Clinical Trial Protocol

Doc. No.: c02304070-07

EudraCT No.:	2018-002177-21
BI Trial No.:	1315.7
BI Investigational Product(s):	BI 836858
Title:	A Phase I/II, Multicenter, Open-label, Dose Escalation and Randomized Trial of BI 836858 in Patients with Low or Intermediate-1 Risk Myelodysplastic Syndromes
Clinical Phase:	Phase I/II
Trial Clinical Monitor:	Telephone: Fax:
Co-ordinating Investigator:	Telephone: Fax:
Status:	**Final Protocol (Revised Protocol (based on Global amendment 4))**
Version and Date:	**Version: 5.0** **Date: 11 SEP 2019**

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CLINICAL TRIAL PROTOCOL SYNOPSIS

Name of company: Boehringer Ingelheim		**Tabulated Trial Protocol**	
Name of finished product: Not Applicable			
Name of active ingredient: BI 836858			
Protocol date: 06 MAR 2014	**Trial number:** 1315.7		**Revision date:** **11 SEP 2019**

Title of trial:	A Phase I/II, Multicenter, Open-label, Dose Escalation and Randomized Trial of BI 836858 in Patients with Low or Intermediate-1 Risk Myelodysplastic Syndromes
Co-ordinating Investigator:	
Trial site(s):	Multicenter trial
Clinical phase:	I/II
Objective(s):	Phase I: To investigate the maximum tolerated dose (MTD), safety and tolerability, pharmacokinetics, exploratory biomarker and efficacy of BI 836858 monotherapy in patients with low or intermediate-1 risk myelodysplastic syndromes (MDS) with symptomatic anemia. Phase II: To investigate safety and efficacy of BI 836858 plus Best Supportive Care (BSC) compared to Best Supportive Care alone in low or intermediate-1 risk MDS patients with symptomatic anemia.
Methodology:	Phase I: open label, single arm, dose escalation, Bayesian logistic regression model (BLRM) with overdose control Phase II: open label, two-arm, randomized, BI 836858 plus BSC vs. BSC Alone
No. of patients:	
total entered:	Approximately 200 patients
each treatment:	Phase I dose escalation: 21 patients Phase I expansion: 6 patients Recruitment in this trial was discontinued prematurely during the Phase I expansion cohort Phase II: Approximately 150 patients, 75 patients each arm
Diagnosis :	Patients with MDS with symptomatic anemia due to low or intermediate-1 risk (i.e., International Prognostic Scoring System (IPSS) score 0-1) who have experienced Erythropoiesis-Stimulating Agent (ESA) treatment failure or low chance of response to ESAs and are refractory to or are not amenable or eligible for approved MDS therapy.

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Main criteria for inclusion:	Phase I: Adult patients with low or intermediate-1 risk MDS who, experienced ESA treatment failure, except for those who have a low chance to respond to ESA treatment and are refractory to or are not amenable or eligible for approved MDS therapy. Phase II: Adult patients with low or intermediate-1 risk MDS
Test product(s):	BI 836858
dose:	The Phase I starting dose is 20 mg. Phase II: Recommended Phase II Dose (RP2D), based on the MTD determined in Phase I
mode of admin.:	Intravenous (i.v.) infusion on Days 1 and 15 of each 28-day cycle
Comparator products:	Phase II only: BSC per Investigator's choice
mode of admin.:	NA
Duration of treatment:	Patients with clinical benefit, PR or CR after the 4th (or 6th) Cycle will receive repeated cycles until relapse after Complete Response (CR), Partial Response (PR), erythroid response (HI-E), Red Blood Cell transfusion independency or Marrow Complete Response (mCR), Progressive Disease (PD), or unacceptable adverse event(s), in the absence of other withdrawal criteria.

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Name of finished product: Not Applicable			
Name of active ingredient: BI 836858			
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Criteria for efficacy:

Primary endpoints (Phase II):

- RBC transfusion independency

Secondary endpoints (Phase I):

- RBC transfusion independency

Secondary endpoints (Phase I and II):

- Hematologic improvement neutrophils (HI-N)
- Hematologic improvement platelets (HI-P)
- Hematologic improvement erythroid (HI-E)
- Time to HI-E response
- Mean hemoglobin increase ≥ 1.5 g/dL
- Duration of response (RBC Transfusion Independency, HI-N, HI-P, HI-E or Objective Response)
- Overall Response (CR, PR and HI)

Criteria for safety:

Primary endpoints (Phase I):

- Maximum Tolerated Dose (MTD)
- Occurrence of Dose Limiting Toxicity (DLT)

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Name of finished product: Not Applicable			
Name of active ingredient: BI 836858			
Protocol date: 06 MAR 2014	**Trial number:** 1315.7		**Revision date:** **11 SEP 2019**
Statistical methods:	Phase I: Descriptive statistics will be used for toxicity, PK parameters, biomarkers and responses. A Bayesian two-parameter logistic regression model (BLRM) with overdose control 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 the Phase I trial, the toxicity probability at each dose level will be calculated to determine the MTD. Phase II: Efficacy and safety evaluation of BI 836858 compared to investigator's choice of BSC based on the binary endpoint response. The analysis will be exploratory; no confirmatory statistical tests are planned for this study.		

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FLOW CHART 1 – INTRODUCTION TREATMENT

Trial Periods	**Screen**	**Introduction Study Treatment**								**FU**
	Screen	**Cycles 1 - 4 (1 Cycle = 28 days)**				**EOC4**	**Cycles 5 & 6****		**EOT**	**FU (No further visits after EoR period upon implementation approval of CTP version 5.0)**
Visit	**1**	**Cx V1**	**Cx V2**	**Cx V3**	**Cx V4**	**C4 V5**	**Cx V1**	**Cx V2**		
Days (in respective cycle)*	**-21 to -1**	**1**	**8 ± 1[1]**	**15**	**22 ±1[1]**	**28 ±2**	**1**	**15**		
Informed consent	x									
Demographics and baseline conditions	x									
Medical history	x									
Review of in-/exclusion criteria	x	x [2]								
Dose assignment (Phase I)	x [3]									
Randomization (Phase II)	x[3]									
LABS/SAFETY ASSESSMENTS										
Safety laboratory parameters incl. urinalysis[4]	x	x	x[1]	x	x[1]	x	x[20]	X[20]	x[20]	
Physical examination ECOG performance status	x	x[5]				x	x[5, 20]		X[20]	
Vital signs, height[6], weight	x	x	x	x	x	x	x[20, 21]	x[20, 21]	x[20, 21]	
Serum pregnancy test [7]	x	x				x	x		x	
12 lead-ECG	x	x				x	X[20]		x[8, 20]	
Adverse events	x	x	x	x	x	x	x	x	x	x[9]
Concomitant therapy	x	x	x	x	x	x	x[22]	x[22]	x[22]	x[9, 22]
DISEASE ASSESSMENTS										
Number of transfusions received	x	←				x[20]	→			

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FLOW CHART 1 – INTRODUCTION TREATMENT (cont.)

Trial Periods	**Screen**	**Introduction Study Treatment**								**FU**
	Screen	**Cycles 1 - 4 (1 Cycle = 28 days)**				**EOC4**	**Cycles 5 & 6****		**EOT**	**FU No further visits after EoR period upon implementation approval of CTP version 5.0)**
Visit	**1**	**Cx V1**	**Cx V2**	**Cx V3**	**Cx V4**	**C4 V5**	**Cx V1**	**Cx V2**		
Days (in respective cycle)*	**-21 to -1**	**1**	**8 ± 1[1]**	**15**	**22 ±1[1]**	**28 ±2**	**1**	**15**		
Bone marrow aspiration[10]	x					x[11]		x[10, 20]	x[8, 11, 20]	
Cytogenetics and molecular genetics of MDS[12]	x					x[13]			x[13, 20]	
Clinical disease assessment[14]						x	x[14, 20]			
TRIAL MEDICATION										
Drug Administration (BI 836858)		x		x			x	x		
Best Supportive Care (Phase II Arm B only)		←		x	→					
Eligibility for subsequent cycles of study treatment		x[18]		x[18]		x[18, 19]	x[18]	x[18]		
End of trial treatment									x[20]	
Other therapies for MDS **(Phase II Only)**										
Vital Status										x[20]

EOC4: End of Cycle 4. Patients with clinical benefit, PR or CR after the 4th Cycle and who are tolerating the study treatment may continue on and into the maintenance treatment cycles until PD or other withdrawal criteria are met as noted in Section 3.3.4.1. For patients who have received 8 administrations of BI 836858, this visit will

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be performed 14 days (±2 days) after the 8th administration of BI 836858. For those patients who received less than 8 administrations, but still in remission, this visit is to be performed 4 months (±2 days) after Cycle 1 Visit 1. Phase II: For patients randomized to BSC, this visit is to be completed 4 months (±2 days) after Cycle 1 Visit 1.

EOT: End of Treatment. The EOT visit is to occur 30 days (+7 days) after the last administration of BI 836858. Patients who permanently discontinue study treatment will complete the EOT and complete Follow-up visits. Refer to Section 3.3.4 for treatment discontinuation criteria. After implementation of CTP version 5.0, no further follow-up visits after End of Residual Effect (EoR), unless follow-up is for S(AE) that occurred before EoR period.

FU: Follow-up starts 4 weeks after the EOT visit; Phase I patients**:** visits or telephone calls will occur at least every 4 weeks for 6 months**.** After the 6th follow-up visit, the patient will be considered off trial. Phase II patients: visits or telephone calls will occur at least every 4 weeks until 12 months after the last administration of BI 836858, after which these visits will occur every 6 months until the end of the trial. After implementation of CTP version 5.0, no further follow-up visits after EoR, unless follow-up is for S(AE) that occurred before EoR period.

* The planned duration of a treatment cycle is 28 days; there will be two administrations of BI 836858 per cycle, on Days 1 and 15. All assessments should be performed prior to dose administration on dosing days, unless otherwise specified.

** These visits are only for those patients who have received BI 836858 that are non-PD and equivocal as to if clinical benefit has been established, per investigator judgment, after 4 Cycles; up to 2 additional introduction cycles allowed prior to end of introduction treatment.

1 Visit window of +1 day only allowed beginning in Cycle 3 and for all subsequent cycles. In Cycles 1 and 2 visit window not allowed d

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

3 After informed consent and review of inclusion/exclusion criteria (timing described in footnote 2). For phase II, randomization should be performed as close to the first treatment dose as possible. It may be performed on the day of the first administration (Cycle 1 day 1) prior to patient treatment, but no later than 21 days after patient signs informed consent.

4 For details refer to Section 5.2.3.1. Urine has to be measured only at screening, EOC4 and EOT. Safety laboratory assessments may be completed up to 2 days prior to administration, or BSC treatment on trial (Phase II). An additional safety lab will be collected on day 2 (i.e., 24 hours after the first administration of BI 836858) and 24 hours after the first higher dose for patients who participate in intra-patient dose escalation. Other lab tests to be included: haptoglobin, direct Coombs test, and bilirubin (direct and indirect).

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

6 Height required only in screening.

7 For women of childbearing potential only. Serum pregnancy test completed at Screening, Visit 1 of each Cycle, EOC4 and EOT. After implementation of CTP version 5.0, pregnancy test results will not be documented by default in the eCRF. Only positive pregnancy tests will be documented via the Pregnancy Monitoring Form (and reported as an AE if applicable).

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8 ECG and bone marrow aspiration will be performed at EOT only if the patient has completed at least 2 cycles (e.g. received 4 administrations) since the EOC4 visit (or additional introduction cycle 5 and 6). After implementation of Protocol version 5.0, ECG and bone marrow sampling is no longer mandatory at defined visits but is performed at the investigator's discretion. Bone Marrow samples should not be shipped to the biomarker lab.

9 Follow-up of AEs not recovered since the EOT. Concomitant therapy during FU is collected only if indicated for treatment of adverse event.

10 Bone marrow aspirate to assess efficacy at EOC4 and at disease progression/relapse or EOT, whichever occurs first. (Refer to Section 5.1.2). Bone marrow aspirate for biomarker analysis at time points are noted in Table 4 (Section 5.6.1). After implementation of Protocol version 5.0, bone marrow sampling for response assessment is no longer mandatory at defined visits (except EOC4) but is performed at the investigator's discretion. Bone Marrow samples should not be shipped to the biomarker lab.

11 Only one sample to be collected at the time of PD or the time of initiation of other MDS therapy, which may be at the EOC4/EOT, if PD or initiation of other MDS therapy occurs during treatment, or during follow-up. After implementation of Protocol version 5.0, bone marrow sampling for response assessment is no longer mandatory at defined visits (except EOC4) but is performed at the investigator's discretion. Bone Marrow samples should not be shipped to the biomarker lab.

12 Data from initial diagnosis can be used if available; otherwise will be collected for this study (Section 5.6.3).

13 Phase II assessments only.

14 Clinical disease assessments can be performed up to 2 days prior to this visit to evaluate if patients are experiencing clinical benefit, PR or CR after the 5th and 6th Cycles and tolerating the study treatment well, based on investigator judgement. These patients who meet these criteria may continue on treatment in the maintenance cycles until PD or other withdrawal criteria are met as noted in Section 3.3.4.1.

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

19 At the EOC4, patients will be evaluated to determine if they have clinical benefit, as defined by IWG objective response (PR or CR) or subjective response (in the absence of objective response) and are tolerating the infusions well and who would like to continue to receive infusions until PD or other criteria for withdrawal are met as noted in Section 3.3.4.1. For each infusion past the 4th cycle, patients will continue to be assessed after each cycle for clinical benefit (objective or subjective response), and that they are tolerating the infusions well and would like to continue until PD or other criteria for withdrawal are met as noted in Section 3.3.4.1.

20 Procedures/assessments not mandatory after implementation of CTP version 5.0, but assessments (e.g. hematology & biochemistry 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 and (S)AE.

21 After implementation of CTP version 5.0, vital signs are mandatory only at the day of administration of BI 836858, results will be documented in the eCRF only if qualifying for an adverse event.

22 After implementation of Protocol version 5.0, Collection of Concomitant Therapy information only if the indication is treatment of an Adverse Event.

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FLOW CHART 2 – MAINTENANCE

Trial Periods	**Maintenance Study Treatment****		**FU**
	Maintenance Cycles X (1 Cycle = 28 days)	**EOT**	**FU (No further FU visits after EoR period upon implementation approval of CTP version 5.0)**
Visit	**MCx[12] V1**		
Days (in respective cycle)*	**1**		
LABS/SAFETY ASSESSMENTS			
Safety laboratory parameters incl. urinalysis[1]	x[12]	x[12]	
Physical examination ECOG performance status	x[2, 12]	x[12]	
Vital signs, weight	x[12, 13]	x[12, 13]	
Serum pregnancy test [3]	x	x	
12 lead-ECG		x[4, 12]	
Adverse events	x	x	x[5]
Concomitant therapy	x[14]	x[14]	x[5, 14]
DISEASE ASSESSMENTS			
Number of transfusions received	←	x[12]	→
Bone marrow aspiration[6,7]		x[4, 7, 12]	
Cytogenetics and molecular genetics of MDS[8]			
Clinical Disease Assessment [9]	x[12]		

TRIAL MEDICATION			
Drug Administration (BI 836858)	x		
Best Supportive Care (Phase II Arm B only)	← x →		
Eligibility for subsequent cycles of study treatment[11]	x		
End of trial treatment		x[12]	
Other therapies for MDS **(Phase II Only)**			
Vital Status			x[12]

EOT: End of Treatment. The EOT visit is to occur 28 days (+7 days) after the last administration of BI 836858. Patients who permanently discontinue study treatment will enter into Follow-up phase after EOT visit. Refer to Section 3.3.4 for treatment discontinuation criteria. After implementation of CTP version 5.0, no further follow-up visits, unless follow-up is for S(AE) that occurred before EoR period.

