Instead, assessments should be performed at the investigator's discretion, based on standard medical care. Refer to updated Flow Chart for specific requirements during treatment period.

6.2.3 Follow-up Period and Trial Completion

6.2.3.1 Extended follow-up period

6.2.3.1.1 Follow-up of Phase I Patients

Patients in the Phase I part will be followed-up for approximately 6 months after the EOT visit, irrespective whether a patient progressed on treatment or not. The first follow-up visit will be performed approximately 3 months and the second follow-up visit approximately 6 months after the EOT visit. Completion of the second follow-up visit will define the individual patient's end of trial participation (also refer to Section 6.2.3.2).

The following information will be collected during the follow-up visits and documented in the eCRF:

- Date and type of contact
- Vital Status: Collect information on progression or relapse, death, lost to follow-up
- Follow-up of adverse events in case they were not yet recovered at EoR visit
- In case the patient receives further anti-cancer treatment: regimen, drug name and start and stop dates

After approval of Protocol version 7.0, no further follow-up visits will be carried out. The last visits of an individual patient after withdrawal from trial treatment will be the EoR visit.

6.2.3.1.2 Follow-up of Phase II Patients

Patients in the Phase II part will be followed-up for overall survival at 3 monthly intervals until death, lost to follow-up or completion of the whole trial (as specified in Section 6.2.3.3)

whatever occurs earlier. For all patients, irrespective whether a patient progressed on treatment or not, the follow-up period for overall survival starts 3 months after the EOT visit.

These visits may also be performed by e.g. telephone interview or via written correspondence in case the patient is unable to visit the Investigator.

The following information will be collected during the follow-up for survival period and documented in the eCRF:

- Date and type of contact
- Vital Status : Collect information on progression or relapse, death, lost to follow-up
- Follow-up of adverse events in case they were not yet recovered at EoR visit
- In case the patient receives further anti-cancer treatment: regimen, drug name and start and stop dates

6.2.3.2 Trial completion for an individual patient

A patient is considered to have completed the trial in case any of the following applies:

- Completion of planned follow-up period including extended follow up (for patients in the Phase I part approximately 6 months after EOT; patients in the Phase II part will be followed-up for vital status until death)
- Lost to follow-up
- Refusal to be followed-up
- Death
- Decision of the Sponsor to end the trial (refer to Section 6.2.3.3)

6.2.3.3 End of the whole trial

The end of the trial will be defined as when both of the following have occurred:

1) All **entered and treated** patients have discontinued trial drug.
2) The last patient has completed the EoR visit.

In the case that the trial is ended by the Sponsor when patients are still being treated and 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

7.1.1 Phase I Dose Escalation

The primary objective of the Phase I Dose Escalation part is to determine the MTD of BI 836858 in combination with an intensive 10 day treatment schedule of decitabine. To determine the MTD, patients are entered sequentially into escalating dose cohorts. The dose-finding will be guided by a Bayesian 5-parameter logistic regression model with overdose control [R13-4806], [R13-4803], [R15-4233].

In the following, DLT denotes a dose-limiting toxicity occurring during the first treatment cycle.

The 5-parameter logistic regression model is defined as follows. Let $\pi_{1,d1}$ be the probability of having a DLT when giving dose d_1 of BI 836858, and $\pi_{2,d2}$ the probability of having a DLT when giving dose d_2 of decitabine, respectively. A logistic regression is used to model the dose-toxicity relationship for each of these drugs individually:

BI 836858: $\mathbf{logit(\pi_{1,d1}) = log(\alpha_1) + \beta_1 log(d_1/d_1^*)}$

Decitabine: $\mathbf{logit(\pi_{2,d2}) = log(\alpha_2) + \beta_2 log(d_2/d_2^*)}$

Here, the doses $d_1^* = 160$ mg and $d_2^* = 20$ mg/m² represent the reference doses for BI 836858 and decitabine, respectively.

Under independence, the probability of a DLT when giving the combination dose d_1, d_2 is obtained as

$$\pi^0_{12,d1,d2} = \pi_{1,d1} + \pi_{2,d2} - \pi_{1,d1}\pi_{2,d2}$$

with corresponding odds

$$odds(\pi^0_{12,d1,d2}) = \pi^0_{12,d1,d2} / (1 - \pi^0_{12,d1,d2}).$$

In order to account for a potential positive (higher toxicity than expected under independence) or negative (lower toxicity than expected under independence) interaction between BI 836858 and decitabine, a dose-dependent interaction term $-\infty<\eta<\infty$ is introduced in the model:

$$odds(\pi_{12,d1,d2}) = odds(\pi^0_{12,d1,d2}) \exp(\eta\, d_1/d_1^*\, d_2/d_2^*)$$

and $\pi_{12,d1,d2}$ is used in the likelihood

$$r_{d1,d2} \sim Binomial(n_{d1,d2}, \pi_{12,d1,d2})$$

where $r_{d1,d2}$ denotes the number of DLTs observed in $n_{d1,d2}$ patients at dose combination d_1, d_2.

Since a Bayesian approach is applied, prior distributions *f* for each of the parameter vectors $\theta_1=(\log(\alpha_1),\log(\beta_1))$, $\theta_2=(\log(\alpha_2),\log(\beta_2))$ and for the interaction term η need to be specified.

The prior distributions for θ_k (k=1,2) will be specified as a mixture of two bivariate normal distributions,

$f(\theta_k) = a_{1,k}\, f_1(\theta_k) + a_{2,k}\, f_2(\theta_k)$

with $a_{1,k}, a_{2,k}$ the prior mixture weights ($a_{1,k} + a_{2,k} = 1$) and

$f_i(\theta_k) = MVN(\mu_{ik}, \sum_{ik})$ (i=1,2) a bivariate normal distribution with mean vector μ_{ik} and covariance matrix $\sum_{ik}$ where

$$\Sigma_{ik} = \begin{pmatrix} \sigma^2_{ik,11} & \sigma_{ik,11}\sigma_{ik,22}\rho_{ik} \\ \sigma_{ik,11}\sigma_{ik,22}\rho_{ik} & \sigma^2_{ik,22} \end{pmatrix}$$

Mixture prior distributions have the advantage that they allow for specification of different logistic dose-toxicity curves, therefore making the prior more robust.

A weakly-informative normal prior distribution will be used for η.

The estimated probability of DLT at each dose level from the model will be summarized using the following intervals:
Under dosing: [0.00, 0.16)
Targeted dosing: [0.16, 0.33)
Over dosing: [0.33, 1.00]

The BLRM-recommended dose for the next cohort is the level at which the probability for the target dosing interval is maximal out of the dose candidates satisfying the overdose control criterion: P(over dosing) < 25%.

However, the maximum allowable dose increment for the subsequent cohort will be no more than 100% of previous dose levels.

The MTD may be considered reached if the following criteria are fulfilled:

1. The posterior probability of the true DLT rate in the target interval [0.16, 0.33) of the MTD is above 0.50, OR
2. At least 15 patients have been treated in the study, of which at least 6 were treated at the MTD.

The SMC may recommend stopping the dose finding phase after the criterion for MTD is fulfilled. Further patients may be included to confirm the MTD. If no DLT is observed at a dose of which the efficacy is considered sufficient, the SMC may decide to include additional patients at this dose level and to declare this dose as the RExP1D.

Prior derivation

To determine the prior distributions for $(\log(\alpha_1), \log(\beta_1))$ and $(\log(\alpha_2), \log(\beta_2))$, a meta-analytic predictive (MAP) approach will be used. For BI 836858 toxicity information from the ongoing 1315.1 Phase I study will be used. For decitabine toxicity information from three

published studies will be incorporated. The historical data used for BI 836858 and decitabine can be found in Table 7.1.1: 1 and Table 7.1.1: 2 respectively.

Table 7.1.1: 1 Historical data for BI 836858

Study	Dose [mg]	N of patients with DLT during Cycle 1 / N of patients
1315.1[(1)]		
	10	0/3
	20	0/3

(1) Using data after the clinical hold. Trial 1315.1 is still ongoing.

Table 7.1.1: 2 Historical data for decitabine

Study	Dose	N of patients with DLT during Cycle 1 / N of patients
Issa et al 2004 [R11-1101][(1)]		
	n.a. [(1)]	7/50
Blum et al 2007 [R15-4796][(2)]		
	n.a. [(2)]	3/25
Blum et al 2010 [R12-3308][(3)]		
	20 mg/m^2 (10 day schedule)	7/53

(1) Phase I study of low-dose prolonged exposure schedules of decitabine in hematopoietic malignancies: No DLTs were reported for this study. The number of DLTs was therefore approximated by the number of non-haematological AEs of CTCAE grade 3 and 4 that would also constitute a DLT in the present trial; data from all investigated decitabine doses and dosing schedules was used: 5x10, 10x10, 15x10, 20x10, 15x15, 15x20, 15x10 [mg/m² x days]

(2) Phase I study of decitabine alone or in combination with valproic acid in AML: No DLTs were reported for this study. The number of DLTs was therefore approximated using the number of non-haematological AEs (possibly attributable to decitabine or valproic acid) of CTCAE grade ≥3 overall cycles that would also constitute a DLT in the present trial. Furthermore, the reported average number of treatment cycles was used to approximate the number of DLTs during the first treatment cycle. Data from all investigated decitabine doses was used: 15 mg/m² x 10 days; 20 mg/m² x 10 days

(3) No DLTs were reported for this study. The number of DLTs was therefore approximated using the number of non-haematological AEs of CTCAE grade ≥3 experienced during the first two cycles of treatment that would also constitute a DLT in the present trial.

The following steps were used to derive the prior distributions for all parameters:

1. $\log(\alpha_1)$, $\log(\beta_1)$:
    a. The meta-analytic-predictive prior was derived using the information in Table 7.1.1: 1, allowing for moderate between-trial heterogeneity. This mixture component was assigned 90% mixture weight.
    b. A second, weakly-informative component was added with 10% mixture weight.
2. $\log(\alpha_2)$, $\log(\beta_2)$:
    a. The meta-analytic-predictive prior was derived using the information in Table 7.1.1: 2, allowing for substantial between-trial heterogeneity. This mixture component was assigned 90% mixture weight.
    b. A second, weakly-informative component was added with 10% mixture weight.
3. η: based on the a priori assumption of no interaction between the two compounds (but with considerable uncertainty for interaction), a normal distribution with mean 0 and standard deviation 0.993 was chosen.