FU: Follow-up starts 4 weeks after the EOT visit; Phase I patients: visits or telephone calls will occur at least every 4 weeks for 6 months. After the 6th follow-up visit, the patient will be considered off trial. Phase II patients: visits or telephone calls will occur at least every 4 weeks until 12 months after the last administration of BI 836858, after which these visits will occur every 6 months until the end of the trial. After implementation of CTP version 5.0, no further follow-up visits, unless follow-up is for S(AE) that occurred before EoR period.

* The planned duration of a treatment cycle is 28 days; there will be one administration of BI 836858 per maintenance cycle, on Day 1.

** These visits are only for those patients with clinical benefit, PR or CR after 4 (or 6) Cycles and who are tolerating the infusions well, may continue until PD or other criteria for withdrawal are met as noted in Section 3.3.4.1.

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1 For details refer to Section 5.2.3.1. Urine has to be measured only at EOT. Safety laboratory assessments may be completed up to 2 days prior to administration.
2 Only every second cycle (i.e. at Maintenance Cycle 1, 3, 5, 7 etc. Visit 1) Physical examination may be completed up to 2 days prior to administration. Eastern Cooperative Oncology Group (ECOG) assessment must be completed on the day of the administration.
3 For women of childbearing potential only. Serum pregnancy test completed at Visit 1 of each Cycle. After implementation of CTP version 5.0, pregnancy test results will not be documented by default in the eCRF. Only positive pregnancy tests will be documented via the Pregnancy Monitoring Form (and reported as an AE if applicable).
4 ECG and bone marrow aspiration will be performed at EOT only if the patient has completed at least 2 cycles (e.g. received 2 administrations) since the EOC4 visit (or additional introduction cycle 5 and 6). After implementation of Protocol version 5.0, ECG and bone marrow sampling for response assessment is no longer mandatory at defined visits but is performed at the investigator's discretion. Bone Marrow samples should not be shipped to the biomarker lab.
5 Follow-up of AEs not recovered since the EOT. Follow-up of new AEs that occurred during REP. Concomitant therapy during FU is collected only if indicated for treatment of adverse event.
6 Bone marrow aspirate to assess efficacy at disease progression/relapse or EOT, whichever occurs first. (Refer to Section 5.1.2). After implementation of Protocol version 5.0, bone marrow sampling for response assessment is no longer mandatory at defined visits but is performed at the investigator's discretion. Bone Marrow samples should not be shipped to the biomarker lab.
7 Only one sample to be collected at the time of PD or the time of initiation of other MDS therapy, which may beat the EOT, if PD or initiation of other MDS therapy occurs during treatment, or during follow-up. After implementation of Protocol version 5.0, bone marrow sampling for response assessment is no longer mandatory at defined visits but is performed at the investigator's discretion.
8 Phase II assessment only.
9 Clinical disease assessments can be performed up to 2 days prior to this Maintenance Cycle 1 Visit 1 to evaluate if patients experienced clinical benefit, PR or CR after the 6th Cycle and are tolerating the study treatment well, based on investigator judgement. These patients who meet these criteria may continue on treatment in the maintenance cycles until PD or other withdrawal criteria are met as noted in Section 3.3.4.1.

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

12 Procedures/assessments not mandatory after implementation of CTP version 5.0, but assessments (e.g. hematology & biochemistry 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 and (S)AE.
13 After implementation of CTP version 5.0, vital signs are mandatory only at the day of administration of BI 836858, results will be documented in the eCRF only if qualifying for an adverse event.
14 After implementation of Protocol version 5.0, collection of Concomitant Therapy information only if the indication is treatment of an Adverse Event.

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ABBREVIATIONS

5-aza	5-azacitidine
ADCC	Antibody Dependent Cellular Cytotoxicity
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine Amino Transferase
AML	Acute Myelogenous Leukemia
ANC	Absolute Neutrophil Count
AP	Alkaline Phosphotase
aPTT	Activated Partial Thromboplastin Time
AST	Aspartate Amino Transferase
ATG	Anti-Thymocyte Globulin
BI	Boehringer Ingelheim
BLRM	Bayesian two-parameter logistic regression model
BM	Bone Marrow
BSC	Best Supportive Care
BUN	Blood Urea Nitrogen
CA	Competent Authority
CBC	Complete Blood Count
CI	Confidence Interval/Coordinating Investigator
CML	Local Clinical Monitor
CPPL	Clinical Pharmacological Project Lead
CR	Complete Response
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Contract Research Organization
CTCAE	Common Terminology Criteria for Adverse Events
CTMF	Clinical Trial Master File
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
DILI	Drug Induced Liver Injury
DLT	Dose Limiting Toxicity

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DMC	Data Monitoring Committee
DNA	Deoxyribonucleic Acid
DSB	Data Safety Board
EC	Ethics Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EMA	European Medicines Agency
EOT	End of Treatment
EPO	Erythropoietin
ESA	Erythropoiesis-Stimulating Agents
EudraCT	European Clinical Trials Database
EWOC	Escalation-with-overdose-control
FDA	Food and Drug Administration
FIH	First In Human
FU	Follow-up
GCP	Good Clinical Practice
G-CSF	granulocyte colony stimulating factor
HI	Hematologic Improvement
HI-E	Hematologic Improvement -Achieve erythroid response
HI-N	Hematologic Improvement - neutrophils
HI-P	Hematologic Improvement - platelets
HIV	Human Immunodeficiency Virus
HMA	Hypomethylating Agents
HPC	Hematopoietic Progenitor Cells
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
INN	International Nonpropriety Names
INR	International Normalized Ratio
IPSS	International Prognostic Scoring System
IRB	Institutional Review Board
ISF	Investigator Site File
IRT	Interactive Response Technologies
i.v.	Intravenous
IVRS/IWRS	Interactive Voice/Web Response System
IWG	International Working Group
LDH	Lactate Dehydrogenase
mAb	Monoclonal Antibody
mCR	Marrow Complete Response
MDSC	Myeloid derived suppressor cells
MDS	Myelodysplastic Syndromes

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MTD	Maximum tolerated dose
NA	Not Applicable
NC	Not calculated
NCI	National Cancer Institute
NK	Natural Killer
OPU	Operative Unit
OR	Objective Response
PD	Progressive Disease
pd	Pharmacodynamics
PGx	Pharmacogenomics
PK	Pharmacokinetics
PLT	Platelet
PR	Partial Response
PT	Prothrombin Time
RBC	Red Blood Cell
RDC	Remote Data Capture
REP	Residual Effect Period
RNA	Ribonucleic Acid
RP2D	Recommended Phase II Dose
SAE	Serious Adverse Event
SCT	Stem Cell Transplantation
SD	Stable Disease
SOC	Standard of Care
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reactions
TCM	Trial Clinical Monitor
TD	Transfusion Dependent
TI	Transfusion Independence
TME	TransMed Expert
TMM	Team Member Medicine
TPO	Thrombopoietin
TSAP	Trial Statistical Analysis Plan
ULN	Upper Limit of Normal
WBC	White Blood Cell
WHO	World Health Organization

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1. INTRODUCTION

1.1 MEDICAL BACKGROUND

Myelodysplastic syndromes (MDS) are a very heterogeneous group of myeloid disorders characterized by peripheral blood cytopenias and increased risk of transformation to acute myelogenous leukemia (AML) (R13-0382).

MDS is primarily a disease of older adults with a median age at diagnosis of approximately 70 years. MDS occurs in three to four individuals per 100,000 in the US population (R13-0364). Prevalence increases with age, e.g. in individuals aged 60 and above, prevalence is 7 to 35 per 100,000 (R13-0364). Due to advanced age, the MDS patient population is frequently affected by other co-morbidities, which often influence treatment decisions. Incidence of MDS is more frequent in males than females (R13-0364). Exposure to prior chemotherapy or radiation therapy is a risk for the development of MDS.

MDS is usually suspected by the presence of cytopenia on a routine analysis of peripheral blood. This prompts evaluation of bone marrow cell morphology (aspirate) and cellularity (biopsy). A manual count of bone marrow blasts is essential for risk assessment. Cytogenetic analysis will facilitate the identification of predictive risk and selection of therapy. Once this information is collected, the risk of the patient may be evaluated based on the scoring system. The International Prognostic Scoring System (IPSS) (R13-0374) was introduced in 1997 and is still the most commonly used score. In 2012, a revised IPSS score (IPSS-R) was introduced (R13-0375).

A number of morphological classifications are in place to classify patients with MDS, the most recent one being the 2008 World Health Organization (WHO) by which MDS are further categorized by their refractory cytopenias, karyotypic features, blast percentages, and number of dysplastic myeloid lineages.

In MDS, cytogenetics is of major importance for prognosis. Clonal cytogenetic abnormalities can be identified in approximately 50% of cases. Patients with normal marrow karyotypes, del(5q) alone, del(20q) alone, and –Y alone have a relatively good prognosis whereas patients with complex abnormalities (three or more chromosome anomalies) or chromosome 7 anomalies have relatively poor prognoses. In addition, various gene mutations have been identified among patients with MDS that influence their prognosis. Such mutations may be present in a substantial proportion of newly diagnosed patients, including patients with normal cytogenetics. The most frequently occurring molecular genetic lesions are mutations in the *TET2, ASXL1, RUNX1, TP53, EZH2, NRAS, KRAS, JAK2, ETV6, CBL*, *SF3B1, SRSF2, ZRSR2, U2AF35, FLT3, DNMT3A, IDH1* and *IDH2* genes. Among these, *TP53, RUNX1, EZH2, ETV6*, and *ASXL1* have been found to be independent predictors of decreased overall survival whereas mutations of *TET2* appear to confer a more favorable prognosis compared to cases without *TET2* mutations. This is an area of active research and during the course of the development of BI 836858 in MDS it is possible that a more detailed understanding of the role of these genetic lesions in disease outcome and drug response will become available.

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Treatment of MDS is based on prognostic factors that predict survival and progression to AML. Currently, the treatment of patients with MDS is guided by the IPSS (R13-0374). This score divides patients into a lower risk subset (low and intermediate-1) and a higher risk subset (intermediate-2 and high), based on the number of cytopenias, percentage of bone marrow blasts, and karyotype. The survival of patients with higher-risk MDS is relevantly different than that of patients with lower-risk disease. Without intervention, median survival of higher-risk patients is close to 12 months (R13-0374). Survival of patients with lower-risk disease is more diverse and ranges from a few months (lower-risk disease with a poor-prognosis) to more than a decade (R13-0374, R13-0373). Therefore, the objectives of therapy are different in lower-risk versus higher-risk disease. While on higher-risk MDS, disease-modifying therapies are aiming at reduction of patients who progress to AML and by improving survival, the therapeutic goals in lower-risk MDS are symptom relief, management of cytopenia, and minimizing the number of transfusions (R13-0377). Chronic anemia remains the most frequent clinical problem in lower-risk MDS, which alters quality of life in those elderly patients. Erythropoiesis-stimulating agents (ESA) generally constitute the first-line treatment for anemia except, in patients with 5q deletion, where lenalidomide brings superior outcomes. Major favorable prognostic factors for response to ESAs are low or no red blood cell (RBC) transfusion requirement (<2 units per month) and baseline serum Erythropoietin (EPO) level <500 U/L. The addition of a myeloid growth factor such as granulocyte colony-stimulating factor (G-CSF) may raise the erythroid response rate. Second line treatments of anemia (including hypomethylating agents (HMA), lenalidomide in the absence of 5q deletion, and anti-thymocyte globulin (ATG)) are less satisfactory, yielding at best one-third of responses, so that many patients eventually require repeated RBC transfusions, a situation in which indications for iron overload prophylaxis are still somewhat disputed. In a minority of lower-risk MDS, thrombocytopenia is the predominating cytopenia, and Thrombopoietin (TPO) agonist receptors are currently being tested in this situation, whereas HMAs or ATG may be useful. Some patients with lower-risk MDS according to IPSS may, at diagnosis or during evolution, have features associated with poorer prognosis, based on new prognostic scoring systems (e.g., IPSS-R, M.D. Anderson score), presence of gene somatic mutations, or resistance to first-line treatment, that may qualify them for more intensive treatment, including in some cases allogeneic stem cell transplant (SCT).

The therapeutic goal in lower risk MDS is to alleviate the cytopenias, most importantly anemia. Therefore, red blood cell transfusions remain an important component of treatment, but exposes patients to insufficient correction of anemia, allo-immunization, and organ iron overload.

1.2 DRUG PROFILE

1.2.1 BI 836858

BI 836858 is a fully human IgG1 antibody specific for CD33.

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CD33 is a myeloid differentiation antigen which is expressed on the cell surface of non-malignant leukocytes of the myeloid lineage and with high frequency on malignant cells in AML, chronic myeloid leukemia and myelodysplastic syndrome (R11-1467, R11-1468, R11-1470, R11-2960). In addition to expression on malignant myeloid blast cells, CD33 expression was reported for leukemic stem cells (R11-1469) and hematopoietic suppressive cells called immature myeloid-derived suppressor cells (MDSC) (R13-4724). 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).

The ADCC activity of BI 836858 was assessed on a panel of AML-derived cell lines and primary AML cells and compared to the ADCC activity of lintuzumab, a humanized CD33-specific antibody which has been in clinical development for AML (R11-1471).

Pre-clinical studies with BI 836858 were performed to assess BI 836858 for the MDS indication (P17-02032).

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1.2.2 Best Supportive Care (BSC)

Best supportive care for MDS includes red blood cell transfusion, platelet transfusion and iron chelation therapy. Initiation of transfusion therapy should be based on clinical evaluation of anemia-related symptoms and co-morbid illness rather than on a defined hemoglobin level, especially because optimal hemoglobin levels are difficult to define for the elderly population. In clinical practice, pre-transfusion hemoglobin levels in MDS are generally maintained between 8 and 10 g/dL.

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2. RATIONALE, OBJECTIVES, AND BENEFIT - RISK ASSESSMENT

2.1 RATIONALE FOR PERFORMING THE TRIAL

MDSCs have recently been recognized as a subset of innate immune cells that can alter adaptive immunity and produce immunosuppression (R13-4724). Human MDSC comprise a heterogeneous population of immature myeloid (CD33+) cells consisting of dendritic cell, macrophage, and granulocyte progenitors that lack lineage maturation markers. It is published that MDSCs, classically linked to immunosuppression, inflammation and cancer, are markedly expanded in the bone marrow of MDS patients and play a pathogenetic role in the development of ineffective hematopoiesis. Characterized by a LIN-HLA-DR-CD33+ phenotype, these clonally distinct MDSC overproduce hematopoietic suppressive cytokines, and function as potent apoptotic effectors targeting autologous hematopoietic progenitors. Preclinical experiments have yielded evidence that depletion of MDSC with BI 836858 in bone marrow from MDS patients ex vivo can effectively improve hematopoiesis. Based on these results, it is hypothesized that BI 836858 may improve hematopoiesis in MDS patients by reduction of CD33-positive MDSC in the bone marrow and, in consequence, support the assumption that treatment with BI 836858 can lead to independency of red blood cell transfusion in patients with lower risk MDS (P17-02032).

It has been described that previous treatments with HMAs or lenalidomide reduce the number and activity of NK cells. [R17-1502, R17-1503, R17-1510]. BI 836858 mediated ADCC depends on functional NK cells. Therefore, it is hypothesized that Lower-Risk MDS patients it without previous HMA or lenalidomide treatments may respond better to BI 836858, providing the rationale for an MTD expansion cohort targeting this group of patients.

Low to intermediate-1 risk MDS patients comprise around 70% of the entire MDS populations. In clinical practice, lower-risk patients are those with expected median survival measured in years, and those who have a lower chance to progress to AML. The main clinical burden in this group of patients is symptomatic cytopenias and their associated complications, such as bleeding, risk of infection and iron overload. The goal of treatment is to alleviate symptomatic cytopenias and abrogate or reduce RBC transfusion requirements leading to better quality of life.

This rationale is supported by FDA and EMA approval of lenalidomide in MDS patients with a del 5q.