    A standard deviation of 0.993 allows for a 7-fold increase/decrease in the odds($\pi_{12,\ d1*,\ d2*}$) of a DLT at the dose combination d_1*, d_2*compared to the odds($\pi^0_{12,\ d1*,\ d2*}$) of a DLT at (d_1*, d_2*) with no interaction between the two compounds. For example, if the true DLT rate under no interaction, i.e. $\pi^0_{12,\ d1*,\ d2}$, was 0.2 (odds = 1/4), the upper 97.5% quantile for the DLT rate (allowing for interaction) would be 0.63636 (odds=7/4). This corresponds to considerable uncertainty for interaction.

The prior distributions are given in Table 7.1.1: 3. The corresponding prior probabilities of a DLT at different doses and the corresponding probability of under-dosing, targeted dosing and overdosing are shown in Table 7.1.1: 4. As can be seen from Table 7.1.1: 4, the combination of 20 mg BI 836858 with 20 mg/m² decitabine has a prior probability of overdosing < 25%. It fulfils the overdose criterion and is therefore a suitable starting dose combination.

Table 7.1.1: 3 Summary of prior distributions

	Prior Component	**Mixture Weight**	**Mean**	**SD**	**Correlation**
BI 836858	MAP	0.9	(-1.395, 0.337)	(1.826, 0.959)	0.306
	Weakly inf.	0.1	(-1.395, 0.337)	(2.000, 1.000)	0.000
Decitabine	MAP	0.9	(-1.883, -0.0004)	(0.633, 1.042)	-0.003
	Weakly inf.	0.1	(-1.883, -0.0004)	(2.000, 1.000)	0.000
η	n.a.	n.a.	0	0.993	n.a.

Table 7.1.1: 4 Prior probabilities of DLT at selected doses

Dose BI 836858 [mg]	Dose decitabine [mg/m²]	Probability of true DLT rate in					Quantiles		
		[0, 0.16)	[0.16, 0.33)	[0.33, 1]	Mean	SD	2.5%	50%	97.5%
20*	20	0.483	0.384	0.133	0.202	0.146	0.040	0.164	0.640
40*	20	0.420	0.394	0.186	0.228	0.165	0.042	0.183	0.714
80	20	0.335	0.353	0.312	0.283	0.202	0.043	0.226	0.820
160	20	0.230	0.232	0.537	0.413	0.277	0.034	0.364	0.954
320	20	0.209	0.126	0.665	0.564	0.355	0.011	0.618	>.999

*** Doses with asterisk meet the overdose criterion (P(over-dosing) < 0.25)).**

The prior distribution may be updated once the trial has started if new relevant data become available. The prior distribution that is used in the BLRM for the purpose of the SMC's determination of the next dose level will be documented in the SMC meeting minutes. Details on the prior distribution for the final analysis will be given in the trial statistical analysis plan (TSAP).

Statistical model assessment

The model was assessed using two different metrics:

1. Hypothetical data scenarios: for various potential data constellations as they could occur in the actual trial, the maximal next doses as allowed by the model and by the 100% escalation limit are investigated. Data scenarios thus provide a way to assess the "on-study" behaviour of the model.

2. Simulated operating characteristics: these illustrate for different assumed true dose-toxicity relationships, how often a correct dose would be declared as MTD by the model. They are a way to assess the "long-run" behaviour of the model.

In summary, the model showed very good behaviour as assessed by these metrics. More details can be found in Section 10.2.

7.1.2 Phase I Extension

In the Phase I Extension part of the trial, a minimum of two times 15 patients will receive treatment with BI 836858 at MTD (or RExP1D if applicable) in combination with either decitabine intensive treatment schedule or decitabine standard treatment schedule.

Based on the overall Phase I data, the SMC will make a final determination of the RP2D. The BLRM will be re-run to confirm that the RP2D satisfies the overdose control criterion.

After completion of recruitment to Phase I Extension Cohort A and Cohort B, the recruitment to this trial is discontinued.

7.1.3 Phase II efficacy comparison

In the phase II part the efficacy of the two arms (BI 836858 in combination with decitabine *vs* decitabine monotherapy) will be compared in an exploratory manner.

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

During the Phase I Dose Escalation part, cohorts of patients treated with BI 836858 in combination with decitabine will be evaluated continuously based on the totality of the safety data available in order to determine the MTD (or RExP1D if applicable).

After determination of the RP2D in the Phase I Extension part and optional additional Dose Escalation cohort(s), a safety analysis report or lean interim CTR will be written to justify the RP2D prior to the initiation of Phase II.

The primary analysis of all primary, secondary and further efficacy endpoints will be conducted at the end of the whole trial (Section 6.2.3.3).

Efficacy analysis in Phase II will be based on the randomised set. This patient set includes all randomised patients, regardless of whether or not they have received treatment. For Phase I, efficacy endpoints will be summarized descriptively based on the treated set. No comparison will be done between cohorts.

The treated set includes all patients who have received at least one dose of study medication (BI 836858 and/or decitabine).

Safety analysis will be based on the treated set and will be summarized separately for patients treated in the Phase I and Phase II part of the trial.

7.3.1 Primary endpoint analyses

Phase I:
In order to estimate the MTD, the occurrence of a DLT in the first treatment cycle will be assessed on an individual patient level. However, for those patients who receive more than one cycle of the combination treatment, all AEs that constitute a DLT will be considered for re-estimation of the MTD based on the BLRM. To obtain this, the model will be re-run including the DLT information from all cycles. Based on both MTD estimates, the recommended dose for the extension cohort (and the Phase II part) will be determined. The MTD will be determined using the BLRM as described in Section 7.1.1. The number of DLTs at each dose level will be presented (all cycles and first cycle separately).

Phase II:
Objective response (CR+CRi) will be analyzed descriptively in terms of objective response rate (ORR), defined as the proportion of patients with complete response (CR) or complete response with incomplete blood count recovery (CRi).

7.3.2 Secondary endpoint analyses

Phase I: The secondary endpoint Objective response (CR+CRi) will be listed only. If considered useful, aggregated tables will be provided where different doses might be grouped.

Phase II: Event-free survival (EFS), relapse-free survival (RFS), remission duration and time to remission will be analyzed descriptively using Kaplan-Meier curves and Cox proportional hazard models. Details of censoring rules will be provided in the trial statistical analysis plan (TSAP).

7.3.4 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 period of 30 days after the last dose of trial medication. Adverse events that start before first drug intake and deteriorate under treatment will also be considered as 'treatment-emergent'.

Adverse events will be graded according to CTCAE Version 4.03 and reported according to BI standards.

Serious adverse events, drug-related adverse events and adverse events of special interest will be tabulated. In addition, events leading to dose reduction or treatment discontinuation will be examined.

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).

Descriptive statistics will be used to describe changes in laboratory tests over time. In addition, all abnormalities of potential clinical significance will be reported. In general, potential clinical significance is defined as at least CTCAE grade 2 and an increase from baseline value by at least one CTCAE grade.

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.

7.4 INTERIM ANALYSES

In Phase I, interim safety evaluations will be performed as considered necessary. In particular safety evaluations will be performed after each dose cohort by the SMC consisting of the Investigators and representatives of the Sponsor (refer to Section 3.1.1). Based on this, the SMC will recommend the next dose level as well as the corresponding cohort size. SMC meeting minutes and outputs provided for these SMC meetings will be documented and archived in the clinical trial master file (TMF). In addition, after determination of the RP2D in the Phase I Extension part of this trial and optional additional Dose Escalation cohort(s), a safety analysis report or lean interim CTR will be written to justify the RP2D.

During the Phase II part of the trial regular monitoring by the internal DMC will be performed to ensure a positive benefit-risk assessment. See Section 3.1.1.

The BI study team will be blinded for the aggregated phase II part data at the treatment level until the trial database lock. See Section 4.1.5.1.

7.5 HANDLING OF MISSING DATA

No imputation will be performed on missing efficacy data.

Missing baseline laboratory values will be imputed by the respective values from the screening visit. No other imputations will be performed on missing data although every effort will be made to obtain complete information on all adverse events and to follow-up the patients for efficacy data.

For partial or missing AE onset and/or end dates, BI internal rules will be applied for imputation.

[redacted]

7.6 RANDOMIZATION

Randomization will be performed in the Phase II part of this trial only. In the Phase I Dose Escalation part of the trial, doses will be assigned based on the decision made by the SMC.

In the Phase I Extension part, first approximately 15 patients will be allocated into to the Cohort A with treatment of BI 836858 in combination with decitabine intensive treatment and then subsequently a further set of approximately 15 patients into Cohort B with treatment of BI 836858 in combination with decitabine standard treatment.

In Phase II, patients will be randomized in a 1:1 ratio to treatment of either BI 836858 in combination with decitabine or decitabine monotherapy. As the type of AML is an important prognostic factor [R07-2768], randomization will be stratified by type of leukemia (*de novo vs* secondary AML). Within each stratum, a central randomization will be performed across all study centres. The method of permuted blocks will be used for the randomization.

An Interactive Response Technology (IRT) will be used to perform the randomization centrally. BI will arrange for the randomization. A randomization list will be generated using a validated pseudo-random number generator, yielding reproducible and non-predictable results. Access to the randomization codes will be controlled and documented.

7.7 DETERMINATION OF SAMPLE SIZE

Phase I:
A maximum of 50 patients are expected for the Phase I part of this trial (including Phase I Dose Escalation and Phase I Extension). Fewer patients might be needed based on the recommendation of the SMC and the criteria specified (see Section 7.1).

Phase II:
For the sample size estimation in Phase II we assume an objective response rate in the BI 836858 + decitabine arm of 70% compared to an objective response rate in the decitabine monotherapy arm of 40%. Based on these assumptions and a sample size of 2x50=100 patients overall the probability of observing an unadjusted difference in objective response rates of more than 20% is approximately 83%.

On the other hand, if the true objective response rates are assumed to be 40% both in the BI 836858 + decitabine arm and the decitabine monotherapy arm, the probability for observing a difference in objective response rate between the two arms of more than 20% is smaller than 2%.

Different scenarios and resulting probabilities for observing a difference in objective response rates of more than 20% are given in Table 7.7: 1.

In summary, a sample size of 2x50=100 patients is considered to be sufficient to clearly differentiate between the two treatment arms in case that a pronounced treatment benefit of BI 836858 + decitabine exists. On the other hand, if there is no or only a small benefit for BI 836858 + decitabine compared to decitabine monotherapy, the sample size is large enough

such that the probability for falsely observing a beneficial outcome for the combination arm is sufficiently small.