Overall treatment options for patients with lower risk MDS, especially for those without a 5q deletion, are limited and benefit to available treatment is not satisfactory. Rates of RBC TI for at least 8 weeks for patients with Low to Intermediate-1 risk MDS with treatment of HMAs or lenalidomide are 15 to 30% without improvement in overall survival. Furthermore the outcomes for those patients who failed treatment with HMAs or lenalidomide are poor with an estimated 3 year overall survival rate of 27% [R11-1106, R17-1501, R17-1504, R17-1505, R17-1506, R17-1507, R17-1508, R17-1509, R17-1521].

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2.2 TRIAL OBJECTIVES

The trial will be performed in two parts: Phase I and Phase II.

The Phase I primary objectives of the trial are to determine the maximum tolerated dose (MTD) and the Recommended Phase II Dose (RP2D) to be used in the Phase II. Secondary objectives include safety, pharmacokinetics, exploratory biomarkers and efficacy of BI 836858 monotherapy. The trial will enroll patients with low or intermediate-1 risk MDS with symptomatic anemia, who at a minimum, experienced ESA treatment failure or do not qualify (serum erythropoietin level > 500 U) for ESA treatment and are refractory to or are not amenable or eligible for approved MDS therapy in the dose escalation phase and for one of the MTD expansion cohorts**.** The second MTD expansion cohort will enroll patients with low or intermediate-1 risk MDS with symptomatic anemia, who experienced ESA treatment failure or do not qualify (serum erythropoietin level > 500 U) for ESA treatment and who have not received prior HMA and/or lenalidomide (this cohort is referred to as "untreated"). Patients with a deletion 5q cytogenetic abnormality will be allowed in Phase I who do not qualify for lenalidomide treatment (Absolute Neutrophil Count (ANC) < 500/µL or platelets <50,000/µl) or who experience primary lenalidomide failure (not for untreated expansion cohort). Lenalidomide failure is defined as lack of hematological improvement after 4 months of therapy, or secondary failure defined as loss of prior lenalidomide response at any time point.

In the randomized Phase II, primary objectives are to investigate the efficacy of BI 836858 plus Best Supportive Care (BSC) vs. Best Supportive Care alone, in low or intermediate-1 risk MDS patients with symptomatic anemia who progressed/became resistant following ESA, and are refractory to or are not amenable or eligible for approved MDS therapy. Secondary objectives include the investigation of safety and tolerability of BI 836858 in this patient population.

2.3 BENEFIT – RISK ASSESSMENT

MDS are a heterogeneous group of clonal neoplasms with a patient median age at diagnosis of
>70 years. ESA remain the first-line treatment of anemia in most lower-risk MDS patients without del 5q. Responses to ESA treatment is transient, but interestingly, approximately 70% of the relapses of anemia after initial response to EPO are not associated with progression to higher-risk MDS but simply to loss of sensitivity of erythroid progenitors to EPO. Despite considerable progress in understanding the etiology and biologic behavior of lower risk MDS, BSC is still the standard of care for patients progressing after treatment with EPO or Hypomethylating Agents (HMA) in countries where it is available.

BI 836858 is a monoclonal antibody, which specifically targets CD33. Targeting CD33 in patients with MDS may potentially offer a benefit; since CD33 is expressed on MDSCs suppressing the bone marrow function (see Section 1.2). In addition, BI 836858 is a potent inducer of ADCC, which results in reduction of MDSCs in MDS-derived bone marrow samples.

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

Considering these data and the experience with other monoclonal antibodies in hemato-oncology indications, infusion-related reactions are likely. Prophylactic measures will be stipulated for primary prevention, and supportive treatments are available (Section 4.1.4). Although rare, a potential for drug-induced liver injury is under constant surveillance by sponsors and regulators. Therefore, this study requires timely detection, evaluation, and follow-up of laboratory alterations of selected liver laboratory parameters to ensure patients´ safety. A Phase I safety analysis report will be prepared based on the Phase I data and made available to regulatory authorities, ethics committees/IRBs and all investigators, and the protocol will be amended prior to initiating Phase II as defined in detail in Section 3.1.1.1. In addition, this study will utilize a Data Safety Board to oversee safety, review dose limiting toxicities and determine dose escalations.

Patients with lower risk MDS with limited or no standard treatment options may benefit from reduction of MDSCs suppressing the bone marrow function. The benefits of participation in this trial and receiving BI 836858 may include response of the disease to the study treatment, better disease control, and improvement of MDS-related symptoms, resulting in better quality of life. Safety will be ensured by monitoring the patients for AEs both clinically and by laboratory testing. The potential benefit of therapy with BI 836858 is expected to outweigh the treatment-related risks.

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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. The data obtained from the trial will determine the MTD and RP2D based on a Bayesian logistic regression model with overdose control. Furthermore, this trial will allow an exploratory efficacy analysis of BI 836858 compared to BSC. The results of the trial will aid in the decision-making on the further development program of BI 836858 in MDS.

The overall structure of the study is described in Figure 3.1: 1.

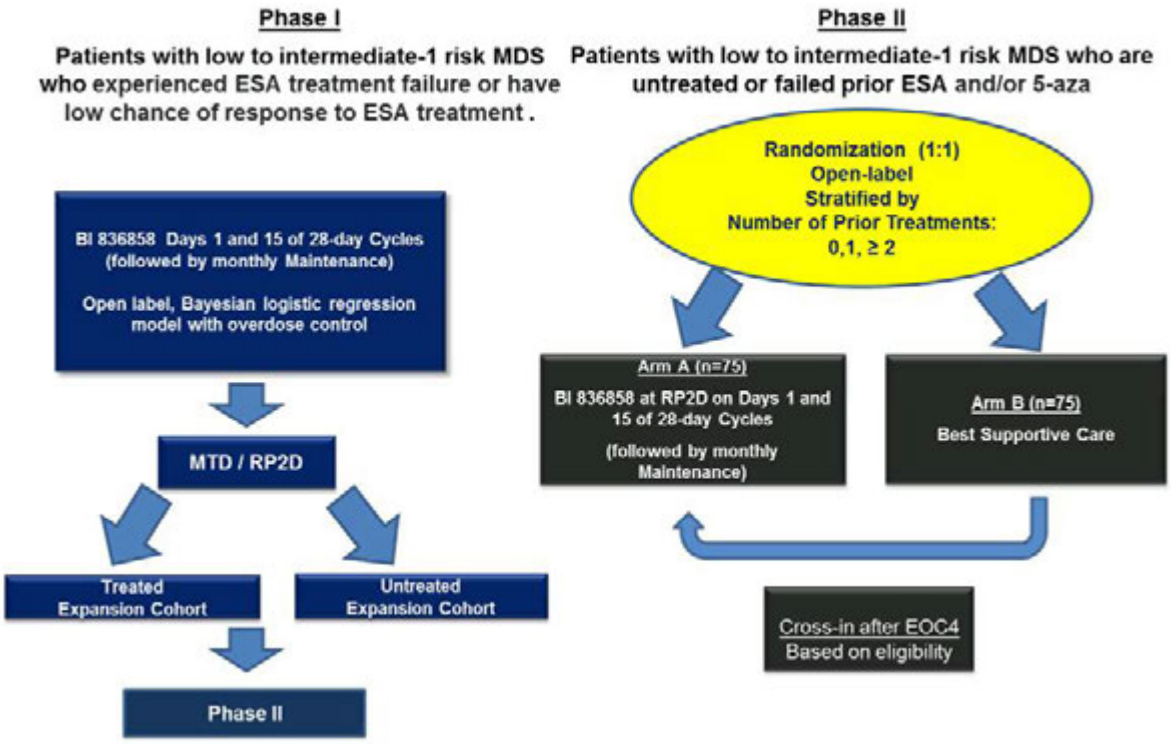

Figure 3.1: 1 Structure of the 1315.7 Phase I/II

Phase I:
In Phase I dose escalation part, patients with low to intermediate-1 risk MDS, who have experienced ESA treatment failure, except for patients who do not qualify for ESA treatment and are refractory to or are not amenable or eligible for approved MDS therapy will be assigned to a dose cohort under investigation. After determination of the MTD/RP2D the same group of patients as for the dose escalation will be enrolled in the first expansion cohort (referred to as "pre-treated" patients). The second expansion cohort will enroll patients with low or intermediate-1 risk MDS with symptomatic anemia, who experienced ESA treatment failure or do not qualify (serum erythropoietin level > 500 U) for ESA treatment and who have not received prior HMA and/or lenalidomide (referred to as "untreated" patients). Treatment failure on ESAs is defined as 1) failure or ceasing to

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show hematologic response after at least 8 weeks of 40,000 to 60,000 IU/week of erythropoietin (EPO) or equivalent or 2) low chance/response to ESA with endogenous serum EPO>500. It is expected that approximately 50 patients will be enrolled.

The Phase I dose-escalation will be guided by a Bayesian logistic regression model with overdose control (refer to Section 7). 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.

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 dose-limiting toxicity within the first cycle (2 administrations – 28 days), 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 (2 administrations – 28 days) 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.

If DLTs are observed in the first two consecutive patients of a previously untested dose level, subsequent enrollment to that cohort will be stopped. The Bayesian logistic regression model will be re-run to confirm that the dose-level still fulfils the EWOC criterion. Based on this information, the Data Safety Board (DSB) 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 DSB may recommend stopping the dose finding phase after the criterion for MTD (Section 5.2.1.2) 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 DSB may decide to include an additional number of patients at the same dose level and to declare this dose as the RP2D. Before the conclusion of Phase I and prior to initiating the Phase II, two expansion cohorts (untreated and pre-treated with HMA and/or lenalidomide) will recruit up to 12 patients per cohort. Overall a minimum of 12 patients (including both expansion cohorts and the last escalation cohort) will receive treatment at RP2D. Patients who show clinical benefit, complete response (CR) or partial response (PR) after 4 cycles and who are tolerating the infusions well may continue to receive additional cycles upon agreement with Investigator and Sponsor until the patient meets any of the criteria for withdrawal as outlined in Section 3.3.4.1.

Recruitment in this trial was discontinued prematurely during the Phase I expansion cohort.

Phase II:

In Phase II, patients will be enrolled in a randomized manner to investigate efficacy and safety of BI 836858 at RP2D in patients who have experienced treatment failure on ESAs, except for patients who do not qualify for ESA treatment. As defined above, treatment failure on ESAs is defined as 1) failure or ceasing to show hematologic response after at least 8 weeks of 40,000 to 60,000 IU/week of erythropoietin (EPO) or equivalent or 2) low chance/response to ESA with endogenous serum EPO>500. For further details regarding

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inclusion of patients in phase II please see inclusion criteria (section 3.3.2). Randomization will be stratified by number of previous lines of MDS therapy (0, 1, >=2), where previous MDS therapy also includes previous ESA therapy (refer to Section 7.5). A total of 150 patients, 75 each arm, will be enrolled in Phase II.

In case there is no evidence of disease progression to high risk MDS or AML after 4 months of treatment (at EOC4), patients randomized to Arm B may cross-in and receive BI 836858 study drug at the discretion of the investigator, providing these patients fulfill all inclusion/exclusion criteria. Alternatively, these patients may continue on in the trial receiving BSC until PD or criteria for withdrawal are met (refer Section 3.3.4.1).

Patients who show clinical benefit, complete response (CR) or partial response (PR) after 4 cycles and who are tolerating the infusions well may continue to receive additional cycles any of the criteria for withdrawal as outlined in Section 3.3.4.1.

The overall treatment structure of the study is described in Figure 3.1: 2.

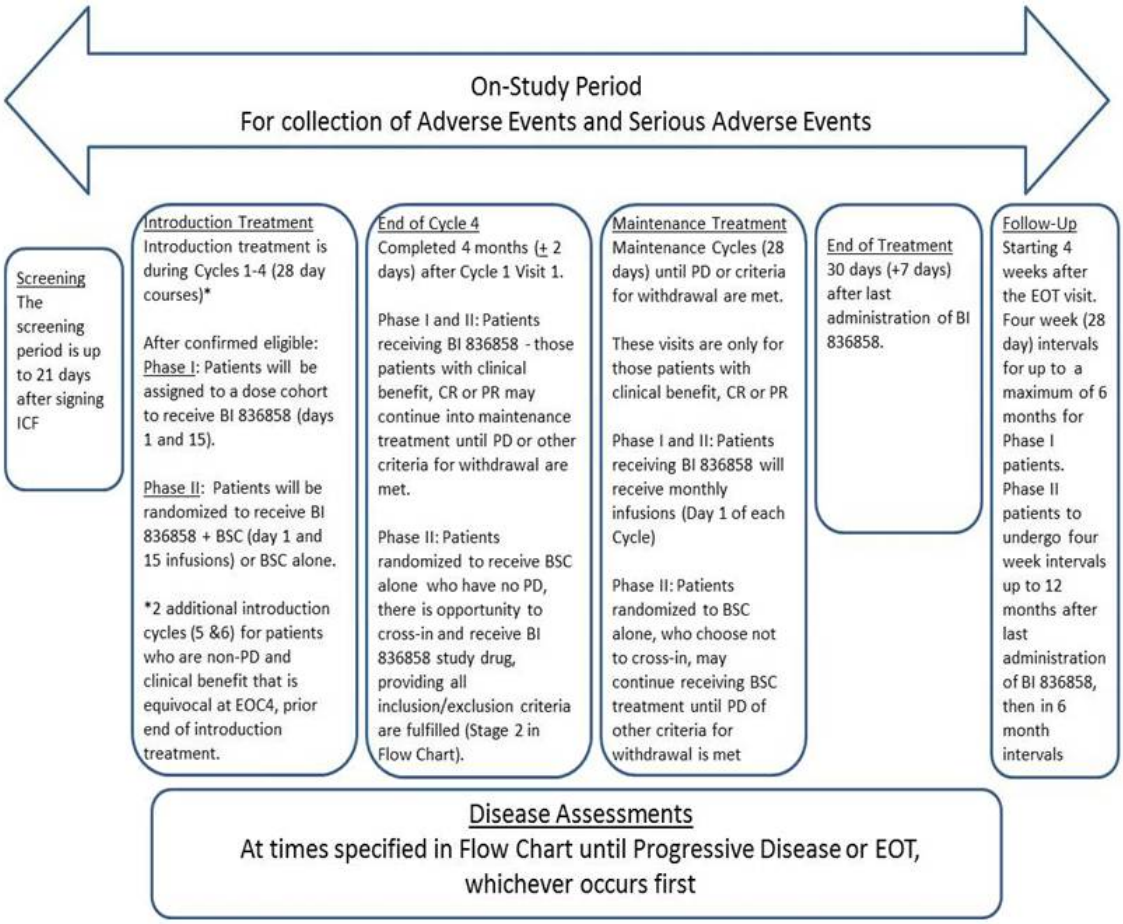

Figure 3.1: 2 Treatment Structure of the 1315.7 Phase I/II study

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3.1.1 Administrative structure of the trial

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

3.1.1.1 Phase I

Adult patients with low to intermediate-1 risk MDS, according to International Working Group (IWG) criteria, who experienced ESA treatment failure, except for patients that do not qualify for ESA treatment and are refractory to or are not amenable or eligible for approved MDS therapy, will be enrolled for the Phase I dose escalation part. After determination of the MTD/RP2D, the same group of patients as for the dose escalation will be enrolled in the first expansion cohort (referred to as "pre-treated" patients). The second expansion cohort will enroll patients with low or intermediate-1 risk MDS with symptomatic anemia, who experienced ESA treatment failure or do not qualify (serum erythropoietin level > 500 U) for ESA treatment and who have not received prior HMA and/or lenalidomide (referred to as "untreated" patients). Approximately three Phase I sites in the United States will participate in the dose escalation portion of Phase I. An additional 2-3 sites in the United States and/or European country(ies) are expected to participate during the cohort expansion portion of Phase I.

The Phase I dose-escalation will be guided by a Bayesian logistic regression model (BLRM) with overdose control (refer to Section 7). The DSB will consist of the Phase I investigators, Team Member Medicine (TMM), Trial Clinical Monitor (TCM), Project Statistician, Clinical Pharmacological Project Lead (CPPL) and TransMed Expert (TME). The information on the overdose risk will be presented by the trial statistician to the DSB. Additional information, such as lower grade adverse events, pharmacokinetics (PK), if available, progressive disease (PD), individual patient profiles and other relevant information will also be presented. Based on this information, the members of the DSB will reach a joint 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 DSB will also recommend the size for the next cohort. However, the final decision on the next cohort size will be made by a mutual decision between the TMM and the Coordinating Investigator (CI). Minutes of the DSB meetings and recommendations will be documented and archived by the TCM. Two expansion cohorts (untreated or pre-treated with HMA and/or lenalidomide) will recruit up to 12 patients per cohort and receive treatment at the RP2D prior to start of Phase II.

Prior to the initiation of Phase II, a Phase I safety analysis report will be prepared and the protocol will be amended based on Phase I results to update the benefit-risk assessment, stipulate the BI 836858 dose to be used in the Phase II part and define details of the patient population to be enrolled in phase II. A summary of safety and efficacy from the dose escalation cohorts and from the expansion cohorts and RP2D will be included in the Phase I safety analysis report. The Phase I safety analysis report and amended protocol will be made available for Health Authority and Ethics Committee/IRB review and approval (where

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applicable) and to all investigators who participate in Phase II. Phase II is not allowed by regulatory authority yet, and Phase II will not be started prior to regulatory approval as required in attending countries. Patients must not be recruited to Phase II until local Health Authority and ethics committee/IRB approvals (where applicable) are granted.

All safety laboratory analyses will be performed locally at each clinic site in the schedule outlined in the Flow Chart.

3.1.1.2 Phase II

Adult patients with low to intermediate-1 risk MDS, who received no prior treatment or progressed/become resistant after ESA and/or approved MDS drugs, such as HMAs will be included in the Phase II. Approximately 20 sites from United States and select European countries will participate in the Phase II.

During this phase, using Interactive Response Technologies (IRT), patients will be randomized in a 1:1 ratio either to arm A (BI 836858 plus BSC) or arm B (BSC alone, per Investigator's choice) to compare the efficacy of BI 836858 to investigator's choice for the treatment of patients with MDS. An internal Data Monitoring Committee (DMC) will be implemented for the Phase II of this trial.

All safety laboratory analyses will be performed by local labs per the schedule outlined in the Flow Chart.

3.2 DISCUSSION OF TRIAL DESIGN, INCLUDING THE CHOICE OF CONTROL GROUP(S)

The Phase I is designed to determine the dose of BI 836858 monotherapy in patients with low to intermediate-1 MDS with symptomatic anemia. The study will be conducted in an open label, single arm dose escalation trial design. Dose escalation and cohort size will be determined based on the recommendation by the DSB, according to a Bayesian Model with overdose control. An escalation with overdose control design will increase a chance of treating patients at efficacious doses while reducing the risk of overdosing. This design is based on practical experience and is a preferable algorithmic method due to its superior ability to identify the dose with the 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). Expansion cohorts will enroll at the RP2D defined during the dose escalation portion of Phase I.

The Phase II of the trial will be conducted as a randomized, open label trial. Patients will be randomized in a 1:1 ratio either to Arm A (BI 836858 + BSC) or Arm B (BSC alone, per Investigator's choice). Due to the fact that the study drug is given via i.v., and that placebo infusions are ethically not acceptable in this context, the trial is performed open-label. Treatment Arm B with BSC will be determined per Investigator's current Standard of Care (SOC) practice.

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Single intra-patient dose escalation will be permitted. See Section 4.1.4 for details**.** Each patient will be monitored closely for infusion-related reactions, as this is a potential side-effect for monoclonal antibodies (mAb).

Safety will be performed at all visits during treatment.

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

3.3 SELECTION OF TRIAL POPULATION

Phase I will enter approximately 50 patients from approximately 3-7 sites in the United States and/or European country(ies). In the Phase I dose escalation part, the trial will recruit patients with lower risk MDS who were either previously untreated or progressed/became resistant following ESA treatment. After determination of the MTD/RP2D, the same group of patients as for the dose escalation will be enrolled in the first expansion cohort. The second expansion cohort will enroll patients with low or intermediate-1 risk MDS with symptomatic anemia, who experienced ESA treatment failure or do not qualify for ESA treatment and who have not received prior HMA and/or lenalidomide.

Phase II will enter approximately 150 patients. Approximately 20 sites from United States and European countries are expected to participate in Phase II.

A log of all patients who signed the informed consent will be maintained in the Investigator Site File (ISF) at the investigational site irrespective of treatment assignment.

3.3.1 Main diagnosis for study entry

Patients with documented diagnosis of MDS according to World Health Organization (WHO) criteria that meets International Prognostic Scoring System (IPSS) classification of low or intermediate-1 risk disease will be eligible for this trial.

3.3.2 Inclusion criteria

1. Documented diagnosis of MDS according to World Health Organization (WHO) criteria that meets International Prognostic Scoring System (IPSS) classification of low or intermediate-1 risk disease at screening as determined by microscopic and standard cytogenetic analyses of the bone marrow and peripheral complete blood count (CBC).
    - Phase I dose escalation: patients who experienced ESA treatment failure or do not qualify (serum erythropoietin level > 500 U) for ESA treatment, and are refractory to or not amenable or eligible for established MDS therapy (HMA, lenalidomide)

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- Phase I expansion:
  - *Expansion cohort 1* ("pre-treated"): patients who experienced ESA treatment failure or do not qualify (serum erythropoietin level > 500 U) for ESA treatment and are refractory to established MDS therapy (HMA and /or lenalidomide)
  - *Expansion cohort 2* ("untreated"): patients who experienced ESA treatment failure or do not qualify (serum erythropoietin level > 500 U) for ESA treatment and who have not received prior HMA and/or lenalidomide (because not amenable or eligible for these treatments)
- Phase II: patients who experienced ESA treatment failure or do not qualify (serum erythropoietin level > 500 U) for ESA treatment. For definition of further details of the phase II patients to be included the protocol will be amended based on Phase I results.

2. Patient has the evidence of symptomatic anemia according to the following criteria:
   - Phase I only: patients must have mean hemoglobin concentration < 10.0 g/dL of 2 measurements (not influenced by RBC transfusion within 7 days of measurement) and having received < 4 units of RBCs within 8 weeks prior to start of treatment OR,
   - Phase I/II: Patients must have received ≥ 2 units of RBCs for hemoglobin ≤ 9.0 g/dL within 8 weeks prior to start of treatment.
3. Patient is non-responsive to, refractory to, or intolerant of ESAs, or ESAs are contraindicated or unavailable, or a documented serum erythropoietin level of > 500 U/L.
4. Eastern Cooperative Oncology Group (ECOG) Performance Status ≤2 (refer to Section 10.2) (R14-0080).
5. Age ≥ 18 years.
6. Written informed consent which is consistent with International Conference on Harmonization – Good Clinical Practice (ICH-GCP) guidelines and local legislation.

3.3.3 Exclusion criteria

1. Patient with IPSS category of Int-2 or high-risk MDS.
2. Phase II only: Patients with a deletion 5q cytogenetic abnormality.
3. Treatment within 28 days prior to Cycle 1 Day 1 with: i) long acting erythropoiesis stimulating agents, ii) long acting Granulocyte colony-stimulating factor (G-CSF), iii) granulocyte- macrophage colony stimulating factor (GM-CSF), iv) 5-aza, lenalidomide or decitabine, or v) iron chelation and within 14 days prior to Cycle 1 Day 1 with short acting erythropoiesis stimulating agents and short acting G-CSF.
4. Patient previously received allogeneic bone marrow or stem cell transplantation.
5. Second malignancy currently requiring active therapy (except for hormonal/anti-hormonal treatment, e.g. in prostate or breast cancer).
6. Neutrophils <1000 /µL (1.0 x 109/L).

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7. Aspartate amino transferase (AST) or alanine amino transferase (ALT) > 2.5 times the upper limit of normal (ULN).
8. Bilirubin >1.5 mg/dL, except for Gilbert's Syndrome or hemolysis.
9. Serum creatinine >2.0 mg/dL.
10. Known human immunodeficiency virus (HIV) infection and/or active hepatitis B infection (defined as presence of Hep B DNA), active hepatitis C infection (defined as presence of Hep C RNA)
11. Presence of concomitant intercurrent illness, or any condition which in the opinion of the Investigator, would compromise safe participation in the study, e.g. active severe infection, unstable angina pectoris, new onset of exacerbation of a cardiac arrhythmia.
12. Psychiatric illness or social situation which in the opinion of the Investigator would limit compliance with trial requirements.
13. Patient receiving concomitant therapy, which in the opinion of the Investigator is considered relevant for the evaluation of the efficacy or safety of the trial drug (refer to **Section 4.2.2**).
14. Female patients of childbearing potential who are sexually active and unwilling to use a medically acceptable method of contraception during the trial and for 6 months after the last administration of BI 836858, i.e. combination of two forms of effective contraception (defined as hormonal contraception, intrauterine device, transdermal patch, implantable or injectable contraceptive, bilateral tubal ligation etc.).
    - Women of childbearing potential are defined as females who:
    - Have experienced menarche and
    - Are not postmenopausal (12 months with no menses without an alternative medical cause) and
    - Are not permanently sterilized (e.g. hysterectomy, bilateral oophorectomy or bilateral salpingectomy
15. Male patients with partners of childbearing potential who are unwilling to use condoms in combination with a second effective method of contraception (defined as hormonal contraception, intrauterine device, condom with spermicide, etc.) during the trial and for 6 months after the last administration of BI 836858.
16. Pregnant or nursing female patients.
17. Treatment with another investigational agent under the following conditions:
    - Within two weeks (4 weeks for biologics) of first administration of BI 836858, or if the half-life of the previous product is known, within 5 times the half-life, whichever is longer.
    - Patient has persistent toxicities from prior MDS therapies which are determined to be relevant by the Investigator.
    - Concomitant treatment with another investigational agent while participating in this trial.

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18. Chronic use, as defined by > 2 weeks of a corticosteroid agent that is ≥ 20 mg/day of prednisone or its equivalent, within 4 weeks prior to first administration of BI 836858.
19. Treatment with an immunomodulatory agent within 4 weeks prior to first administration of BI 836858.
20. Patient received prior treatment with a CD33 antibody.
21. In the opinion of the Investigator patient is unable or unwilling to comply with the protocol.

3.3.4 Removal of patients from therapy or assessments

3.3.4.1 Removal of individual patients

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

- The patient withdraws consent. Patients are free to discontinue their participation in this trial at any time without providing a reason to withdraw trial treatment.
- The patient requires prohibited treatment as specified in Section 4.2.2 or concomitant drugs which in the opinion of the investigator may interfere with the investigational product.
- Delay in start of subsequent treatment cycle of more than 8 weeks due to a drug-related event (e.g. delay in recovery of blood counts). Refer to section 4.1.4.
- The patient is no longer able to participate for other medical reasons (e.g. adverse events unrelated to therapy or disease progression, concomitant diagnoses, pregnancy, surgery or administrative reasons). The Investigator may also stop a patient's participation if the patient is no longer able to complete trial visits or trial-required procedures.

A patient can be withdrawn from the trial after discussion between the Investigator and the Sponsor if eligibility criteria are violated and/or the patient fails to comply with the protocol.

All withdrawals will be documented and the reason for withdrawal recorded and discussed, as necessary, in the final report of the trial. If a patient is withdrawn from the trial treatment, the end of active treatment (EOT) visit will be performed. All patients who discontinue active treatment will continue and complete follow-up visits, after the EOT visit. Every effort should be made to follow-up with patients in case an adverse event (AE) is still ongoing at the time of withdrawal. If a patient is withdrawn from the trial due to consent withdrawal, no further visits will be completed.

A patient has to discontinue trial drug administration in case:

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

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Patients who have not completed at least 2 administrations (1 cycle) of BI 836858 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 2 administrations (1 cycle) of BI 836858 for reasons other than BI 836858 related toxicity will be replaced.

3.3.4.2 Discontinuation of the trial by the sponsor

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

1. Failure to meet expected enrolment goals overall or at a particular trial site,
2. Emergence of any efficacy/safety information that could significantly affect continuation of the trial, or
3. Violation of GCP, the Clinical Trial Protocol (CTP), or the contract by a trial site or investigator, disturbing the appropriate conduct of the trial.
4. The investigator / the trial site will be reimbursed for reasonable expenses incurred in case of trial termination (except in case of the third reason).

Recruitment in this trial was discontinued prematurely during the Phase I expansion cohort.

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4. TREATMENTS

4.1 TREATMENTS TO BE ADMINISTERED

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

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

4.1.1 Identity of BI investigational product and comparator product(s)

The characteristics of the test product are below.

- Substance (INN): BI 836858
- Pharmaceutical form: Concentrate for solution for infusion
- Source: Boehringer Ingelheim Pharma GmbH & Co. KG
- Unit strength: 10 mg/mL (vials with 10mL)
- Daily dose: See Section 4.1.3
- Duration of use: Single administration every 14 days
- Route of administration: Intravenous
- Posology: Rate controlled infusion
  (Volume: 250 mL)

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

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4.1.2 Method of assigning patients to treatment groups

In Phase I of the trial, patients will be assigned into escalating dose cohorts and Phase I Expansion cohorts using IRT. After determination of the MTD/RP2D, Phase I safety analysis report and protocol amendment (see section 3.1.1.1), Phase II enrollment will be initiated.

In Phase II of the trial, utilizing IRT, patients will be randomized to a 1:1 ratio of either BI 836858 plus BSC or BSC alone. When a patient qualifies for the trial, randomization should be performed just prior to Cycle 1 Day 1, or as close to the first treatment dose as possible. It may be performed on the day of the first administration prior to patient treatment, but no later than 21 days after patient signs informed consent.

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

4.1.3 Selection of doses in the trial

The starting dose for this trial will be the confirmed safe dose tested in the FIH study of BI 836858 which is an anticipated fixed dose of 20mg of BI 836858.

A fixed dose regimen was chosen as opposed to the dose adjusted by Body Surface Area based on a recent publication by Wang et al. The individual and population performance of body size-based and fixed dosing in adults were compared for 12 oncology approved mAbs (R10-6267). Although both dose regimens demonstrated similar performance, the fixed dose was recommended since it offered advantages in the ease of dose preparation and a lower chance of dosing errors.

Phase I:
The dose is planned to be escalated in cohorts at pre-defined dose levels based on a maximum escalation of 100%. The provisional dose levels are 20mg, 40mg, 80mg, 160mg, and 320mg. Intermediate or lower dose levels, depending on the number of DLTs observed in the study, may be investigated if agreed upon between Investigator and Sponsor.

For any dose-escalation cohort, at least 3 patients will be required, but two out of those patients must be evaluable patients to escalate dose in next cohort. The DSB will also recommend the size for the next cohort between three to six patients. However, the final decision on the next cohort size will be made by a mutual decision between the TMM and the Coordinating Investigator (CI). After all patients in a cohort have either experienced a DLT or have been observed for at least one cycle (28 days – 2 administrations) without experiencing a DLT, the BLRM will be updated with the newly accumulated data and the overdose risk will be calculated. Based on the model and on additional information (PK, PD patient profiles), the members of the DSB will reach a joint decision on the next dose level to be investigated.

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During the cohort dose escalation phase, entry into the initial 20mg dose cohort will be allowed after a minimum of 7 days from the first administration of the first patient, and subsequently between patient 2 and 3. If the cohort expands to 6 patients, the 7-day observation period between the subsequent patients must be followed. For subsequent cohorts, enrollment will be allowed after a minimum of 3 days from the first administration of each patient.