Table 7.7: 1 Evaluation of the probabilities of observing a treatment difference objective response rate depending on assumed response rate and sample size.

Assumed true objective response rate decitabine monotherapy	Assumed true objective response rate BI 836858 + decitabine	Sample size (randomization ratio)	Probability observing difference in Objective response rate bigger than 20%
40%	65%	100 (1:1)	0.67
40%	**70%**	**100 (1:1)**	**0.83**
40%	75%	100 (1:1)	0.94
40%	**40%**	**100 (1:1)**	**0.02**
40%	65%	80 (1:1)	0.64
40%	70%	80 (1:1)	0.79
40%	75%	80 (1:1)	0.91
40%	40%	80 (1:1)	0.03
40%	65%	120 (1:1)	0.68
40%	70%	120 (1:1)	0.85
40%	75%	120 (1:1)	0.95
40%	40%	120 (1:1)	0.01

Probabilities based on simulations (n= 1000000 iterations) using R 2.14.2.

8. INFORMED CONSENT, DATA PROTECTION, TRIAL RECORDS

The trial will be carried out in compliance with the protocol, the ethical principles laid down in the Declaration of Helsinki, in accordance with the ICH Harmonized Tripartite Guideline for Good Clinical Practice (GCP), relevant BI Standard Operating Procedures (SOPs), and relevant regulations.

Standard medical care (prophylactic, diagnostic and therapeutic procedures) remains in the responsibility of the treating physician of the patient.

The Investigator will inform the Sponsor immediately of any urgent safety measures taken to protect the trial patients against any immediate hazard, and also of any serious breaches of the protocol or of 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.

Insurance Cover: The terms and conditions of the insurance cover will be made available to the Investigator and the patients, and stored in the ISF (Investigator Site File).

8.1 TRIAL 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.

This trial will require genetic testing of samples from all participating patients, i.e. there is no option for patients to participate in this trial without agreement to have samples taken for biomarkers and pharmacogenetic testing. However, patients will have the option to agree or reject to have DNA samples stored for future testing (DNA-biobanking, refer to Section 5.5.2).

8.2 DATA QUALITY ASSURANCE

A quality assurance audit/inspection of this trial may be conducted by the Sponsor, Sponsor's designees, or by IRB / IEC 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 (eCRF) for individual patients will be provided by the Sponsor. 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 reported in the eCRF must be consistent with the source data or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the trial; current medical records must also be available.

For eCRFs all data must be derived from source documents.

- Patient identification (gender, year of birth)
- Patient participation in the trial (substance, trial number, patient number, date patient was informed and date when consent was obtained)
- Dates of Patient's visits, including dispensing of trial medication
- Medical history (including trial indication and concomitant diseases, if applicable)
- Medication history
- Adverse events and outcome events (onset date (mandatory), and end date (if available))
- Serious adverse events (onset date (mandatory), and end date (if available))
- Concomitant therapy (start date, changes)
- Originals or copies of laboratory results (in validated electronic format, if available)
- Bone marrow assessments
- Completion of Patient's Participation in the trial
- Prior to allocation of a patient to a treatment into a clinical trial, there must be documented evidence in the source data (e.g. medical records) that the trial participant meets all inclusion criteria and does not meet any exclusion criteria. The absence of records (either medical records or testing conducted specific for a protocol) to support inclusion/exclusion criteria does not make the patient eligible for the clinical trial.

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. eCRF and all source documents, including progress notes and copies of laboratory and medical test results must be available at all times for review by the Sponsor's clinical trial monitor, auditor and inspection by health authorities (e.g. FDA). The Clinical Research

Associate (CRA) / on site monitor and auditor may review all eCRF, 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 adverse reaction 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 Investigator's Brochure (c02324887-03).
For decitabine this is the EU SPC (R15-4802), or another regulatory label document.

The current versions of these reference documents are provided in the ISF. No AEs are classified as listed for matching placebo, trial design, or invasive procedures.

8.4.2 Expedited reporting to health authorities and IEC / IRB

Expedited reporting of serious adverse events, e.g. suspected unexpected serious adverse reactions (SUSAR) to health authorities and IEC / IRB, will be done according to local regulatory requirements.

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 IRB / IEC and the regulatory authorities.

8.6 TRIAL MILESTONES

The **start of the trial** is defined as the initiation of the first site.
The "Last Patient Out" date, defined as the last patient in the whole trial completing the last visit, defines **end of the trial** (i.e. the end of the whole trial). The "**Last Patient Drug Discontinuation**" (LPDD) date is defined as the date on which the last patient at an individual trial site ends trial treatment (as scheduled per protocol or prematurely). Individual Investigators will be notified of suspected unexpected serious adverse reactions (SUSARs) occurring with the trial medication until 30 days after LPDD at their site. **Early termination of the trial** is defined as the premature termination of the trial due to any reason before the end of the trials as specified in this protocol.
Temporary halt of the trial is defined as any unplanned interruption of the trial by the Sponsor with the intention to resume it.

Suspension of the trial is defined as an interruption of the trial based on a Health Authority request.

The IEC / competent authority in each participating EU member state will be notified about the trial milestones according to the respective laws.
A final report of the clinical trial data will be written only after all patients have completed the trial in all countries (EU or non-EU) to incorporate and consider all data in the report.
The Sponsor will submit to the EU database a summary of the final trial results within one year from the end of a clinical trial as a whole, regardless of the country of the last patient (EU or non-EU).
When the trial is completed, the Investigator should inform the head of the trial site of the completion in writing, and the head of the trial site should promptly inform the IRB and Sponsor of the completion in writing.

8.7 PROTOCOL VIOLATIONS

The Investigator should document any deviation from the protocol regardless of their reasons. Only when the protocol was not followed in order to avoid an immediate hazard to trial patients or for other medically compelling reason, the Principal Investigator should prepare and submit the records explaining the reasons thereof to the Sponsor, and retain a copy of the records.

8.8 COMPENSATION AVAILABLE TO THE PATIENT IN THE EVENT OF TRIAL RELATED INJURY

In the event of health injury associated with this trial, the Sponsor is responsible for compensation based on the contract signed by the trial site.

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10. APPENDICES

10.1 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

10.2 STATISTICAL APPENDIX INCLUDING MODEL PERFORMANCE AND DATA SCENARIOS

The model was assessed by two different metrics: hypothetical on-study scenarios and long-run operational characteristics.

Hypothetical data scenarios

Hypothetical data scenarios are shown in Table 10.2: 1. These scenarios reflect the potential on-study data constellations and related escalation as allowed by the model and the 100% escalation limit. For each scenario, the probability of overdose for the current dose, as well as the next potential dose and related probabilities of under-dosing, target dosing and over-dosing are shown.

For example, scenario 1.1 represents the case that no DLT is observed in 3 patients at the starting dose of 20 mg BI 836858 and 20 mg/m² decitabine. In this case, the next dose permitted by the model and by the 100% escalation rule is 40 mg of BI 836858 and 20 mg/m² decitabine. Similarly, scenario 1.2 represents the case that no DLT is observed in 3 patients at the alternative starting dose of 40 mg BI 836858 and 20 mg/m² decitabine (refer to Section

4.1.3). In this case, the next dose combination permitted by the model and by the 100% escalation rule is 80 mg of BI 836858 and 20 mg/m² decitabine.

Scenario 6 represents the case that no DLT is observed in the first cohort of 3 patients at 20 mg of BI 836858 and 20 mg/m² decitabine, and 2 DLTs are observed in the cohort of 3 patients at 40 mg of BI 836858 and 20 mg/m² decitabine. In this case, the model allows de-escalation to 20 mg of BI 836858 and 20 mg/m² decitabine.

Scenario 13 illustrates a case where no DLTs are observed in the first three cohorts, and then two DLTs occur in the fourth cohort of 3 patients at 160 mg of BI 836858 and 20 mg/m² decitabine. In this case the model allows de-escalation to 80 mg of BI 836858 and 20 mg/m² decitabine. Finally, scenario 14 represents a case where no DLTs are observed in the first four cohorts and then two DLTs occur in the cohort of 3 patients at the intermediate dose level of 240 mg of BI 836858 and 20 mg/m² decitabine. Despite the fact that no DLTs were seen in the previous four cohorts (12 patients in total), the model reacts immediately to the data observed at the combination of 240 mg BI 836858 plus 20 mg/m² decitabine and requires a de-escalation of BI 836858 to 160 mg. Scenarios 13 and 14 illustrate the adaptive behaviour of the model even in extreme situations.

Table 10.2: 1 Hypothetical data scenarios

Scenario	**Dose Combination BI [mg]/ DAC[mg/m²]**	**# DLT**	**# Pat**	**Current Dose Combination: P(OD)**	**Next possible Dose Combination BI [mg]/ DAC[mg/m²]**	**Next Dose Combination**		
						P(UD)	**P(TD)**	**P(OD)**
1.1	20/20	0	3	0.040	40/20	0.559	0.365	0.076
2.1	20/20	1	3	0.153	40/20	0.309	0.468	0.222
3.1	20/20	2	3	0.417	NA	NA	NA	NA
1.2	40/20	0	3	0.056	80/20	0.475	0.376	0.150
2.2	40/20	1	3	0.204	40/20	0.314	0.482	0.204
3.2	40/20	2	3	0.509	NA	NA	NA	NA
4	20/20 40/20	0 0	3 3	0.027	80/20	0.545	0.344	0.111
5	20/20 40/20	0 1	3 3	0.103	80/20	0.326	0.430	0.244
6	20/20 40/20	0 2	3 3	0.291	20/20	0.282	0.557	0.161
7	20/20 40/20 20/20	0 2 0	3 3 3	0.070	40/20	0.284	0.548	0.168
8	20/20 40/20 20/20	0 2 1	3 3 3	0.177	20/20	0.210	0.613	0.177
9	20/20 40/20	1 0	3 3	0.086	80/20	0.372	0.427	0.201
10	20/20 40/20	1 1	3 3	0.239	40/20	0.228	0.533	0.239
11	20/20 40/20	1 2	3 3	0.516	NA	NA	NA	NA

con't

Table 10.2: 1 Hypothetical data scenarios (con't)