Enrollment into the next dose cohort is allowed after the previous dose cohort is found to be safe for all patients in this cohort (e.g. at least 28 days after the first administration of drug in the last patient entered into the cohort). For the purposes of determining dose escalation, Dose Limiting Toxicities will be assessed based on safety data from Cycle 1 (2 administrations – 28 Days), however DLTs will be monitored beyond Cycle 1 and throughout the trial.

If no DLT is observed at a dose that efficacy is considered sufficient, the DSB may decide to include additional number of patients at the same dose level and to declare this dose level as the RP2D. Before the conclusion of Phase I and prior to initiating the Phase II, two expansion cohorts (untreated or pre-treated with HMA and/or lenalidomide) will recruit up to 12 patients per cohort (overall a minimum of 12 patients – inclusive of the last dose escalation cohort) and receive treatment at RP2D. In the expansion cohorts new patients may be enrolled at any time without observation period.

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

Cohort	Day first patient in cohort receives infusion	Earliest day next patient can be entered
Initial 20 mg	Day 1	Day 8
All other dose levels in cohort dose escalation	Day 1	Day 3
RP2D Expansion cohorts	Day 1	Any time

A one-week observation period must be followed between the first administration of BI 836858 and the start of treatment of the subsequent patient for all patients in the 20 mg cohort.

Phase II:

Patients will be randomized in a 1:1 ratio either to Arm A, to be treated at the RP2D of BI 836858 plus BSC or Arm B, BSC alone, per Investigator's choice. Patients can be enrolled at any time during this trial without observation period.

Patients randomized to Arm B (BSC alone) have the opportunity to cross-in to receive BI 836858 study drug after 4 months of treatment (EOC4) have elapsed since Cycle 1 Visit 1, following a disease assessment confirmation at this visit, if patients have not progressed to high-risk MDS or AML. At the time-point of cross-in patients must meet all

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inclusion/exclusion criteria, which includes stopping of any ESA and/or iron chelation therapies.

4.1.4 Drug assignment and administration of doses for each patient

Prior to inclusion of a new patient during the cohort dose escalation phase, the Investigator has to confirm the actual dose tier of BI 836858 for the patient with the Sponsor who oversees the cohort dose escalation steps and the safety data of patients from all trial sites. BI 836858 will be administered as an intravenous infusion every 14 days under the supervision of the Investigator or designated personnel.

BI 836858 may be administered at any time during the day.

it is recommended to start the infusion during the morning hours.

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

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

If BI 836858 has been well tolerated without signs of infusion-related reactions in the first administration, glucocorticoid premedication may be reduced to a dose equivalent to 50 mg prednisolone for the second through fourth administrations, and in case this is well tolerated reduce the glucocorticoid with the 5th infusion (25 mg with the 5^{th} and 0 mg with the 6^{th} infusion.) However, in case an administration of BI 836858 was not well tolerated the premedication with prednisolone can be re-escalated up to 100 mg.

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

(1) Neutrophils ≥1000 /µL (1.0×10^9/L)

(2) Platelets ≥50,000 /µL (50×10^9/L), unless CTCAE Grade 3 or 4 thrombocytopenia was preexistent prior to trial entry. Patients who go from Grade 3 to Grade 4 thrombocytopenia after treatment may continue on study provided that post-transfusion platelet count is at least 20,000/uL before therapy is given.

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

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In case criterion 1 and 2 are not fulfilled, blood counts and/or the adverse event should be re-evaluated for up to three weeks and documented in the eCRF. In case of a treatment delay, the Sponsor must be notified.

Administration of the trial drug has to be stopped temporarily in case of a DLT (see Section 5.2.1.1). Patients may continue therapy only after recovery from the DLT to a CTCAE level which allows further therapy based on Investigator assessment and only with a reduced dose of BI 836858. The new dose of BI 836858 must be finally agreed on between the Sponsor and the Investigator. The reduced dose will be valid for all following treatment cycles in the individual patient. A reduction of the dose will be allowed only once for an individual patient during the whole trial. In case a patient experiences a second episode of DLT with the reduced BI 836858 dose, the treatment has to be permanently discontinued. Likewise, treatment has to be discontinued in case the DLT is not reversible. Patients who discontinue treatment will complete an End of Trial Visit and follow-up visits.

Intra-patient dose escalation may be considered after agreement between investigator and sponsor for selected patients. It is restricted to patients who have completed and received a minimum of 8 administrations of BI 836858 and tolerate the treatment well at the time of dose escalation. Intra-patient dose escalation can only be performed at a time when the next higher dose cohort has been reviewed and considered safe by the DSB. The dose escalation step is limited to the dose which has been administered to the next higher cohort. Only one dose escalation will be permitted for a patient. Dose escalations can only occur on Day 1, or Visit 1 of a cycle. After the first dose at the higher dose level, patients have to be monitored for at least 24 hours after the end of the infusion, including a safety laboratory 24 hours after the first administration of the escalated dose of BI 836858. Patients who have escalated to a higher dose and who experience toxicities may be permitted to reduce back to a lower dose, following the criteria described above. A log of all patients pre-screened and enrolled into the study (i.e. having given informed consent) will be maintained in the Investigator Site File (ISF) at the investigational site irrespective of whether they have been treated with investigational drug or not.

4.1.5 Blinding and procedures for unblinding

4.1.5.1 Blinding

The trial will be conducted in an open-label. Blinding is not applicable. However, to reduce bias, the BI study team will be blinded from the aggregated Phase II data at the treatment level until the primary analysis for Phase II.

4.1.5.2 Procedures for emergency unblinding

Not applicable.

4.1.6 Packaging, labelling, and re-supply

BI 836858 will be supplied in 10 mL vials containing 100 mg BI 836858. For details of packaging and the description of the label, refer to the ISF. Medication will be delivered to

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the Investigator's pharmacy where the total dose per patient will be prepared upon request from the Investigator.

For preparation of BI 836858 infusion solution, the content of the vial of BI 836858 will be diluted in 0.9% sodium chloride. The content of several vials may be needed for administration of the requested dose. For further details, please refer to the instructions included in the ISF. The full volume of the diluted compound will be 250 ml.

4.1.7 Storage conditions

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

4.1.8 Drug accountability

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

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

- approval of the study protocol by the Institutional Review Board (IRB) / Independent Ethics Committee (IEC),
- availability of a signed and dated clinical trial contract between the sponsor and the Head of Trial Center,
- approval/notification of the regulatory authority, e.g. competent authority,
- availability of the curriculum vitae of the principal Investigator,
- availability of a signed and dated CTP or immediately imminent signing of the CTP,
- availability of the proof of a medical licence for the principal investigator,
- availability of the FDA Form 1572 if applicable.

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

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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 (G-CSF) will be allowed (other than ESAs), but growth factors should be avoided during the first four administrations (2 cycles) for better assessment of safety and response parameters. G-CSF should not be given prophylactically.

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

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

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

After implementation of CTP version 5.0 collection of Concomitant Therapy information only if the indication is treatment of an (S)AE.

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

Patients must not be receiving any concurrent treatment for MDS while on study. Exceptions will be made for supportive therapies such as transfusions or use of growth factors. The use of colony stimulating factor (G-CSF) will be allowed (other than ESAs), but growth factors should be avoided during the first four administrations (2 cycles) of BI 836858 for better assessment of safety and response parameters. G-CSF should not be given prophylactically.

Iron chelation therapy are permitted to those Phase II patients randomized to BSC only, however these treatments are not allowed for patients receiving BI 836858 in this study.

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.

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4.2.2.2 Restrictions on diet and life style

No restrictions apply with regard to diet, water intake or life style.

4.3 TREATMENT COMPLIANCE

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

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5. VARIABLES AND THEIR ASSESSMENT

5.1 EFFICACY – PHARMACODYNAMICS

5.1.1 Endpoints of efficacy

The efficacy endpoints will be assessed at the time points specified in the Flow Chart.

For definition of response criteria please refer to Section 5.1.2.3.

Primary Endpoint: (Phase II)

- RBC Transfusion Independency

Secondary endpoints: (Phase I)

- RBC Transfusion Independency

Secondary endpoints: (Phase I and II)

- Hematologic improvement neutrophils (HI-N)
- Hematologic improvement platelets (HI-P)
- Hematologic improvement erythroid (HI-E)
- Time to HI-E response
- Mean hemoglobin increase ≥ 1.5 g/dL
- Duration of Response (RBC Transfusion Independency, HI-N, HI-P, HI-E or Objective Response)
- Overall Objective Response (OR) [Complete Response (CR), Partial Response (PR), and Hematologic Improvement (HI)]

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5.1.2 Assessment of efficacy

5.1.2.1 Bone marrow aspirate and peripheral blood

Response will be assessed in bone marrow (BM), peripheral blood and clinically as specified in the Flow Chart.

The investigator's overall assessment of the disease and confirmation of non-PD/non-relapse status will be required for the decision to continue with the next cycle of study treatment.

At baseline a BM aspirate is required. A BM biopsy will be required if aspiration is inadequate. During response assessment after treatment initiation, a BM aspirate will be sufficient and no BM biopsy will be required unless the aspirate results in a *punctio sicca* (dry tap) in which case a BM biopsy will be performed. The first scheduled bone marrow sample for response assessment will be performed at the end of Cycle 4. The BM aspirate (or biopsy if aspirate is inadequate) will be scheduled for response assessment at the EOC4 and at the time of disease progression/relapse or EOT, whichever occurs first. The classification of response is defined in Section 5.1.2.3.

An unscheduled BM examination should be performed as soon as possible when progression or relapse of MDS is suspected (based on clinical or laboratory findings) irrespective of the next scheduled BM assessment.

5.1.2.3 Assessment and definition of response criteria

Response to treatment will be evaluated according to the International Working Group (IWG) 2006 criteria (R13-0369). The evaluation period for transfusion independence and response will last from randomization (for phase II / first administration for phase I) until discontinuation of treatment.

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Transfusion independence (TI)

- Red blood cell (RBC) transfusion independence and platelet transfusion independence will be evaluated in patients who are transfusion dependent at baseline. Percentages will be calculated using all treated patients as the denominator.
- A patient is considered transfusion independent at baseline if the patient has had no transfusions during the 56 days prior to and including the first day of treatment. Otherwise, the patient is considered to be transfusion dependent.
- A patient is considered transfusion independent if the patient has had no transfusions over the course of ≥ 56 consecutive days.

Hematologic improvement (HI)

The HI will be evaluated in patients with abnormal pretreatment values defined as follows:

- Erythroid response (HI-E): Patients with a pretreatment hemoglobin <11 g/dL demonstrate erythroid response if their hemoglobin increases by ≥1.5 g/dL for at least eight weeks, and there is a reduction in the units of red cell transfusions by an absolute number of at least four red cell transfusions per eight weeks compared with the pretreatment transfusion number in the previous eight weeks. Only red cell transfusions given for a hemoglobin ≤9 g/dL pretreatment will count in the red cell transfusion response evaluation.
- Platelet response (HI-P) — Patients with a pretreatment platelet count <100 x 10^9/L demonstrate a platelet response if there is an absolute platelet increase of ≥30 x 10^9/L for patients starting with >20 x 10^9/L platelets. For those with an increase from 10 x 10^9/L to >20 x 10^9/L must have an increase of at least 100 percent.
- Neutrophil response (HI-N) — Patients with a pretreatment neutrophil count <1 x 10^9/L demonstrate a neutrophil response if they have an at least 100 percent increase and an absolute increase >0.5 x 10^9/L.
- Mean hemoglobin increase ≥ 1.5 g/dL — Time Frame: Up to approximately 48 weeks. Proportion of subjects achieving hemoglobin (Hgb) increase from baseline ≥ 1.5 g/dL over any consecutive 56-day period in absence of Red blood cell (RBC) transfusions.

Duration of Response

- Response duration analysis is defined only for patients who achieve CR or mCR or RBC Transfusion Independency and is measured from the first date of achieving a response 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, response 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.

Complete Response (CR)

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- Bone marrow: ≤5 % blasts with normal maturation of all cell lines*
- Persistent dysplasia will be noted*
- Peripheral blood:
    - Hgb ≥ 11 g/dL
    - Platelets >100 x 10^9/L
    - Neutrophils > 1.0 x 10^9/L
    - Blasts 0 %

*Dysplastic changes should consider the normal range of dysplastic changes

Partial Response (PR)

- All CR criteria if abnormal before treatment except:
    - Bone marrow blasts decreased by ≥50 % to pre-treatment but still >5 %
    - Cellularity and morphology not relevant

Marrow Complete Response (mCR)

- Bone marrow: ≤ 5 % blasts and decrease by ≥50 % over pretreatment
- Peripheral blood: if HI responses, they will be noted in addition to marrow CR

Stable Disease (SD)

- Failure to achieve at least PR, but no evidence of progression for >8 weeks

Relapse after CR or PR

- At least 1 of the following:
    - Return to pre-treatment bone marrow blast percentage
    - Decrement of ≥50 % from maximum remission/response levels in granulocytes or platelets
    - Reduction in Hgb concentration by ≥ 1.5 g/dL or transfusion dependence after a period of RBC transfusion independence

Progressive disease (PD)

- Patient with less than 5 % blasts: ≥ 50 % increase in blasts to > 5 % blasts
- Patient with 5 %-10 % blasts: ≥50 % increase to > 10 % blasts
- Patient with 10 %-20 % blasts: ≥ 50 % increase to >20 % blasts
- Patients who meet any of the following criteria:
    - At least 50 % decrement from maximum remission/response in granulocytes or platelets;

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- Reduction in Hgb by ≥2 g/dL;
- Transfusion dependence after a period of RBC transfusion independency; or

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5.2 SAFETY

Recruitment in this trial was discontinued prematurely during the Phase I expansion cohort. With the aim to minimize the burden for trial participants, after approval of CTP version 5.0, the mandatory protocol procedures described below in sections 5.2.2 Assessment of adverse events, 5.2.3 Assessment of safety laboratory parameters 5.2.4, Electrocardiogram, 5.2.5 Assessment of other safety parameters, and 5.3.1 Physical Examinations are reduced for all patients who continue to receive trial medication in treatment cycles ≥5. 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 section 5.2.2, which remains unchanged).

5.2.1 Endpoint(s) of safety

Primary Endpoints: (Phase I)

- Maximum Tolerated Dose (MTD)
- Occurrence of Dose Limiting Toxicity (DLT)

Other Endpoints: (Phase I and II)

- Incidence and intensity of treatment related adverse events according to CTCAE Version 4.0 (R09-2850)

The primary objective of the Phase I part is to assess the safety of the drug in humans and to determine the MTD of BI 836858. For details on determination of MTD, please refer to sections 3.1, 5.2.1.2 and 7.3.1.

The safety of BI 836858 in the Phase I and II will be assessed by a descriptive analysis of incidence and intensity of adverse events graded according to CTCAE (version 4.0), the incidence of non disease-related adverse events qualifying for dose limiting toxicity (DLT), laboratory data and results of physical examination.

5.2.1.1 Dose limiting toxicity (DLT)

The Dose Limiting Toxicity is defined as follows:

- Grade ≥ 3, according to CTCAE version 4.0, non disease-related**,** non-hematologic adverse events, with the following exceptions:
  - Any laboratory abnormality, which is not considered clinically significant by the investigator or resolves spontaneously or can be recovered with appropriate treatment within 5 days

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  - For patients with neutrophils <500 /µL (0.5 x 10^9/L) at start of treatment febrile neutropenia with neutrophils <500 /µL (0.5 x 10^9/L) or infection with neutrophils <500 /µL (0.5 x 10^9/L) will not constitute a DLT if they can be recovered with appropriate treatment within 14 days.

- Inability to deliver the full dose of the study drug according to the assigned dose level within cycle 1 due to drug-related adverse events.

- Absence of hematological recovery as following:

  - Neutrophils: Grade 4 (if Grade 0/1 at baseline) OR < 100 /µL (0.1 x 10^9/L) and decrease of > 75% from baseline (if Grade ≥ 2 at baseline) for > 7 days

  - Platelets: Grade 4 (if Grade 0/1 at baseline) OR < 10000/µL (10 × 10^9/L) for > 7 days and decrease of > 75% from baseline (if Grade ≥ 2 at baseline)

- Treatment delay of ≥ 4 weeks of the start of Cycle 2

  - If Cycle 2 is not started until 57th day from Day 1 of Cycle 1 as a result of drug related AE, it is considered as DLT.

Infusion-related reactions associated with the administration of BI 836858 will not be regarded as a DLT. The exception is anaphylaxis which occurs despite premedication with glucocorticoid or which does not resolve with glucocorticoid.

5.2.1.2 Maximum Tolerated Dose (MTD)

The MTD may be considered reached if the probability that the true DLT rate in the target interval (16%-33%) is sufficiently large. For detailed definition see Section 7.1.

The DSB 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 DSB may decide to include additional number of patients at this dose level and to declare this dose as the MTD and RP2D.

5.2.1.3 Recommended Phase 2 Dose (RP2D)

Before the conclusion of Phase I and prior to initiating the Phase II, two expansion cohorts (untreated or pre-treated with HMA and/or lenalidomide) will recruit up to 12 patients per cohort (overall minimum of 12 patients – inclusive of the last dose escalation cohort) and receive treatment at RP2D.

Based on the Phase I data, the DSB will make a final determination of the RP2D, which must not exceed the MTD. The Phase I safety analysis report, including the rationale of RP2D determination will be prepared prior to the initiation of Phase II as described in detail in 3.1.1.1.

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5.2.2 Assessment of adverse events

5.2.2.1 Definitions of adverse events

Adverse event

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

Serious adverse event

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

Intensity of adverse event

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

Causal relationship of adverse event

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

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

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

Worsening of the underlying disease or other pre-existing conditions

Worsening of the underlying disease or of other pre-existing conditions will be recorded as an (S)AE in the eCRF.

Changes in vital signs, ECG, physical examination, and laboratory test results

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Changes in vital signs, ECG, physical examination and laboratory test results will be recorded as an (S)AE in the eCRF , if they are judged clinically relevant by the investigator.

Protocol-specified Adverse Events of Special Interest (AESI)

The following are considered as Protocol-specified Adverse Events of Special Interest:

- Infusion-related reactions (CTCAE grade 3 or higher)
- Any event that qualifies for a dose limiting toxicity (refer to Section 5.2.1.1)
- Drug Induced Liver Injury (DILI)

  Hepatic injury defined by the following alterations of liver parameters:

  - For patients with normal liver function (ALT, AST and bilirubin within normal limits) at baseline 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.
    - Patients showing these lab abnormalities need to be followed up according to Section 10.1.2 of this clinical trial protocol (CTP) and the "DILI checklist" provided in the ISF.

  - For patients with impaired liver function at baseline an elevation of AST and/or ALT ≥5 fold ULN combined with an elevation of total bilirubin≥2 fold ULN measured in the same blood draw sample.
    - Patients showing these lab abnormalities need to be followed up according to Section 10.1.2 of this clinical trial protocol and the “DILI checklist” provided in ISF.

AESI are to be reported in an expedited manner similar to Serious Adverse Events (within 24 hours), even if they do not meet any of the seriousness criteria - for details please see Section 5.2.2.2.

5.2.2.2 Adverse event and serious adverse event reporting

All adverse events, serious and non-serious, occurring during the course of the clinical trial (i.e., from signing the informed consent onwards through the residual effect period (REP) (30 days after the last drug administration, Table 5.2.2.2: 1)) will be collected, documented and reported to the sponsor by the investigator on the appropriate CRF(s) / eCRFs / SAE reporting forms. Reporting will be done according to the specific definitions and instructions detailed in the ‘Adverse Event Reporting’ section of the Investigator Site File.

For each adverse event, the investigator will provide the onset date, end date, intensity/CTCAE grade (according to CTCAE, version 4.0, R09-2850), treatment required, outcome, seriousness, and action taken with the investigational drug or BSC treatment(s). The investigator will determine the relationship of the investigational drug to all AEs as defined in Section 5.2.2.1.

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The Residual Effect Period (REP) for BI 836858 is 30 days. Therefore all events reported within 30 days after the last trial medication will be considered on drug. All adverse events will be reported up until the last per protocol visit (EOT) which is 30 days after the last dose of trial medication. The investigator does not need to actively monitor patients for adverse events once the clinical trial has ended. However, if the investigator becomes aware of an SAE(s) that occurred after the patient has completed the clinical trial (including any protocol required REP and / or follow-up), it should be reported by the investigator to the sponsor if considered relevant by the investigator.

Table 5.2.2.2: 1 AE/SAE reporting requirements

Time Period	Reporting Requirements
From signature of informed consent until 30 days after last administration of study drug	Report all AEs, SAEs regardless of relatedness. This includes all events leading to death.
Post treatment (>30 days after last administration of study drug) until end of follow-up	Report AEs and SAEs which are considered related to study drug, study design / procedures or if considered relevant by the investigator. Please note: The event(s) leading to death (other than progressive disease) should always be reported as SAE in this trial
During and after post treatment (after the patient has completed the clinical trial)	If the investigator becomes aware of an SAE(s) it should be reported by the investigator to the sponsor if considered relevant by the investigator

The investigator must report the following events if using paper process SAE form via fax immediately (within 24 hours) to the sponsor: SAEs and non-serious AEs relevant to the SAE(s), and AESI.

BI has set up a list of AEs which are defined to be always serious. In order to support the investigator with the identification of these “always serious adverse events”, if a non-serious AE is identified to be serious per BI definition, a query will be raised. The investigator must verify the description and seriousness of the event. If the event description is correct, the item “serious” needs to be ticked and an SAE has to be reported in expedited fashion following the same procedure as above. The list of these adverse events can be found via the RDC-system.

The SAE form is to be forwarded to the defined unique entry point identified for the BI OPU (country-specific contact details will be provided in the Investigator Site File). This immediate report is required irrespective of whether the investigational product has been administered or not and irrespective of causal relationship. It also applies if new information to existing SAEs or AESIs becomes available.

Exemption to SAE Reporting

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Disease progression/relapse of the underlying condition is a study endpoint for analysis of efficacy. Disease progression/relapse is exempted from reporting as a (S)AE. Progression/relapse of the subject's underlying condition will be recorded in the appropriate pages of the (e)CRF as part of efficacy data collection. Death due to disease progression/relapse is to be recorded on the appropriate (e)CRF page and not on a SAE form.

Examples of exempted events of disease progression/relapse are:

- Progression/relapse of underlying condition (Progressive disease PD): if PD is clearly consistent with the suspected progression as defined by the respective response criteria.
- Hospitalization/Procedures due solely to the progression/relapse of underlying condition Clinical symptoms and/or signs of progression/relapse (with or without confirmation by objective criteria), if the symptom can exclusively be determined to be due to the progression/relapse of the underlying condition and meets the expected pattern of progression/relapse for the disease under study.

If the observed event is not unequivocally due to progression/relapse of the underlying condition and there is a reasonable possibility for a causal relationship to administration of study medication, the event must be reported as (S)AE on both the SAE form and the (e)CRF.

Exempted events are collected and tracked following the protocol-specified monitoring plan. Exempted events are monitored at appropriate intervals preferably by an independent committee such as a Data Monitoring Committee.

Pregnancy

In rare cases, pregnancy might occur in clinical trials. Once a female subject has been enrolled into the clinical trial, after having taken study medication, the investigator must report immediately any drug exposure during pregnancy to the sponsor. Drug exposure during pregnancy has to be reported immediately (within 24 hours or next business day whichever is shorter) to the defined unique entry point for SAE forms of the respective BI OPU (country-specific contact details will be provided in the Investigator Site File). The outcome of the pregnancy associated with the drug exposure during pregnancy must be followed up. In the absence of an (S)AE, only the Pregnancy Monitoring Form for Clinical Trials and not the SAE form is to be completed. The ISF will contain the Pregnancy Monitoring Form for Clinical Trials (Part A and Part B).

After implementation of CTP version 5.0, pregnancy test results will not be documented by default in the eCRF. Only positive pregnancy tests will be documented via the Pregnancy Monitoring Form (and reported as an AE if applicable).

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5.2.3 Assessment of safety laboratory parameters

5.2.3.1 General safety laboratory parameters

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

Hematology	Hemoglobin, red blood cell count (RBC), white blood cell count (WBC) with differential (neutrophils, basophils lymphocytes, monocytes, eosinophil), platelets (PLT)
	Reticulocytes have to be measured only at Visit 1 of every second cycle, EOC4, EOT.
Biochemistry	Glucose, sodium, potassium, calcium, inorganic phosphate, creatinine, AST, ALT, alkaline phosphatase (AP), lactate dehydrogenase (LDH), bilirubin, urea (preferred) or BUN, total protein, albumin, uric acid
	Serum immunoglobulin levels (IgG, IgM, IgA) and direct antiglobulin (direct Coombs) test have to be measured only every 2 cycles, EOC4 and EOT.
Coagulation	Activated partial thromboplastin time (aPTT), prothrombin time (PT), international normalised ratio (INR) where indicated (e.g. treatment with vitamin K antagonists)
Urine	pH, glucose, erythrocytes, leukocytes, protein, nitrite will be analysed by dipstick and reported as semiquantitative measurements. In case of pathological findings, further evaluation should be performed and results documented.
Pregnancy test	A serum pregnancy test needs to be obtained at the time points indicated in the Flow Chart in patients of childbearing potential.

Additional safety labs will be collected on day 2 of Cycle 1 (i.e., 24 hours after the first administration of BI 836858) and after the first infusion of a higher dose, following intra-patient dose escalation (i.e. 24 hours after the first administration of the higher dose). Other lab tests to be included for these visits: haptoglobin, direct antiglobulin/Coombs test, bilirubin (direct and indirect) and free hemoglobin. Non pre-existing abnormal laboratory values (CTCAE Grade 3 or higher) will be followed up every 48 hours until these laboratory values are back to at least CTCAE Grade 1 or baseline.

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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5.2.3.2 Cytogenetics and molecular genetics

The results of molecular genetic testing undertaken at the time of initial diagnosis will be entered into the eCRF. This includes karyotyping (chromosomal banding), the testing of specific cytogenetic alterations by *in-situ* hybridization and the detection of somatically-acquired mutations.

5.2.4 Electrocardiogram

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 or qualified individual delegated by the PI. Additional examinations should be done whenever the Investigator deems necessary.

5.2.5 Assessment of other safety parameters

5.2.5.1 Vital signs

Vital signs (blood pressure, heart rate and body temperature) will be recorded at every visit during screening, treatment, EOC4 and EOT. Additional time points for blood pressure and heart rate at the day of administration of BI 836858 are: prior to the start of premedication, prior to the start of BI 836858 infusion, and in 30 (±10) minute intervals throughout the course of the infusion of BI 836858 and 60 (±10) minutes after the end of the infusion, thereafter every 4-8 hours until at least 24 hours after start of the infusion. In case of an infusion-related reaction, the Investigator should decide whether to intensify or prolong monitoring of vital signs of the patient.

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

After implementation of CTP version 5.0 the vital signs are mandatory only at the day of administration of BI 836858 (see above). Results will be documented in the eCRF only if qualifying for an adverse event.

5.2.5.2 Physical examination

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

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5.4 APPROPRIATENESS OF MEASUREMENTS

Determination of MTD is based on toxicities graded according to CTCAE version 4.0 (R09-2850). The CTCAE criteria are commonly used in the assessment of AEs in oncology and hemato-oncology patients. The criteria to be used for evaluation of MDS are internationally accepted as standard of practice for haematologists worldwide.

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6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

During the introduction treatment phase, patients will receive administration with BI 836858 every 14 days. Patients are required to be hospitalized under close surveillance with access to intensive care for at least 24 hours after the first administration of BI 836858 to allow close monitoring for infusion-related reactions or other AEs. After good tolerability of the first administration of BI 836858, the Investigator may evaluate the risk for an infusion-related reaction and other AEs in view of relevant comorbidities or MDS-related symptoms, and as a result, the patient may receive subsequent infusions in the out-patient setting.

In case a patient misses a visit within one treatment cycle and the patient comes to the clinic between the missed and the next scheduled visit, the delayed visit should be scheduled as soon as possible and documented with the actual date and the reason for the delayed visit.

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

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

The investigations as outlined in the Flow Chart will be performed at the respective visits as described in detail in the following sections. All assessments should be performed prior to dose administration on dosing days, unless otherwise specified.

With the aim to minimize the burden for trial participants, after approval of CTP version 5.0, the mandatory protocol procedures are reduced for all patients who continue to receive trial medication in treatment cycles ≥5. Instead, safety 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.

Findings during safety assessments are documented in the eCRF only if qualifying for an adverse event (see sections 5.2.2, which remain unchanged).

6.2.1 Screening and run-in period(s)

The screening period (Visit 1), i.e. the phase after informed consent and before the first administration of the trial drug, may be as long as 21 days. The site should call Interactive Response Technologies (IRT) after informed consent is signed to register the patient as enrolled.

The patient will be officially entered (randomized for Phase II) via IRT after all the eligibility criteria are met.

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

- Informed consent
- Demographics (sex, birth date, race) and baseline conditions

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- Medical history
- Review of inclusion and exclusion criteria (patient eligibility)
- Dose assignment (during cohort dose escalation of Phase I only, before the first administration of the trial drug and after informed consent and review of in- and exclusion criteria)
- Safety laboratory (hematology, biochemistry including serum immunoglobulin levels and direct antiglobulin test, coagulation, urine; for details please refer to Section 5.2.3.1)
- Physical examination, height, weight, vital signs and ECOG performance score
- Serum pregnancy test in women of childbearing potential
- 12-lead ECG
- Adverse Events
- Concomitant therapy
- Bone marrow aspiration for disease assessment
- Molecular genetics and cytogenetics of MDS (Historical/available data for Phase I patients and required at screening for Phase II patients)
- Number of transfusions (up to 3 months prior to start of treatment)

- Phase II: Randomization may be at the latest performed on Cycle 1 Visit 1, but before start of therapy

6.2.1.1 Re-screening

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

6.2.2 Treatment period(s)

6.2.2.1 Visit 1 and Visit 3 – day of BI 836858 administration

Phase II: these visits will also occur for BSC patients,

The first dose of study medication should occur no later than 21 days after the informed consent is signed.

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

- Review of inclusion and exclusion criteria (patient eligibility), in the first administration only
- Safety lab parameters before trial drug administration as specified in Section 5.2.3.1
- Physical examination and ECOG performance score completed Day 1 of every second cycle beginning with cycle 1. Physical exam may be completed up to 2 days prior to administration and ECOG must be completed on the day of the administration. Height only at Day 1 of first cycle. If the first administration of BI 836858, or BSC treatment

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on trial (Phase II) is completed within 3 days of the screening visit, these examinations do not need to be repeated
- Vital signs at time points specified in Section 5.2.5.1 and weight
- Serum pregnancy test in women of childbearing potential (Day 1 of every Cycle)
- 12-lead ECG (required at Visit 1 of each cycle)
- Adverse events (AEs)
- Changes in concomitant therapies
- Number of transfusions

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

Phase II only: Patients randomized to BSC should be treated on BSC, as indicated by investigator, throughout Introduction Treatment Cycles

6.2.2.2 Visit 2 and Visit 4 (± 1 day window allowed beginning in Cycle 3)

Phase II: these visits will also occur for BSC patients,

In Cycles 1 and 2, visits will occur at Day 8 and Day 22. Beginning in Cycle 3 and thereafter, patients will come to the clinic only for infusions and will not be required to complete the visits on Day 8 and Day 22 unless medically indicated. On the Visit 2 and Visit 4 days, the following parameters and investigations will be obtained and / or performed:

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

Phase II only: Patients randomized to BSC should be treated on BSC, as indicated by investigator, throughout Introduction Treatment Cycles

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6.2.2.3 End of Cycle 4 (EOC4)

This visit includes an evaluation for further treatment. Those patients with clinical benefit, CR or PR and who are tolerating the infusions well may continue until PD or other criteria for withdrawal are met as noted in Section 3.3.4.1. For those patients who have received 8 administrations, this visit is to be performed 14 days (± 2 days) after the 8th administration of BI 836858. For those patients who have received < 8 administrations, who are still in remission, this visit is to be performed 4 months (±2 days) after Cycle 1 Visit 1. Phase II: For patients randomized to BSC, this visit to be completed 4 months (±2 days) after Cycle 1 Visit 1.