Scenario	**Dose Combination BI [mg]/ DAC[mg/m²]**	**# DLT**	**# Pat**	**Current Dose Combination: P(OD)**	**Next possible Dose Combination BI [mg]/ DAC[mg/m²]**	**Next Dose Combination**		
						P(UD)	P(TD)	P(OD)
12	20/20 40/20 80/20 160/20	0 0 0 0	3 3 3 3	0.066	240/20	0.587	0.203	0.210
13	20/20 40/20 80/20 160/20	0 0 0 2	3 3 3 3	0.669	80/20	0.427	0.475	0.098
14	20/20 40/20 80/20 160/20 240/20	0 0 0 0 2	3 3 3 3 3	0.665	160/20	0.263	0.514	0.223

Operational characteristics

Operating characteristics are a way to assess the long-run behaviour of a model. Under an assumed true dose-toxicity curve, metrics such as the probability of recommending a dose with true DLT rate in the target interval can be approximated via simulations. Table 10.2: 2 describes 4 assumed true dose-toxicity scenarios which were used to assess the operating characteristics of the model. These scenarios reflect a wide range of possible cases as follows:

- Scenario 1: aligned with prior means
- Scenario 2: high-toxicity scenario
- Scenario 3: low-toxicity scenario
- Scenario 4: low-toxicity followed by high-toxicity

Table 10.2: 2 Assumed true dose-toxicity scenarios

Scenario		BI 836858 dose (mg)				
	P(DLT)	20	40	80	160	320
1 (Prior)		0.202	0.228	0.283	0.413	0.564
2 (High Tox)		0.250	0.270	0.340	0.400	0.600
3 (Low Tox)		0.060	0.100	0.120	0.180	0.250
4 (Low-High)		0.060	0.100	0.211	0.340	0.400

For each of these scenarios, 1000 trials were simulated. It was then assessed how often a dose was declared as MTD with true DLT rate in the under-, targeted or over-dosing range. Furthermore, the average, minimum and maximum number of patients per trial and the average number of DLTs per trial are reported. Results are shown in Table 10.2: 3.

Table 10.2: 3 Simulated operating characteristics

Scenario	% of trials declaring the MTD with true DLT rate in				# Patients	# DLTs
	Underdose	Target dose	Overdose	Stopped	Mean (Min-Max)	Mean (Min-Max)
1: Prior	0.0	79.8	1.3	18.9	12.40 (3 - 27)	2.96 (1 - 8)
2: HighTox	0.0	45.3	22.1	32.6	11.12 (3 - 30)	3.14 (1 - 8)
3: Low Tox	68.8	29.8	0.0	1.4	17.21 (3 - 36)	2.07 (1 - 7)
4: Low-High	24.6	68.5	5.5	1.4	15.42 (3 - 39)	2.44 (1 - 7)

In Scenarios 1 and 4, more than 60% of the simulated trials correctly declared the MTD as a dose with true DLT rate in the target interval [0.16, 0.33).

Namely, in scenario 1, which reflects the case that the true dose-toxicity is aligned with prior means, 79.8% of the simulated trials declared the MTD as a dose with true DLT rate in the target interval [0.16, 0.33). In scenario 4 (Low-high scenario), the percentage of simulated trials with correctly identified MTD was 68.5%.

In Scenario 2 (high-toxicity scenario), 45.3% of the simulated trials declared a dose as MTD which has its true DLT rate in the targeted toxicity range. However, since in this scenario 80 mg has a DLT probability of 0.34 which is relatively close to the upper bound of the target interval [0.16, 0.33), the BI 836858 dose of 80 mg was quite often determined as MTD, namely in 21.6% of the simulated trials. When considering this as MTD as well, the rate of simulated trials with correctly identified MTDs would add up to 66.9%. Furthermore, in scenario 2, the starting dose has already 0.25 probability of observing a DLT in the first cohort. This contributes to the high percentage (32.6%) of all simulated trials for which the trial is stopped since none of the doses is considered tolerable anymore. This is an expected situation for a high-toxicity scenario.

In scenario 3 (low-toxicity scenario) 29.8% of the simulated trials declared the MTD with true toxicity rate in the target interval and 68.8% declared a MTD with true DLT rate in the underdose interval. This is an expected situation for a low-toxicity scenario.

The mean patient numbers range from 11.12 (high-toxicity scenario) to 17.21 patients (low-toxicity scenario) and the maximum number of patients was 39. Therefore, the patient numbers are as expected and increase when moving away from the high-toxicity scenario.

In summary, the considered data scenarios show a reasonable behaviour of the model and the operating characteristics demonstrate a good precision of MTD determination.

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

Number of global amendment		1
Date of CTP revision		01 Mar 2016
EudraCT number		2015-002892-30
BI Trial number		1315.2
BI Investigational Product(s)		BI 836858
Title of protocol		An open-label, Phase I/II trial to determine the maximum tolerated dose and investigate safety, pharmacokinetics and efficacy of BI 836858 in combination with decitabine in patients with acute myeloid leukemia
To be implemented only after approval of the IRB / IEC / Competent Authorities	X	
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		Flow Chart (page 7)
Description of change		Two additional biochemistry time points have been added (Cycle 1: Day 9 and Day 16)
Rationale for change		Correction of typo (missing “x” in original protocol version)
Section to be changed		Flow Chart (page 10 and 11)
Description of change		All columns with details for “Cycle ≥ 7” deleted and corresponding items included in modified columns “Cycle ≥ 4”.
Rationale for change		Treatment with decitabine for 3 days per cycle is not a recommended dosing in the current Dacogen SmPC. Amended as proposed by the German Regulatory Authority
Section to be changed		Table 2 (page 15)
Description of change		Sample number “C2S9” added for time point Cycle

		2, Visit 3 Day 22.
Rationale for change		Correction to add missing sample number "C2S9".
Section to be changed		Table 2 (page 15)
Description of change		[redacted]
Rationale for change		
Section to be changed		1.2.1
Description of change		Added text: "infusion-related reaction"
Rationale for change		Abbreviated term IRR spelled out when first mentioned.
Section to be changed		Section 3.1
Description of change		Clause "i.e. at least 15 patients have been treated in the Phase I Dose Escalation part of the trial, of which at least 6 were treated at the MTD." was deleted.
Rationale for change		Redundant information removed as reference to the full MTD criteria was already made in that sentence.
Section to be changed		3.3.1
Description of change		Definition for refractory AML "defined as persisting AML after at least two induction cycles" was added in paragraph "Main diagnosis for trial entry".
Rationale for change		Definition added as recommended by the German Regulatory Authority, as many patients achieve CR after 2nd induction attempt.
Section to be changed		3.3.2
Description of change		Definition for refractory AML "defined as persisting AML after at least two induction cycles" was added in "Inclusion criterion #1".
Rationale for change		Definition added as recommended by the German Regulatory Authority, as many patients achieve CR after 2nd induction attempt.
Section to be changed		3.3.2
Description of change		The following two paragraphs were re-located within the inclusion criteria, i.e. cut form item #1 and pasted to the end of the list of inclusion

		criteria: "Please note that prior therapy for MDS is allowed for all patients participating in Phase I and Phase II of this trial. Prior treatment with hydroxyurea in order to reduce high WBC and treatment with hydroxyurea to control the WBC count during the first treatment cycle is allowed (refer to Section 4.2.2.1)."
Rationale for change		The two paragraphs were moved within the inclusion criteria for more clarity as they are applicable for patients in both phases of the trial.
Section to be changed		3.3.2. / 3.3.3.
Description of change		Inclusion criterion #1 and exclusion criterion #4, both dealing with prior treatment for MDS, were re-worded.
Rationale for change		Wording was modified to increase clarity as recommended by the German Regulatory Authority.
Section to be changed		3.3.3
Description of change		Exclusion criterion #16: "condom with spermicide" was deleted from list of examples.
Rationale for change		Example removed as requested by the German Regulatory Authority.
Section to be changed		3.3.3
Description of change		Exclusion criterion #18 was changed to include details about biologics. Added text: "for biologics 4 weeks or 5 half-lives, whichever is longer".
Rationale for change		Amended as proposed by the German Regulatory Authority.
Section to be changed		4.1.3.
Description of change		New text added: "If medically indicated, individual administrations of decitabine may be skipped. Any skipped dose must not be administered at a later time during that cycle. The decitabine treatment duration in the following cycle should occur as prescribed, provided the re-treatment criteria (see Section 4.1.4.2) are fulfilled."
Rationale for change		Added to allow more flexibility for Investigators to individually customize decitabine treatment if medically indicated.

Section to be changed		4.1.3.1 and 4.1.3.2
Description of change		Table 4.1.3.1: 1 and Table 4.1.3.2: 1 modified: separate description of decitabine dosing for "Cycle 7 and further, until 'progression or toxicity'" was deleted and is now included in section "Cycle 4 and further, until 'progression or toxicity'". Accordingly, the mandatory reduction of decitabine dosing to 3 consecutive days in Cycle 7 and further was deleted.
Rationale for change		Treatment with decitabine for 3 days per cycle is not a recommended dosing in the current Dacogen SmPC. Amended as proposed by the German Regulatory Authority.
Section to be changed		4.1.3.1 and 4.1.3.2
Description of change		New text added below Table 4.1.3.1: 1 and Table 4.1.3.2: 1: "In case the initially planned treatment duration (as assigned prior to Day 1 of any new cycle) is not considered to be safe by the Investigator (e.g. due to myelotoxicity in precedent cycle), Day 4 and/or Day 5 may be omitted in the current and all subsequent cycles."
Rationale for change		Added to allow more flexibility for Investigators to individually customize decitabine treatment in case of myelotoxicity or other adverse events in previous cycles.
Section to be changed		4.1.4
Description of change		Deleted text: The treatment schedule of decitabine will be also reduced to administration on 3 consecutive days of each cycle (i.e. Day 1 to Day 3 of each subsequent cycle).
Rationale for change		Treatment with decitabine for 3 days per cycle is not a recommended dosing in the current Dacogen SmPC. Amended as proposed by the German Regulatory Authority.
Section to be changed		4.1.4.2
Description of change		Several modifications in the paragraph detailing the "re-treatment criteria" (e.g. changes in cut-off for platelet counts; added text)
Rationale for change		Modified to increase alignment of trial-specific re-treatment criteria with the current Dacogen SmPC,

		as suggested by the German Regulatory Authority.
Section to be changed		5.1.2
Description of change		Definitions for Event-free survival (EFS) and Time to remission was reworded.
Rationale for change		Modified to remove definition inconsistencies with the corresponding reference in Section 5.1.3 (Further Endpoints).
Section to be changed		5.3.6.1
Description of change		C-reactive protein was added to biochemistry laboratory panel in section "General safety laboratory parameters".
Rationale for change		Amended as proposed by the German Regulatory Authority.
Section to be changed		5.4.2.1
Description of change		Deletion of the prefix "K_3" from "K_3EDTA" to "EDTA".
Rationale for change		Error in the original version of the CTP, K_3-tubes will no longer be used.
Section to be changed		5.4.2.1
Description of change		[redacted]
Rationale for change		
Section to be changed		7.1.1
Description of change		Table 7.1.1: 1: Correction of "Dose [mg]" for historical data for BI 836858.
Rationale for change		Error in original version of the CTP.
Section to be changed		7.1.1
Description of change		Text added: The prior distribution may be updated once the trial has started if new relevant data become available. The prior distribution that is used in the BLRM for the purpose of the SMC's determination of the next dose level will be documented in the SMC meeting minutes. Details on the prior distribution for the final analysis will be given in the trial statistical analysis plan (TSAP).
Rationale for change		Additional information given for more clarity on

		how newly available historical data may be used.
Section to be changed		7.1.2
Description of change		Text amended by adding details about the two types of combination treatment used in the Phase I Extension part.
Rationale for change		Additional information given for more clarity.
Section to be changed		7.3
Description of change		Definition of treated set amended to include "all patients who have received at least one dose of study medication (BI 836858 and/or decitabine)."
Rationale for change		Modified in order to have consistency in the use of the term "study medication" across all trial phases.
Section to be changed		7.5.1
Description of change		[redacted]
Rationale for change		
Section to be changed		7.5.2
Description of change		[redacted]
Rationale for change		

Number of global amendment		2
Date of CTP revision		09 June 2016
EudraCT number		2015-002892-30
BI Trial number		1315.2
BI Investigational Product(s)		BI 836858
Title of protocol		An open-label, Phase I/II trial to determine the maximum tolerated dose and investigate safety, pharmacokinetics and efficacy of BI 836858 in combination with decitabine in patients with 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	X	
Section to be changed		Flow Chart (pages 9 and 12, foot note # 12)
Description of change		The time point for bone marrow aspirate (and biopsy if indicated) to assess efficacy changed from “at end of cycle 3 and then every other cycle thereafter” to “at end of cycle 2 and then every other cycle thereafter”.
Rationale for change		Correction of typo. Disease assessment with bone marrow aspirate (and biopsy if indicated) is required at the end of cycle 2 rather than the end of Cycle 3 in order to allow a treatment decision at the end of Cycle 2. The overall number of BM assessments remains unchanged, only the timing is shifted within the treatment phase.
Section to be changed		6.2.2
Description of change		The time point for bone marrow aspirate (and biopsy if indicated) for local response assessment changed from “at end of cycle 3 and then every other cycle thereafter” to “at end of cycle **2** and then every other cycle thereafter”.

Rationale for change		Correction of typo. Disease assessment with bone marrow aspirate (and biopsy if indicated) is required at the end of cycle 2 rather than the end of Cycle 3 in order to allow a treatment decision at the end of Cycle 2. The overall number of BM assessments remains unchanged, only the timing is shifted within the treatment phase.

Number of global amendment		3
Date of CTP revision		16 Dec 2016
EudraCT number		2015-002892-30
BI Trial number		1315.2
BI Investigational Product(s)		BI 836858
Title of protocol		An open-label, Phase I/II trial to determine the maximum tolerated dose and investigate safety, pharmacokinetics and efficacy of BI 836858 in combination with decitabine in patients with acute myeloid leukemia
To be implemented only after approval of the IRB / IEC / Competent Authorities	X	
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		Flow Chart (pages 9 and 12, foot note # 7)
Description of change		The term “total bilirubin” was deleted from the list of “other lab test to be included” on Day 10.
Rationale for change		As total bilirubin is already included in the standard panel of biochemistry safety lab test, the term “total bilirubin” was deleted from the description of “other lab test to be included” on Day 10.
Section to be changed		Flow Chart (pages 8, 9 and 12, foot note # 11)
Description of change		On Day 16 the “X” indicating local “Disease assessment with peripheral blood and clinical assessment” was removed and the following sentence added to foot note 11: “In Cycle 1 at Day 16 (± 2 days) the BM aspirate is required for central lab assessment for biomarkers only, i.e. no mandatory local disease assessment on that day”.
Rationale for change		Text added for more clarity to indicate that on Day 16 the BM sample is not a “separate portion” of the BM sample collected for local disease assessment, but that the BM sample on that day is

		only for biomarker assessments at the central laboratory. Local disease assessment is not mandatory on Day 16 of Cycle 1.
Section to be changed		Flow Chart (pages 9 and 12, foot note # 12)
Description of change		The following sentence was added to foot note 12: "The BM sample collection at the end of Cycle 2 is not a mandatory trial procedure in patients with ≥ 5% blasts in peripheral blood."
Rationale for change		Explanatory text added to indicate that BM sample collection is a mandatory test at the end of Cycle 2 only in case there are no blasts or < 5% blasts in peripheral blood. This is to align with BM collection recommendations in tables 4.1.3.1: 1 and 4.1.3.2: 1.
Section to be changed		Table 1
Description of change		In column "Time in relation to dosing" the explanatory text describing the time points was re-worded for several time points for more clarity.
Rationale for change		Collection time points remain unchanged; only explanatory text added or modified for clarification.
Section to be changed		Table 2
Description of change		In column "Time in relation to dosing" the explanatory text describing the time points was re-worded for several time points for more clarity.
Rationale for change		Collection time points remain unchanged; only explanatory text added or modified for clarification.
Section to be changed		Table 3
Description of change		[redacted]
Rationale for change		
Section to be changed		Table 3
Description of change		Foot note e) added to the three "X" indicating that blood samples on C1D9 and C1D10 are to be taken only from patients receiving BI 836858 (i.e. not required for patients in Phase II who are

		randomized to treatment “Arm 2” with decitabine monotherapy).
Rationale for change		Patients in Phase II in treatment “Arm 2” with decitabine monotherapy don’t receive any infusions with BI 836858, so the blood collections on Day 9 and Day 10 are not required for those patients.
Section to be changed		Table 3
Description of change		Foot note f) added to the “X” indicating bone marrow aspiration for biomarker analysis at EOT.
Rationale for change		The bone marrow aspirate at EOT is mandatory only in patients who did not end treatment due to PD or relapse, and patients who did not have a BM aspirate within the past four weeks.
Section to be changed		3.1
Description of change		The minimum requirement for the number of administrations with BI 836858 was updated from “at least 2” to “at least 3” in the section describing the minimum requirements for patients in order to be evaluable within the dose escalation cohort.
Rationale for change		Patients should have received all 3 scheduled administrations of BI 836858 in Cycle 1 to be evaluable for DLT assessment.
Section to be changed		3.3
Description of change		The number of expected patients to be entered during the Phase I Dose Escalation part of the trial was amended from 4 to 2 patients per month.
Rationale for change		The recruitment rate was amended to reflect the expected enrolment rate, consideringe the mandated waiting period of at least 7 (or 3) days between the 1st administration of BI 836858 and initiation of treatment with decitabine to the next patient in treatment Cohort 1 (or Cohort 2 or higher).
Section to be changed		3.3.3.
Description of change		Exclusion criterion #10 was re-worded by adding “total” to the bilirubin.
Rationale for change		Re-worded for more clarity, as the original text also meant “total bilirubin”.
Section to be changed		3.3.3.
Description of change		Exclusion criterion #16 was amended and “bilateral

		tubal occlusion" was added to the list of examples for effective contraception, while the term "tubal occlusion" was removed from the list of examples for permanent sterilization.
Rationale for change		Amended to reflect the most recent version of the "CTFG (Clinical Trial Facilitation Group) recommendations on contraception and pregnancy testing in clinical trials" and corresponding BI "Guidance on Contraception in Clinical Trials"
Section to be changed		3.3.4.1
Description of change		The following sentence was added to the list of criteria that require removal of individual patients from trial treatment: "Start of subsequent treatment cycle needs to be delayed by longer than 8 weeks due to a drug-related event (e.g. delay in recovery of blood counts or awaiting resolution of toxicity; please refer to Section 4.1.4.2)."
Rationale for change		Text added for more clarity and to specify a time frame for the maximum permissible delay for the start of a subsequent treatment cycle in case of a drug-related event.
Section to be changed		3.3.4.1
Description of change		The minimum requirement for the number of administrations with BI 836858 was updated from "at least 2" to "at least 3" in the following two sentences: "Patients who have not completed at least 3 administrations of BI 836858 during cycle 1 due to BI 836858-related toxicity will not be replaced; this will be considered as a DLT. However, patients who have not completed at least 3 administrations (1 cycle) of BI 836858 for reasons other than BI 836858-related toxicity will be replaced."
Rationale for change		The minimum requirement for the number of administrations with BI 836858 was changed to at least 3, as this is the scheduled number of administrations of BI 836858 for Cycle 1.
Section to be changed		4.1.3.1 and foot note c) in Table 4.1.3.1: 2 (BI 836858 dose escalation scheme)
Description of change		Text and foot note c) added in the description of planned BI 835858 dose escalation scheme: "Dose levels above 40 mg will only be explored after safety data from monotherapy studies with

		BI 836858 have become available and if data from PK and pharmacodynamics analysis support further dose escalation."
Rationale for change		Explanatory text added to clarify that dose levels of BI 836858 above 40 mg will only be explored after specific criteria are fulfilled and if recommended by SMC.
Section to be changed		4.1.3.1
Description of change		The minimum requirement for the number of administrations with BI 836858 was updated from "at least 2" to "at least 3" in the following sentence: "However, in the case that only 2 patients are evaluable and neither has experienced a DLT within the Cycle 1 (i.e. patient has received at least 3 administrations of BI 836858 and reached end of Cycle 1; please refer to Section 5.3.2) then dose escalation can occur based on these 2 patients.
Rationale for change		The minimum requirement for the number of administrations with BI 836858 was changed to at least 3, as this is the scheduled number of administrations of BI 836858 for Cycle 1.
Section to be changed		4.1.4
Description of change		The following sentence was added in the paragraph describing how to proceed with the very 1st infusion of BI 836858 on the planned Day 9 of Cycle 1: "In case the platelet count prior to the 1st planned infusion with BI 836858 on Day 9 (or Day 10 at the latest) is not ≥ 25,000/µL, the patient must be transfused to at least 25,000 platelets/µL."
Rationale for change		The requirement that patients must have platelet counts ≥ 25.000/µL prior to infusion with BI 836858 was only written in Section 4.1.4.2 (Re-treatment criteria). As this general safety criterion applies to all infusions with BI 836858, that criterion must also be respected for the very 1st infusion of BI 836858 in Cycle 1.
Section to be changed		4.1.4.2
Description of change		At two instances the symbol " > " was replaced by " ≥ " when the meaning was "at least 25,000 platelets/µL" ("greater or equal to 25,000 platelets/µL")
Rationale for change		Correction of a typo.