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

- Safety lab parameters and urine analysis as specified in Section 5.2.3.1
- Physical examination, weight and ECOG performance score
- Vital signs at time points specified in Section 5.2.5.1
- Serum pregnancy test in women of childbearing potential
- 12-lead ECG
- Adverse events (AEs)
- Changes in concomitant therapies
- Bone marrow aspiration
- Molecular genetics and cytogenetics of MDS (Phase II patients only)
- Number of transfusions

- Clinical disease assessment - Eligibility for further administration may be performed up to 2 days prior to this visit

Phase II: For patients that are randomized to Arm B (BSC), following disease assessment confirmation at this visit, if patients have not progressed to high-risk MDS or AML, there is the opportunity to cross-in and receive BI 836858 study drug, providing they fulfil all inclusion/exclusion criteria. Alternatively, these patients may continue on in the Maintenance Cycles receiving BSC treatment until PD or other criteria for withdrawal are met.

6.2.2.4 Cycles 5 and 6 (additional Introduction Treatment Cycles Visits 1 and 2)

These visits are only for those patients who have received BI 836858 that are non-PD and equivocal as to if clinical benefit has been established, per investigator judgement after 4 Cycles. Two additional introduction treatment cycles are allowed prior to end of introduction treatment.

The Day 1 of Cycle 5 and Visit 5 of Cycle 4 may occur on the same day. Tests that are done on both Visit 5 of Cycle 4 and Visit 1 of the Cycle 5 do not need to be repeated. Refer to the CRF instructions on data entry. In case the Cycle 5 Day 1 is delayed pending

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retreatment eligibility, the Cycle 5 Day 1 will be calculated based on the actual day of the treatment.

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

- Safety lab parameters before trial drug administration as specified in Section 5.2.3.1
- Physical examination and ECOG performance score completed every second cycle beginning with cycle 1. Physical exam may be completed up to 2 days prior to administration and ECOG must be completed on the day of the administration
- Vital signs at time points specified in Section 5.2.5.1 and weight
- Serum pregnancy test in women of childbearing potential (Day 1 of every Cycle)
- 12-lead ECG (required at Visit 1 of each cycle)
- Adverse events (AEs)
- Changes in concomitant therapies
- Bone marrow aspiration (at the discretion of the Investigator).
- Number of transfusions

- Administration of BI 836858
- Clinical disease assessment
- Eligibility for further administration may be performed up to 2 days prior to this visit

6.2.2.5 Maintenance Cycles (Visit 1)

These visits are only for those patients with clinical benefit, CR or PR. Procedures already done at EOC4 or at end of Cycle 6, for patients who completed the additional Introduction Treatment Cycles, (i.e., safety lab, pregnancy test) do not need to be repeated at Maintenance Cycle 1 Visit 1 if this visit is within 7 days from EOC4 (or at end of Cycle 6). The patients will receive monthly infusions until PD or other criteria for withdrawal are met as noted in Section 3.3.4.1.

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

- Safety lab parameters before trial drug administration as specified in Section 5.2.3.1
- Physical examination every other cycle starting with cycle 1 (may be completed up to 2 days prior) and ECOG performance score
- Vital signs at time points specified in Section 5.2.5.1 and weight
- Serum pregnancy test in women of childbearing potential (Day 1 of every Cycle)
- Adverse events (AEs)
- Changes in concomitant therapies
- Bone marrow aspiration (at the discretion of the Investigator).
- Number of transfusions

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- Administration of BI 836858
- Clinical disease assessment - Eligibility for further administration may be performed up to 2 days prior to this visit

Phase II only: Patients randomized to BSC, who choose not to cross-in, may continue on in the Maintenance Cycles receiving BSC treatment until PD or other criteria for withdrawal are met.

6.2.3 End of treatment and follow-up period

6.2.3.1 End of treatment (EOT)

The EOT visit is to occur 30 days (+7 days) after the last administration of BI 836858.

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

- Safety lab parameters and urine analysis as specified in Section 5.2.3.1
- Physical examination including weight and ECOG performance score
- Vital signs at time points specified in Section 5.2.5.1
- Serum pregnancy test in women of childbearing potential
- 12 lead ECG (completed only in patients who receive at least 2 Cycles since EOC4 visit)
- Adverse events (AEs)
- Changes in concomitant therapies
- Number of transfusions

- Bone marrow aspirate (completed only in patients who receive at least 2 Cycles since EOC4 visit)
- Molecular genetics and cytogenetics of MDS (Phase II patients only)
- End of trial treatment. This will include the reason for conclusion of treatment if applicable, premature discontinuation of treatment, and date of last administration of the trial drug

6.2.3.2 Follow-up

Follow-up visits or telephone calls will be performed after the patient has completed or discontinued treatment according to protocol or is not eligible for further treatment cycles. Follow-up visits or telephone calls will begin 4 weeks after the EOT visit. Follow-up will end in case the patient is lost to follow-up or in case the Investigator and Sponsor agree not to pursue further follow-up visits. In Phase I, Follow-up visits should be performed at 4 week intervals for 6 months**.** After the 6 month assessment, patients will be considered off trial. In Phase II, Follow-up visits should be performed at 4 week intervals for the first 12 months or earlier if appropriate as determined by the Investigator, and thereafter in 6 month intervals.

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At the last follow-up visit (Phase I and Phase II), an end of trial assessment will be performed and documented in the eCRF. For follow-up of patients with adverse events which have not recovered at the last planned follow-up visit please refer to Section 5.2.2.2.

The following will be obtained and / or performed:

- AEs since last visit/contact in case they occurred during the residual effect period (30 days after the last trial drug administration) or are considered drug-related (see Section 5.2.2.1)
- Follow-up of AEs in case they were not yet recovered at EOT
- Concomitant therapy indicated for treatment of an AE
- Number of transfusions
- Treatment with any other MDS therapy (report date of treatment and drug)
- Vital status evaluated at each follow-up visit

After implementation of CTP version 5.0, no further follow-up visits after EoR, unless follow-up is for S(AE) that occurred before EoR period.

6.2.3.3 End of the whole trial

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

1. All entered and treated patients have discontinued study 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 provided that treatment continuation is in the best interest of the patient, based on clinical trial results and the investigator´s benefit risk assessment for an individual patient. 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.

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7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 STATISTICAL DESIGN - MODEL

Phase I Dose Finding

The objective of the design is to determine the MTD defined as the highest dose with less than 25% risk of the true DLT rate being above 33%. The phase I dose-finding will be guided by a Bayesian 2-parameter logistic regression model with overdose control (R13-4806; R13-4803). These designs have been shown to be superior regarding the precision of MTD determination compared to 3+3 designs and have been particularly endorsed by the FDA (R13-4881).

The model is formulated as follows:

$\text{logit}(p(d)) = \log(\alpha) + \beta * \log(d/d^*)$,

where $\text{logit}(p) = \log(p/(1-p))$.

$p(d)$ represents the probability of having a DLT in the first cycle at dose d, $d^* = 160$mg is the reference dose, allowing for the interpretation of α as the odds of a DLT at dose d^*, and $\theta = (\log(\alpha), \log(\beta))$ with $\alpha, \beta > 0$ is the parameter vector of the model.

Since a Bayesian approach is applied, a prior distribution $\pi(\theta)$ for the unknown parameter vector θ needs to be specified. This prior distribution will be specified as a mixture of three multivariate normal distributions, i.e.

$\pi(\theta) = \varphi_1\pi_1(\theta) + \varphi_2\pi_2(\theta) + \varphi_3\pi_3(\theta)$

with

φ_i, $i = 1, 2, 3$ the prior mixture weights ($\varphi_1 + \varphi_2 + \varphi_3 = 1$)

and

$\pi_i(\theta) = \text{MVN}(\mu_i, \Sigma_i)$

the multivariate normal distribution of the i-th component with mean vector μ_i and covariance matrix Σ_i, with

$$\Sigma_i = \begin{pmatrix} \sigma_{i,11}^2 & \sigma_{i,11}\sigma_{i,22}\rho_i \\ \sigma_{i,11}\sigma_{i,22}\rho_i & \sigma_{i,22}^2 \end{pmatrix}$$

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

Prior derivation

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For the current study, no relevant information in the form of human data was available, since no study in a comparable population has been conducted. Therefore, the three mixture components were established as follows:

1. A weakly informative prior was derived reflecting the a priori assumption that the median DLT rate at the starting dose of 20mg would equal 1%, and the median DLT rate at the anticipated MTD of 320mg would equal 20%. This yields μ_1 = (-2.189, 0.146). The standard deviations were set such that large uncertainty about the parameter means is reflected, and the correlation was set to 0, thus yielding $\sigma_{1,11} = 2$, $\sigma_{1,22} = 1$ and $\rho_1 = 0$, respectively. The prior weight φ_1 for the first component was chosen as 0.9.

2. A high-toxicity weakly informative prior was derived reflecting the case that the compound would be much more toxic than expected. For this prior component, it was assumed that the median DLT rate at the starting dose of 20mg would equal 10%, and the median DLT at the anticipated MTD of 320mg would equal 50%. These assumptions yield μ_2 = (-0.549, -0.233). The standard deviations and correlations were set identical to the weakly informative prior, i.e. $\sigma_{2,11} = 2$, $\sigma_{2,22} = 1$ and $\rho_2 = 0$, respectively. The prior weight φ_2 for the second component was chosen as 0.05.

3. A low-toxicity weakly informative prior was derived reflecting the case that the compound would be much less toxic than expected. For this prior component, it was assumed that the median DLT rate at the starting dose of 20mg would equal 1%, and the median DLT at the anticipated MTD of 320mg would equal 2%. These assumptions yield μ_3 = (-4.068, -1. 372), i.e. basically a flat curve. The standard deviations and correlations were set to $\sigma_{3,11} = 5$, $\sigma_{3,22} = 0.01$, therefore almost fixing the slope parameter to its mean. The correlation was set to 0, i.e. $\rho_3 = 0$. The prior weight φ_3 for the third component was chosen as 0.05.

A summary of the prior distribution is provided in Table 7.1: 1. Additionally, the prior probabilities of DLT at different doses, as well as the corresponding probability of under-, targeted and overdosing, are shown in Table 7.1: 2. Graphically, the prior medians with accompanying 95% credible intervals are shown in Figure 7.1. As can be seen from both, the Table and the Figure, the prior medians of the DLT probabilities are in-line with the prior medians derived from the weakly informative prior, and the uncertainty around the medians is large, showing the low amount of information this prior provides. This is also supported by the prior sample size, i.e. the information contained in the prior. This is approximately equal to 1.5 patients, i.e. about half the weight the first cohort in the study will have.

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Table 7.1: 1 Summary of prior distribution

Prior Component	Mixture Weight	Mean vector	SD vector	Correlation
1: Weakly inf.	0.900	-2.189 0.146	2.000, 1.000	0.000
2: High Tox	0.050	-0.549 -0.233	2.000, 1.000	0.000
3: Low Tox	0.050	-4.068 -1.372	5.000, 0.010	0.000

Table 7.1: 2 Prior probabilities of DLT at selected doses

Dose	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	0.873	0.059	0.069	0.072	0.161	<0.001	0.007	0.641
40	0.829	0.080	0.091	0.094	0.181	<0.001	0.015	0.721
80	0.752	0.109	0.138	0.133	0.208	<0.001	0.036	0.802
160	0.596	0.159	0.244	0.215	0.253	0.001	0.103	0.894
320	0.400	0.159	0.441	0.365	0.329	0.002	0.257	0.992

Doses printed in bold face meet the overdose criterion (P(overdose) < 0.25))

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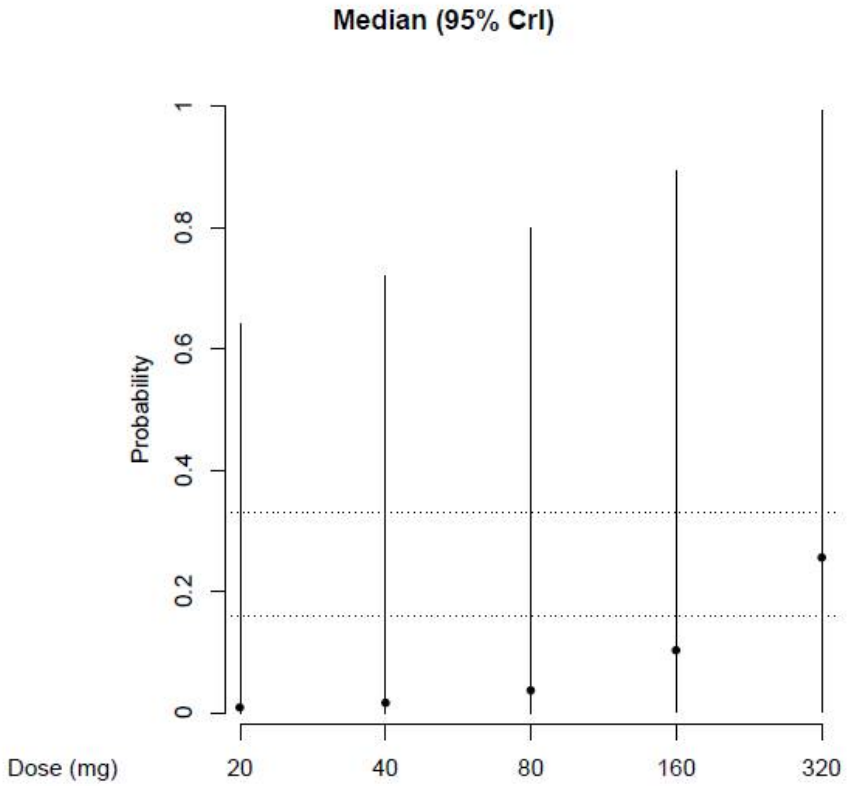

Figure 7.1 Prior medians and 95% credible intervals

The MTD may be considered reached if one of the following criteria is fulfilled

1. The posterior probability of the true DLT rate in the target interval (16%-33%) is above 50%, OR

2. At least 12 patients have been treated at MTD, including the two expansion cohorts.

The DSB may recommend stopping the dose finding phase after the criterion for MTD 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 DSB may decide to include additional number of patients at this dose level and to declare this dose as the recommended dose for phase 2 (RP2D).

Recruitment in this trial was discontinued prematurely during the dose expansion cohort.

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

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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 10.3.

Phase II efficacy comparison

In the phase II part the efficacy of the two arms (BI 836858 vs. investigator's choice) will be compared in an exploratory manner.

7.2 NULL AND ALTERNATIVE HYPOTHESES

No formal hypothesis testing is planned in this trial. This is an exploratory Phase I/II study with the main objective of dose finding (Phase I) and treatment effect estimation (Phase II).

7.3 PLANNED ANALYSES

Two analysis populations are defined for efficacy and safety analyses. For the Phase I the full analysis set (Phase I) is defined, in analogy to the intention to treat population as the treated set with respect to Phase I; i.e. all patients of Phase I who have received at least one single dose of BI 836858 will be considered, including the patients who have been replaced for any reason (refer to Section 3.3.4.1). For the Phase II the full analysis set (Phase II) is defined, in analogy to the intention to treat population as the randomized set with respect to Phase II; i.e. all patients randomized. No per protocol population will be used for analyses. However protocol violations will be described.

7.3.1 Primary analyses

7.3.1.1 Assessment of the MTD in phase I

In order to determine the MTD the occurrence of a DLT in the first cycle will be assessed on an individual patient level. The MTD will be determined as described in Section 7.1.