Section to be changed		4.1.4.2
Description of change		The clause “for up to three weeks” was deleted from the sentence describing the need for weekly re-evaluation of blood counts and/or adverse events in case the applicable re-treatment criteria are not fulfilled.
Rationale for change		The maximum delay to start a subsequent cycle is changed to 8 weeks; accordingly, the weekly re-evaluation of blood counts and/or adverse events should continue beyond 3 weeks.
Section to be changed		4.1.4.2
Description of change		The following 3 sentences were added in section describing re-treatment criteria: “Subsequent cycles can be delayed up to 2 weeks to meet the above criteria. Longer delays should be discussed with the Coordinating Investigator. Patients with delays longer than 8 weeks due to a drug-related event (e.g. delay in recovery of blood counts or awaiting resolution of toxicity) will be withdrawn from study.”
Rationale for change		Text added to specify a time frame for maximum permissible delay for start of subsequent treatment cycle.
Section to be changed		4.1.4.2
Description of change		The term “same” was deleted and further information on specific re-treatment criteria was added in the following sentence: “Furthermore, the re-treatment criteria absence of fever (≥ 38.5°C) and/or uncontrolled infection and platelets ≥ 25,000/µL apply for the weekly administrations of BI 836858 after Day 1 of any given cycle,….”
Rationale for change		Explanatory text added to further specify what was meant by the term “same” within the context of re-treatment criteria.
Section to be changed		4.1.4.3
Description of change		Text changed from: “The period of delay is not limited in time.” to “The period of delay is limited to a maximum of 8 weeks”.
Rationale for change		Text amended to align with updated information in Section 4.1.4.2 about maximum permissible delay for start of subsequent treatment cycle.
Section to be changed		5.3.1

Description of change		The following sentence was added in DLT definition: "Patients who do not experience a DLT but do not receive all 3 planned administrations of BI 836858 during Cycle 1 for reasons other than toxicity or tolerability will not be evaluable for DLT and cannot be used to establish the MTD."
Rationale for change		Text added for more clarity to indicate that patients must have received all 3 infusions in Cycle 1 in order to be evaluable for DLT.
Section to be changed		5.3.6.1
Description of change		Description of when to collect samples for serum immunoglobulin levels (IgG, IgM, IgA) and direct antiglobulin changed from "only every 8 weeks (starting from Day 1 of Cycle 1)" to "only every other cycle (starting from Day 1 of Cycle 1)".
Rationale for change		Re-worded for more clarity and alignment of sample collection with the collection time points for other samples, which are defined within the treatment cycles and not strictly in weeks.
Section to be changed		5.3.6.1
Description of change		The term "total bilirubin" was deleted from the list of "other lab test to be included" on Day 10.
Rationale for change		As total bilirubin is already included in the standard panel of biochemistry safety lab test, the term "total bilirubin" was deleted from the description of "other lab test to be included" on Day 10.
Section to be changed		5.5
Description of change		The term "biopsy" was removed from the paragraph describing the time points for bone marrow sample collection for biomarker analysis.
Rationale for change		Only bone marrow aspirate samples will need to be collected and shipped to the central laboratory for biomarker assessments, but no bone marrow biopsies.
Section to be changed		5.5
Description of change		[redacted]
Rationale for change		[redacted]

Section to be changed		5.5.1
Description of change		The following text was added: "All biomarker samples, bone marrow and peripheral blood, are to be collected prior to administration of trial medication unless otherwise specified."
Rationale for change		Text added for more clarity on timing of biomarker sample collection in relation to dosing.
Section to be changed		6.2.1
Description of change		The bullet point describing safety laboratory assessments at screening was changed from • Safety laboratory (hematology, biochemistry including serum immunoglobulin levels and direct antiglobulin test, coagulation, urine; for details please refer to Section 5.3.6) to • Safety laboratory (hematology, biochemistry, coagulation, urine; for details please refer to Section 5.3.6)
Rationale for change		"Serum immunoglobulin levels and direct antiglobulin test" was removed from the list of laboratory tests at screening, as this was inconsistent with Section 5.3.6 of the protocol. Sample collection for "serum immunoglobulin levels and direct antiglobulin test" only starts on Day 1 of Cycle 1.
Section to be changed		6.2.2
Description of change		The term "WBC" was replaced by "the blast count" in the sentence "During Phase I and Phase II the decitabine treatment schedule for Cycles ≥ 2 will be individually customized depending on the blast count at the end of previous cycle."
Rationale for change		Correction of terminology.
Section to be changed		6.2.2
Description of change		Text describing the planned procedures on the bone marrow sample collected on Day 16 of Cycle 1 modified (deleted text: "and biopsies for local response assessment") to indicate that only biomarker assessments at central laboratory will be performed.
Rationale for change		Local response assessment is not mandatory at Day 16 of Cycle 1.

Section to be changed		6.2.2
Description of change		The following sentences were added: "The BM sample collection at the end of Cycle 2 is not a mandatory trial procedure in patients with ≥ 5% blasts in peripheral blood. From Cycle 2 onwards, BM samples can be taken up to 7 days before the scheduled visit 4 (EOC)".
Section to be changed		Explanatory text added to indicate that BM sample collection is a mandatory test at the end of Cycle 2 only in case there are no blasts or < 5% blasts in peripheral blood. This is to align with BM collection recommendations in tables 4.1.3.1: 1 and 4.1.3.2: 1.
Section to be changed		Table 7.1.1: 3 (Summary of prior distributions) and Table 7.1.1: 4 (Prior probabilities of DLT at selected doses)
Description of change		Prior distributions and probabilities have been updated.
Rationale for change		The BI reference dose in the program used to derive the prior has been incorrectly specified as 20 mg instead of 160 mg as written in the protocol. This has been corrected.
Section to be changed		9.1
Description of change		For references R15-3877 and R15-5032 (NCCN Guidelines) the link to the website was corrected by replacing "https://www" with term "website".
Rationale for change		Correction of website link for formal reasons.
Section to be changed		10.2 and Table 10.2: 1 (Hypothetical data scenarios) and Table 10.2: 2 (Assumed true dose-toxicity scenarios) and Table 10.2: 3 (Simulated operating characteristics)
Description of change		Hypothetical data scenarios and operational characteristics have been updated.
Rationale for change		The BI reference dose in the program used to derive the prior has been incorrectly specified as 20 mg instead of 160 mg as written in the protocol. This has been corrected.

Number of global amendment		4
Date of CTP revision		06 July 2017
EudraCT number		2015-002892-30
BI Trial number		1315.2
BI Investigational Product(s)		BI 836858
Title of protocol		An open-label, Phase I/II trial to determine the maximum tolerated dose and investigate safety, pharmacokinetics and efficacy of BI 836858 in combination with decitabine in patients with acute myeloid leukemia
To be implemented only after approval of the IRB / IEC / Competent Authorities	X	
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		[redacted]
Description of change		
Rationale for change		
Section to be changed		[redacted]
Description of change		
Rationale for change		

Section to be changed		[redacted]
Description of change		
Rationale for change		
Section to be changed		4.1.4.2
Description of change		Clarification text added to re-treatment criteria that for patients with active leukemia with grade 4 thrombocytopenia (platelets < 25,000/µL): patients may continue on trial treatment only when "there is no evidence of bleeding" and post-transfusion platelet count is at least 25,000/µL.
Rationale for change		Re-treatment criteria in Section 1) aligned with the corresponding text in Section 2) of this paragraph.
Section to be changed		5.3.9
Description of change		Corrected from BI 83658 to BI 836858.
Rationale for change		Correction of typo.
Section to be changed		[redacted]
Description of change		
Rationale for change		
Section to be changed		[redacted]
Description of change		

		[redacted]
Rationale for change		
Section to be changed		6.2.2
Description of change		[redacted]
Rationale for change		
Section to be changed		6.2.2
Description of change		Weekly visits (for collection of vital signs and safety labs) are no longer mandatory for patients with CR and • who have completed the first treatment cycle with maintenance therapy (monthly administration of BI 836858) • for patients in Phase II randomized into treatment Arm 2 with decitabine monotherapy
Rationale for change		More flexibility added to the visit schedule for patients in CR to reduce the burden of weekly visits from the patients (e.g. to accommodate planning of vacation).

Number of global amendment		5
Date of CTP revision		22 Jun 2018
EudraCT number		2015-002892-30
BI Trial number		1315.2
BI Investigational Product(s)		BI 836858
Title of protocol		An open-label, Phase I/II trial to determine the maximum tolerated dose and investigate safety, pharmacokinetics and efficacy of BI 836858 in combination with decitabine in patients with acute myeloid leukemia
To be implemented only after approval of the IRB / IEC / Competent Authorities	X	
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		Correction of address of Coordinating Investigator [redacted]
Rationale for change		[redacted] relocated to new clinic at [redacted]
Section to be changed		CTP Synopsis
Description of change		Correction of address of Coordinating Investigator [redacted]
Rationale for change		[redacted] relocated to new clinic at [redacted]
Section to be changed		CTP Synopsis
Description of change		Text added in **'Objectives'** section for Phase I Extension to display the option for additional patients to be enrolled in existing or additional dose escalation cohorts.
Rationale for change		[redacted]

		[redacted] It was therefore decided by the SMC and the Sponsor to include the option for further Dose Escalation cohorts to allow testing of higher doses of BI 836858 prior to starting the Phase II part of the trial.
Section to be changed		CTP Synopsis
Description of change		Text added in **'Methodology'** section for Phase I Extension: "If deemed necessary by the Sponsor and the SMC (Safety Monitoring Committee): Option to open further Phase I Dose Escalation cohort(s) to determine the RP2D, [redacted] and safety data with either the intensive or the standard decitabine schedule, as specified for each cohort separately prior to starting enrolment."
Rationale for change		[redacted] It was therefore decided by the SMC and the Sponsor to include the option for further Dose Escalation cohorts to allow testing of higher doses of BI 836858 prior to starting the Phase II part of the trial.
Section to be changed		CTP Synopsis
Description of change		Update in section **'No. of patients'** from approximately "150 patients" to now to "160-170 patients".
Rationale for change		Updated to reflect patients entered into the additional optional Phase I Dose Escalation cohort(s) to be recruited prior to starting the Phase II part of the trial.
Section to be changed		CTP Synopsis
Description of change		Text added in section **'total entered'**: "Phase I option for additional dose tiers: option to add further Dose Escalation cohort(s) with at least 3 patients each (based on SMC recommendation)"
Rationale for change		Updated to reflect patients entered into the additional optional Phase I Dose Escalation cohort(s) to be recruited prior to starting the Phase II part of the trial.

Section to be changed		CTP Synopsis
Description of change		Update in section **'each treatment'** for Phase I Dose Escalation and Extension from (approx. 50)" to now "(approx. 60-70)"
Rationale for change		Updated to reflect patients entered into the additional optional Phase I Dose Escalation cohort(s) to be recruited prior to starting the Phase II part of the trial.
Section to be changed		CTP Synopsis
Description of change		Update in section **'diagnosis'** to specify the patient population to be entered in potential additional dose tiers.
Rationale for change		Same patient population to be entered in potential additional dose tiers as for Phase I Extension and Phase II.
Section to be changed		CTP Synopsis
Description of change		Information about the test product dose updated to: The Recommended Phase II Dose (RP2D) is based on the MTD determined in Phase I. Text in brackets "(or RExP1D)"deleted.
Rationale for change		Updated to reflect patients entered into the additional optional Phase I Dose Escalation cohort(s) to be recruited prior to starting the Phase II part of the trial.
Section to be changed		Flow Chart
Description of change		Cycle 1 Visit 1 was updated with an additional column for newly added treatment Day 8 with individual "x" for visit-specific procedures (identical to Day 9 procedures).
Rationale for change		Day 8 added as a separate treatment day for application of the initial BI 836858 infusion as split dose (20 mg BI 836858 at the very first administration on Day 8).
Section to be changed		Flow Chart
Description of change		Foot note #6 was updated with the additional information on the Day 8 procedures and the timely relation to following days in visits.
Rationale for change		Day 8 added as a separate treatment day for application the initial BI 836858 infusion as split dose (20 mg BI 836858 at the very first administration on Day 8). Same flexibility (+ 1

		day) allowed as before, i.e. subsequent visits to be shifted accordingly.
Section to be changed		Flow Chart
Description of change		Foot note #6 was updated to reflect the additional lab sample collection for TLS monitoring and the specific requirements for collection time points. Reference to updated Table 1 added.
Rationale for change		Newly introduced TLS monitoring requires a stricter adherence to the collection time points.
Section to be changed		List of Abbreviations
Description of change		Added: TLS – Tumor Lysis Syndrome
Rationale for change		Abbreviation newly introduced as the term is referenced in several paragraphs in the amended CTP.
Section to be changed		Table 1
Description of change		One additional column added to indicate the time points for newly introduced TLS monitoring. One additional line added to indicate which parameters are for central laboratory assessment and which is for local lab assessment. Two new footnotes # and ## added with further information on use of local laboratory for TLS monitoring and how to avoid duplicate sampling.
Rationale for change		Additional TSL monitoring introduced to allow for early detection of signs for potential TLS. Footnotes updated/ added for more clarity.
Section to be changed		Table 1
Description of change		[redacted] additional rows added to indicate the sampling time points for [redacted] and TLS monitoring on newly introduced BI 836858 infusion Day 8. Footnote *** updated with information on Day 8 and subsequent treatment days.
Rationale for change		Day 8 added as a separate treatment day for administration of the initial BI 836858 infusion as split dose (20 mg BI 836858 at the very first administration on day 8). [redacted] TLS monitoring added to match with Day 9 lab sampling. Footnotes updated for more clarity.
Section to be changed		Table 3
Description of change		Two additional columns added for samples to be

		collected on the newly added treatment Day 8. Footnotes * and [e)] updated with information on Day 8 and subsequent treatment days.
Rationale for change		Day 8 added as a separate treatment day for administration of the initial BI 836858 infusion as split dose (20 mg BI 836858 at the very first administration on day 8). [redacted] Footnotes updated for more clarity.
Section to be changed		2.2
Description of change		Text updated in section **'Objectives'** to display the option for additional patients to be enrolled in existing or additional dose escalation cohorts: "… and to decide if the RExP1D will become the Recommended Phase II Dose (RP2D) of BI 836858 in combination with decitabine in patients ≥ 65 years of age, or if additional patients need to be enrolled in existing or additional dose escalation cohorts."
Rationale for change		Updated to reflect patients entered into the additional optional Phase I Dose Escalation cohort(s) to be recruited prior to starting the Phase II part of the trial.
Section to be changed		2.3
Description of change		Text added in section '**Benefit-Risk Assessment':** A case of tumor lysis syndrome (TLS) with fatal outcome was reported in trial 1315.2 in AML. The patient was diagnosed with AML with extramedullary disease (skin (confirmed), abdominal and mediastinal lymph nodes (suspected)) assigned to a dose of 80 mg BI 836858 in combination with decitabine, and classified as low risk for TLS based on LDH and WBC (R18-1901). The event triggered measures for this trial to ensure patients safety including a modification of the infusion schedule (see Section 4.1.3) to mitigate the risk for rapid onset of activity and additional mandatory laboratory monitoring for early detection of TLS (see Section 5.3.6 and Table 1).
Rationale for change		New safety information and associated safety measures added.

Section to be changed		3.1
Description of change		Several paragraphs updated and/or text added in section '**Overall Trial Design and Plan**' to reflect the changes associated with the option to enroll additional patients in existing or additional dose escalation cohorts for determination of the R2PD. Added text: "If deemed necessary by the Sponsor and the SMC, based on a comprehensive review of available clinical trial data, [redacted] additional patients may be enrolled after the extension cohorts into pre-existing or new dose escalation cohorts to further optimize the BI 836858 dose and determine the RP2D. Dose escalation steps for additional dose cohorts will be defined according to the rules as outlined for the phase I dose escalation part of this protocol. The decitabine schedule to be used for each cohort will be determined by the Sponsor in agreement with the SMC and documented in the SMC meeting minutes."
Rationale for change		[redacted] It was therefore decided by the SMC and the Sponsor to include the option for further Dose Escalation cohorts to allow testing of higher doses of BI 836858 prior to starting the Phase II part of the trial.
Section to be changed		Figure 3.1: 1
Description of change		The figure describing the '**Overall structure of the trial Phase I'** was updated to include "OPTIONAL further Dose Escalation: Open-label, dose escalation of BI 836858 weekly in combination with decitabine treatment in 28-day cycles" as the 3rd part in Phase I Extension.
Rationale for change		See above - same as for Section 3.1
Section to be changed		3.2
Description of change		Several paragraphs updated and/or text added in section '**Discussion of Trial Design, including the Choice of Control Group'** to reflect the changes associated with the option to enroll additional

		patients in existing or additional dose escalation cohorts. Text added: "If deemed necessary by the Sponsor and the SMC, based on a comprehensive review of available clinical trial data, [redacted] additional patients may be enrolled after the extension cohorts into pre-existing or new dose escalation cohorts to further optimize the BI 836858 dose and determine the RP2D."
Rationale for change		See above - same as for Section 3.1
Section to be changed		3.3.3
Description of change		Exclusion criterion 9 was updated by deleting "for patients not on therapeutic vitamin K antagonists (phenprocoumon, warfarin)" to now read: Prothrombin time > 1.5 x ULN
Rationale for change		Additional information not needed as Exclusion criterion "Prothrombin time > 1.5 x ULN" applies to all patients.
Section to be changed		3.3.4.1
Description of change		Last bullet point updated with new information regarding the newly introduced first treatment on Day 8 and subsequent treatment days.
Rationale for change		Item was updated to maintain the initial logic of allowing one day of delay in starting trial treatment with BI 836858.
Section to be changed		4.1.2
Description of change		Text added in section **'Method of assigning patients to treatment groups'**: "In case there will be further Dose Escalation cohort(s) in the Phase I Extension part of the trial, this will be consecutive cohorts of escalating doses of BI 836858 plus decitabine, using the BLRM with overdose control. The number of patients and the decitabine schedule to be used for each cohort will be determined by the Sponsor in agreement with the SMC."
Rationale for change		See above - same as for Section 3.1
Section to be changed		4.1.3
Description of change		New text added in section **'Selection of doses in the trial'**: "The very first dose of BI 836858 will be split

		across two consecutive days: a fixed dose of 20 mg will be administered on Day 8 (or Day 9 at the latest) and the rest of the full planned dose for that week will be administered the following day. For example a planned dose of 80 mg will be administered as 20 mg i.v. infusion on Day 8 and 60 mg i.v. infusion on Day 9 (or 20 mg i.v. infusion on Day 9 and 60 mg i.v. infusion on Day 10 at the latest).
Rationale for change		Due to a new safety finding (fatal case of TLS) it was decided to introduce an additional safety measure by splitting the very first dose of BI 836858 (Day 8 and Day 9, or Day 9 and Day 10 at the latest).
Section to be changed		Table 4.1.3.1: 2
Description of change		**Footnote [a)]** in Table 4.1.3.1: 2 was updated to reflect that the first administration of BI 836858 will take place on Day 8 instead of Day 9 (or on Day 9 at the latest). **Footnote [d)]** in Table 4.1.3.1: 2 was updated by adding the following text: "Additional Phase I Dose Escalation cohorts may also be opened if deemed necessary by the Sponsor and the SMC following the Phase I Extension cohorts of the trial."
Rationale for change		See above - same as for Sections 3.1(for footnote d) and 4.1.3 (for foot note a)
Section to be changed		4.1.3.1
Description of change		Text added in section describing '**Treatment in the Phase I Dose Escalation part of the trial**': "For the optional Dose Escalation Cohorts following Extension Cohorts A and B, a time interval of at least 3 days must have elapsed between the 1st administration of BI 836858 for each new patient treated. This means that start of trial treatment with decitabine (Cycle 1_Day 1) for the next subsequent patient may occur at the earliest on Cycle 1 Day 4 of the previous patient."
Rationale for change		In other trials with BI 836858 a higher dose of 160 mg has already been tested and was found to be safe. A time interval of at least 3 days between start of trial treatment in subsequent patients within one cohort is considered adequate in this setting.