Based on the data observed in the trial other models might be considered either additionally or replacing the primary model. For feasibility or other reasons a different dose might be considered as the recommended dose for Phase II.

7.3.1.2 Assessment of the primary endpoint in Phase II

The primary endpoint for efficacy in Phase II is RBC transfusion independency derived from the data of all cycles. The primary analysis will be done for all patients of the full analysis set (Phase II). Each patient will be assigned to RBC transfusion independency yes/no based on the criteria described in Section 5.1.1. Analyses for the primary endpoint will be performed both pooled as well as separately for the two strata (see Section 7.5).

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7.3.1.3 Statistical group comparison

All statistical group comparisons will be performed with respect to the full analysis set (phase II). Odds ratios, confidence intervals, and chi-square test will be used to compare treatments in an exploratory manner if appropriate. The exploratory nature of these analyses will be considered when interpreting the significance levels. P-values derived from statistical tests smaller than 5% will only be reported as nominally significant regarding the small sample size in each treatment schedule.

7.3.2 Secondary analyses

Secondary time-to-event endpoints will be analyzed by using Cox proportional hazard models and Kaplan-Meier curves. Hazard ratios will be derived for the phase II part. Secondary endpoints that are binomial (like response rates) will be analyzed similarly to the primary endpoint for Phase II.

Secondary endpoints in phase I will be listed only. If considered useful, aggregated tables will be provided where different dosages might be grouped.

Details of the primary as well as the secondary analyses will be specified in the trial statistical analysis plan (TSAP).

7.3.3 Safety analyses

All treated patients (both Phase I and Phase II) will be included in the safety analyses. Two analyses will be performed. The first analysis of safety will be performed for the first part of the trial (determination of the MTD, first cycle only, treatment regimen = initial dose at the start of the treatment, treated set (Phase I only)). This descriptive analysis will evaluate the MTD for the monotherapy of BI 836858 in MDS patients. The second analysis will be performed with respect to all cycles and will act as a support for the determination of the MTD (treated set (both Phase I and Phase II)). In addition a sensitivity analysis for the second expansion cohort will be conducted. Further details will be described in the TSAP.

Events that started within the period starting with the first administration of the treatment and ending four weeks (30 days) after the last administration of treatment will be considered as having occurred on treatment. In general, later events will be attributed to the post-study period and will be presented separately. However, post-study events will be examined to determine whether they need to be combined with on-treatment events in an additional table.

Adverse events will be graded according to CTCAE Version 4.0 (R09-2850) and reported according to BI standards. *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).*

Serious adverse events will be tabulated. In addition, events leading to dose reduction or treatment discontinuation will be examined, but may not be reported as individual tables, depending upon the extent of overlap. Descriptive statistics will be used to describe changes in laboratory tests over time. In addition, all abnormalities of potential clinical significance

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will be reported. In general, potential clinical significance is defined as at least CTCAE Grade 2 and an increase in CTCAE classification from baseline.

7.3.4 Interim analyses

7.3.4.1 Phase I

In the Phase I, interim safety evaluations will be performed as considered necessary. In particular safety evaluations will be performed after each dose cohort by the DSB consisting of the investigators and representatives of the sponsor (refer to Section 3.1.1). Based on this the DSB will recommend the next dose level as well as the corresponding cohort size. DSB meeting minutes and outputs provided for these DSB meetings will be documented and archived in the clinical trial master file (CTMF).

A Phase I safety analysis report will be prepared prior to the initiation of Phase II. A summary of safety and efficacy from the dose escalation cohorts and from the expansion cohorts will be included in the Phase I safety analysis report. Results of this evaluation will be documented, archived and made available for Health Authority and Ethics Committee/IRB review and approval (where applicable) and to all investigators who participate in the Phase II. Such an analysis will be defined in more detail in the TSAP.

7.3.4.2 Phase II

After approximately 100 patients are evaluable for the primary endpoint, an internal DMC consisting of representatives of the sponsor will perform an interim analysis for internal project purposes. At this time point it will be evaluated whether the results so far necessitate adjustments in the total sample size. Results of this analysis will be kept confidential and will not be communicated to the trial team and the investigators. No interim Clinical Trial Report (CTR) will be provided. Further details of these analyses will be specified in the statistical analysis plan and the DMC charter.

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7.4 HANDLING OF MISSING DATA

No imputation will be performed on missing efficacy data.

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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.

7.5 RANDOMIZATION

Randomization will be performed in the phase II part of this trial only. In Phase I, doses will be assigned based on the decision made by the DSB (see Section 7.3.4.). In Phase II, the randomization ratio is 1:1 for the two treatment arms, i.e. BI 836858 plus BSC vs. BSC alone, per investigator's choice. Randomization will be stratified by number of previous lines of MDS therapy (0, 1, ≥ 2), where previous MDS therapy also includes previous ESA therapy**.** Randomization will be performed using IVRS/IWRS. Boehringer Ingelheim Pharma GmbH & Co. KG, Clinical Trial Support Group or a CRO appointed by the Sponsor will provide the randomization lists using a validated randomization number generating system. Access to the randomization codes will be controlled and documented.

7.6 DETERMINATION OF SAMPLE SIZE

7.6.1 Determination of the maximum tolerated dose

A maximum of 50 patients (including patients at MTD) will be expected for the dose finding part. Fewer patients might be needed based on the recommendation of the DSB and the criteria specified (see Section 7.1)

7.6.2 Calculation of phase II sample size

For the estimation of patient number in the second part we assume a RBC transfusion independency rate in the BI 836858 arm of 35% compared to a RBC transfusion independency rate in the BSC arm of 5%. Based on these assumptions and a sample size of 2x75=150 patients overall the probability of observing an unadjusted difference in RBC transfusion independency rates of more than 25% is approximately 81%. On the other hand, if the true RBC transfusion independency rates are assumed to be 35% both in the BI 836858 arm and the BSC arm, the probability for observing a difference in RBC transfusion independency rate between the two arms of more than 25% is smaller than 1%. Different scenarios and resulting probabilities for observing a difference in RBC transfusion independency rates of more than 25% are given in Table 7.6.1.

In summary, a sample size of 2x75=150 patients is considered to be sufficient to clearly differentiate between the two treatment arms in case that a pronounced treatment benefit of BI 836858 exists. On the other hand, if there is no or only a small benefit for BI 836858 compared to the BSC arm, the sample size is large enough such that the probability for falsely observing a beneficial outcome for the BI 836858 arm is sufficiently small.

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Table 7.6: 1 Evaluation of the probabilities of observing a treatment difference in RBC transfusion independency rate depending on assumed response rate and sample size.

Assumed RBC Transfusion Independency Rate BI 836858	Assumed RBC Transfusion Independency Rate Inv. Choice, BSC	Sample Size BI 836858	Sample Size Inv. Choice, BSC	Probability observing difference in RBC Transfusion Independency Rate bigger than 25%
0. 35	0.05	75	75	0.81
0. 30	0.05	75	75	0.52
0. 40	0.05	75	75	0.95
0. 35	0.35	75	75	<0.01
0. 35	0.25	75	75	0.02
0. 35	0.15	75	75	0.25
0.2	0.05	75	75	0.03

Probabilities based on simulations (n= 100000 iterations) using SAS v.9.3.

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8. INFORMED CONSENT, DATA PROTECTION, TRIAL RECORDS

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

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

The rights of the investigator and of the sponsor with regard to publication of the results of this trial are described in the investigator contract. As a general rule, no trial results should be published prior to finalisation of the Clinical Trial Report.

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

8.1 STUDY APPROVAL, PATIENT INFORMATION, AND INFORMED CONSENT

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

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

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

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

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8.2 DATA QUALITY ASSURANCE

A quality assurance audit/inspection of this trial may be conducted by the sponsor or sponsor's designees or by IRBs/IECs or by regulatory authorities. The quality assurance auditor will have access to all medical records, the investigator's trial-related files and correspondence, and the informed consent documentation of this clinical trial.

8.3 RECORDS

Case Report Forms (CRFs) for individual patients may be provided by the sponsor, either on paper or via remote data capture (RDC). For drug accountability, refer to Section 4.1.8.

8.3.1 Source documents

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

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

For eCRFs all data must be derived from source documents.

8.3.2 Direct access to source data and documents

The investigator / institution will permit trial-related monitoring, audits, IRB / IEC review and regulatory inspection, providing direct access to all related source data / documents. CRFs/eCRFs and all source documents, including progress notes and copies of laboratory and medical test results must be available at all times for review by the sponsor's clinical trial monitor, auditor and inspection by health authorities (e.g. FDA). The Clinical Research Associate (CRA) / on site monitor and auditor may review all CRFs/eCRFs, and written informed consents. The accuracy of the data will be verified by reviewing the documents described in Section 8.3.1.

8.4 LISTEDNESS AND EXPEDITED REPORTING OF ADVERSE EVENTS

8.4.1 Listedness

To fulfil the regulatory requirements for expedited safety reporting, the sponsor evaluates whether a particular adverse event is "listed", i.e. is a known side effect of the drug or not. Therefore a unique reference document for the evaluation of listedness needs to be provided. The current version of the Investigator's Brochure (U11-2766) for BI 836858 and reference documents are filed in the Investigator Site File (ISF). No AEs are classified as listed for matching placebo, study design, or invasive procedures.

8.4.2 Expedited reporting to health authorities and IECs/IRBs

Expedited reporting of serious adverse events, e.g. suspected unexpected serious adverse reactions (SUSARs) to health authorities and IECs/IRBs, will be done according to local

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regulatory requirements. Further details regarding this reporting procedure are provided in the Investigator Site File.

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 COMPLETION OF TRIAL

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

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10. APPENDICES

10.1 CLINICAL EVALUATION OF LIVER INJURY

10.1.1 Introduction

Alterations of liver laboratory parameters, as described in Section 5.2.2.1 (AESI) are to be further evaluated using the following procedures:

10.1.2 Procedures

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

In addition,

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

  and report these via the CRF.

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

Clinical chemistry

alkaline phosphatase, albumin, PT or INR, CK, CK-MB, coeruloplasmin, α-1 antitrypsin, transferrin, amylase, lipase, fasting glucose, cholesterol, triglycerides

Serology

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

Hormone

Thyroid stimulating hormone

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Haematology

White blood count + differential, haemoglobin, thrombocytes

In case AST/ALT remain elevated and the previous testing does not provide a likely cause for the elevation, the following tests should be performed: Epstein Barr Virus (VCA IgG, VCA IgM), herpes simplex virus (IgG, IgM), varicella (IgG, IgM), parvovirus (IgG, IgM), toxoplasmosis (IgG, IgM).

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

10.2 EASTERN COOPERATIVE ONCOLOGY GROUP (ECOG) PERFORMANCE STATUS

ECOG PERFORMANCE STATUS

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 selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

10.3 STATISTICAL APPENDIX INCLUDING MODEL PERFORMANCE AND DATA SCENARIOS

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

Hypothetical data scenarios

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Hypothetical data scenarios are shown in Table 10.3: 1. These scenarios reflect 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 dose and over-dosing are shown.

For example, scenario 1 represents the case that no DLT is observed in three patients at the starting dose of 20mg. In this case, the next dose permitted by the model and by the 100% escalation rule is 40mg. Similarly, scenario 5 represents the case that no DLTs are observed in the first cohort of three patients at 20mg, and 1 DLT is observed in the second cohort of 3 patients at 40mg. In this case, the model requires to re-enroll at the current dose level of 40mg. Scenario 7 shows the case that 1 DLT is observed in three patients at the starting dose of 20mg and 1 DLT is observed in the second cohort of three patients at the same dose level of 20mg. The model then allows a de-escalation to 10mg.

Finally, scenario 8 and 9 illustrate a case where no DLTs are seen in the first four cohorts, and then 2 DLTs occur in 3 patients in the next cohort. Based on scenario 8, the model and the 100% escalation limit allow to escalate up to 320mg. In scenario 9, it is then assumed that 2 DLTs occur at this dose level. 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 320mg and requires a de-escalation to 160mg. This case illustrates the adaptive behaviour of the model even in extreme situations.

Table 10.3: 1 Hypothetical data scenarios

Scenario	**Dose (mg)**	**# DLT**	**# Pat**	**Current Dose: P(OD)**	**Next Dose**	**Next Dose**		
						P(UD)	**P(TD)**	**P(OD)**
1	20	0	3	0.010	40	0.914	0.062	0.024
2	20	1	3	0.222	20	0.503	0.275	0.222
3	20	2	3	0.668	N/A	N/A	N/A	N/A
4	20 40	0 0	3 3	0.004	80	0.894	0.080	0.026
5	20 40	0 1	3 3	0.102	40	0.639	0.259	0.102
6	20 40	0 2	3 3	0.369	20	0.470	0.349	0.181
7	20 20	1 1	3 3	0.289	10	0.484	0.347	0.168
8	20 40 80 160	0 0 0 0	3 3 3 3	0.016	320	0.625	0.156	0.219

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Table 10.3: 1 Hypothetical data scenarios (cont.)

Scenario	Dose (mg)	# DLT	# Pat	Current Dose: P(OD)	Next Dose	Next Dose		
						P(UD)	P(TD)	P(OD)
9	20	0	3					
	40	0	3					
	80	0	3					
	160	0	3					
	320	2	3	0.709	160	0.688	0.259	0.053

Operating 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 simulation. Table 10.3: 2 describes 5 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: non-logistic dose-toxicity scenario

- Scenario 5: low-tox followed by high-tox

Table 10.3: 2 Assumed true dose-toxicity scenarios

Scenario		Dose (mg)					
		10	20	40	80	160	320
1 (Prior)	P(DLT)	0.057	0.072	0.094	0.133	**0.215**	0.365
2 (High Tox)		0.120	**0.20**	**0.320**	0.440	0.550	0.680
3 (Low Tox)		0.020	0.040	0.080	0.100	0.140	**0.250**
4 (Non-Logistic)		0.050	0.080	0.130	**0.280**	**0.320**	0.380
5 (Low-High)		0.020	0.040	0.080	0.320	0.440	0.550

Bold numbers indicate true DLT rates in the target interval [0.16-0.33).

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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-dose 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 10.3: 3.

Table 10.3: 3 Simulated operating characteristics

Scenario	% of trials declaring an MTD with true DLT rate in				# Patients	# DLT
	underdose	target dose	overdose	STOPPED	Mean (Min-Max)	Mean (Min- Max)
1	45.1	42.5	10.7	1.7	23.05 (3 – 39)	3.674 (1 – 8)
2	3.7	62.6	10.4	23.3	15.61 (3 – 33)	4.384 (2 – 10)
3	68.3	31.3	0	0.4	24.74 (3 – 45)	3.169 (1 – 9)
4	34.5	59.5	3.5	2.5	20.99 (3 – 39)	4.162 (1- 10)
5	35.0	56.6	8.0	0.4	21.09 (3 – 39)	4.328 (1 – 11)

In scenario 1, which reflects the case that the true dose-toxicity is aligned with prior means, 42.5% of the simulated trials declared a dose as MTD with true DLT rate in the targeted dose range. Since 80mg has a DLT probability of 0.133 which is relatively close to the lower bound of the target interval (0.16), this dose was identified quite often as MTD, namely in 36.1% of the simulated cases. When considering this as an MTD as well, the target rate would add up to 78.6%.

In Scenario 2 (high-toxicity scenario), the starting dose has already >10% probability of observing at least 2 DLTs in the first cohort. This contributes to the high percentage (23.3%) 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.

Scenario 3 (low-toxicity scenario) shows a similar effect as for Scenario 1. The probability of observing a DLT at 160mg is 0.14 and therefore close to the lower bound of the target interval. Adding up the corresponding probability of declaring this dose as an MTD (45.0%) leads to a target rate of 76.2%.

In scenarios 4 and 5, more than 50% of the simulated trials declared a dose as MTD with true DLT rate in the targeted dose range.

The mean patient numbers range from 15.6 patients (high-toxicity scenario) to 24.7 patients (low-toxicity scenario) and the maximum number of patients was 