Section to be changed		4.1.3.2
Description of change		Text added in section describing the treatment in the "**Phase I Extension**" part of the trial: "If deemed necessary by the Sponsor and the SMC, there will be an option to open further Dose Escalation cohort(s) following the extension cohorts to optimize or confirm the RP2D, based on additional biomarker, PK/PD and safety data. For further details on dose escalation procedures refer to **Section 4.1.3.1**."
Rationale for change		See above - same as for Section 3.1
Section to be changed		4.1.3.3
Description of change		The text in this section was updated to reflect that the first administration of BI 836858 will take place on Day 8 instead of Day 9 (or on Day 9 at the latest).
Rationale for change		See above - same as for Section 4.1.3
Section to be changed		4.1.4
Description of change		The text in this section was updated to reflect that the first administration of BI 836858 will take place on Day 8 instead of Day 9 (or on Day 9 at the latest).
Rationale for change		See above - same as for Section 4.1.3
Section to be changed		4.1.4.1
Description of change		Text describing the premedication was updated to reduce the obligatory premedication from the first four to only the first two administration of BI 836858. During subsequent administrations allow for flexibility of glucocorticoid dose depending on occurrence of IRR grade 2 or higher.
Rationale for change		Treatment with glucocorticoids may interfere with activity of effector-cells; in patients without IRRs during the first infusion (Day 8+9) mandatory premedication with glucocorticoid should be reduced to 50 mg for the 2nd infusion (Day 16), and in case of good tolerability even be omitted in subsequent infusions. As this option is limited to patients with IRRs grade 1 or without IRRs, this approach is considered to offer the best possible activity to patients with the lowest risk for severe IRRs based on previous tolerability.
Section to be changed		4.2.1

Description of change		Additional information entered as a new paragraph "Prevention and treatment of Tumor Lysis Syndrome (TLS): Risk for TLS should be assessed as per published guidelines prior to starting treatment with BI836858 (R18-1901). All patients should receive adequate hydration prior to start of each administration of BI 836858 in Cycle 1. Prophylactic administration of anti-hyperuricaemic agents (e.g. allopurinol, rasburicase) should be considered according to individual patient risk. Laboratory monitoring for TLS is mandatory as outlined in Table 1 and Section 5.3.6.1. In patients developing laboratory or clinical signs of a tumor lysis syndrome (e.g. hyperkalemia, hyperphosphatemia, hyperuricemia and hyperuricosuria, hypocalcemia, and acute renal failure), accepted treatments standards as per published recommendations must be applied (R18-1901, R10-4517)."
Rationale for change		Implemented as an urgent safety measure, as careful monitoring and early medical intervention can minimize the risk for severe TLS.
Section to be changed		4.2.2.2
Description of change		Text updated from "at least 24 h" to now "approximately 48 hours" to reflect the prolonged requirement for hospitalization in treatment Cycle 1 on Day 8 and Day 9.
Rationale for change		Due to the newly introduced treatment Day 8 in Cycle 1 and the intensive blood sampling for PK, ADA and TLS lab parameters on Day 8 and Day 9, it is required to keep trial participants as in-patients for two days (approximately 48 hours).
Section to be changed		5.3.1
Description of change		Text corrected in DL T section from "at least 2 administrations of BI 836858" to "at least 3 administrations of BI 83685" to align with corresponding text in CTP Section 3.3.4.1.
Rationale for change		Correction of typo.
Section to be changed		5.3.3
Description of change		Text added in section describing "**Recommended Phase II Dose (RP2D)":** If deemed necessary by the Sponsor and the SMC, there will be an option

		to open further Dose Escalation cohort(s) following the extension cohorts to determine the RP2D, based on additional biomarker, PK/PD and safety data.
Rationale for change		Updated to reflect patients entered into the additional optional Phase I Dose Escalation cohort(s) to be recruited prior to starting the Phase II part of the trial.
Section to be changed		5.3.6.1
Description of change		Text added in section describing "**General safety laboratory parameters"** to describe the new screening for laboratory evidence of tumor lysis syndrome.
Rationale for change		Implemented as an urgent safety measure, as careful monitoring and early medical intervention can minimize the risk for severe TLS.
Section to be changed		5.3.8.1
Description of change		Tumor Lysis Syndrome (TLS) added to the AESI list.
Rationale for change		TLS added to list of AESIs to minimize risk of delayed reporting.
Section to be changed		5.5
Description of change		The text in this section was updated to reflect that the first administration of BI 836858 will take place on Day 8 instead of Day 9 (or day 9 at the latest). The reference to "[days]…of decitabine treatment" was deleted, as not all patients will receive treatment with decitabine on Day 8 and day 9.
Rationale for change		See above - same as for section 4.1.3 and correction of unclear reference.
Section to be changed		6.2.2
Description of change		The text in this section was updated to reflect that the first administration of BI 836858 will take place on Day 8 instead of Day 9 (or on Day 9 at the latest).
Rationale for change		See above - same as for Section 4.1.3
Section to be changed		7.4
Description of change		Text added in section describing "**Planned Analysis"** to describe the optional additional Dose Escalation cohort(s).
Rationale for change		Updated to reflect patients entered into the

		additional optional Phase I Dose Escalation cohort(s) to be recruited prior to starting the Phase II part of the trial.
Section to be changed		7.4
Description of change		Text added in section describing "**Interim Analysis"** to describe the optional additional Dose Escalation cohort(s).
Rationale for change		Updated to reflect patients entered into the additional optional Phase I Dose Escalation cohort(s) to be recruited prior to starting the Phase II part of the trial.

Number of global amendment		6
Date of CTP revision		21 Aug 2019
EudraCT number		2015-002892-30
BI Trial number		1315.2
BI Investigational Product(s)		BI 836858
Title of protocol		An open-label, Phase I/II trial to determine the maximum tolerated dose and investigate safety, pharmacokinetics and efficacy of BI 836858 in combination with decitabine in patients with acute myeloid leukemia
To be implemented only after approval of the IRB / IEC / Competent Authorities	X	
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		**After the Sponsor's decision to discontinue development of BI 836858 and to stop further recruitment of patients into study 1315.2, trial participants still on treatment and with clinical benefit from BI 836858 and decitabine are kept on treatment in this trial (as per protocol section 6.2.3.3).** **With the aim to minimize the burden for trial participants, the mandatory protocol procedures are reduced for all patients in treatment cycles >7.** **Changes have been made in the following sections:** **Synopsis – section "Number of patients"** Actual number of patients entered/treated in Phase I Dose Escalation (**16 patients**) and in Phase I Extension (**33 patients**) was added. **One new sentence added:**

		"After completion of recruitment to Phase I Extension Cohort A and Cohort B, the recruitment to this trial is discontinued." • **Flow chart**: Section describing "Cycles ≥ 4" supplemented with additional information (new column) describing procedures in "Cycle >7" to reflect the assessments per visit. Clarifications added in the existing footnotes *****), 11, 12 and 13; new footnotes 19, 20 and 21 added.   • **3.1 Overall Trial Design and Plan** Clarification added about discontinuation of recruitment to this trial. • **3.3.4.2 Discontinuation of the trial by the Sponsor** Clarification added about discontinuation of recruitment to this trial. • **5.3. Assessment of Safety** Clarifications added about reduced mandatory protocol procedures for treatment cycles >7 with reference to updated Flow chart. **New text:** After completion of recruitment to Phase I Extension Cohort A and Cohort B, the recruitment to this trial is discontinued. With the aim to minimize the burden for trial participants, after approval of Protocol version 7.0, the mandatory protocol procedures described below in sections 5.3.4 (Physical Examination), 5.3.6 (Safety laboratory

		parameters), 5.3.7 (Electrocardiogram), are reduced for all patients who continue to receive trial medication in treatment cycles >7. Instead, routine safety assessments should be performed at the investigator's discretion, based on standard medical care. For details refer to Flow Chart. Findings are documented in the eCRF only if qualifying for an adverse event (see sections 5.3.8 and 5.3.9, unchanged). • **5.3.5 Vital Signs** **New text:** After implementation of Protocol version 7.0 the vital sign results will be documented in the eCRF only if qualifying for an adverse event (see sections 5.3.8 and 5.3.9, unchanged). • **6.2.2 Treatment period (also 6.2.2.1 and 6.2.2.2)** Clarifications added about reduced mandatory protocol procedures for treatment cycles >7 with reference to updated Flow chart. **New text:** **"**With the aim to minimize the burden for trial participants, after approval of Protocol version 7.0, the mandatory protocol procedures are reduced for all patients who continue to receive trial medication in treatment cycles >7. Refer to *updated* Flow Chart for specific requirements during treatment period. […] (after approval of Protocol version 7.0 BM assessments will be done at the investigator's discretion)". • **6.2.3.1.1 Follow-up of Phase I Patients** Clarification added about discontinuation of recruitment to this trial and no follow-up visits after completion of EoR visit. • **6.2.3.2 Trial completion for an individual patient** Clarification added about discontinuation of recruitment to this trial.

		• **6.2.3.3 End of the whole trial** Clarification added about the definition of the end of the whole trial. No follow-up visit after the last patient has had the EoR visit. • **7.1.2 Phase I Extension** Clarification added about discontinuation of recruitment to this trial.

APPROVAL / SIGNATURE PAGE

Document Number: c03377067 **Technical Version Number:8.0**

Document Name: clinical-trial-protocol-version-07

Title: An open label, Phase I/II trial to determine the maximum tolerated dose and investigate safety, pharmacokinetics and efficacy of BI 836858 in combination with decitabine in patients with acute myeloid leukemia

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Author-Clinical Trial Leader	[redacted]	22 Aug 2019 14:00 CEST
Author-Trial Clinical Pharmacokineticist		22 Aug 2019 14:55 CEST
Approval-Team Member Medicine		22 Aug 2019 15:31 CEST
Author-Trial Statistician		26 Aug 2019 11:02 CEST
Approval-Therapeutic Area [redacted]		26 Aug 2019 11:06 CEST
Verification-Paper Signature Completion		26 Aug 2019 11:38 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed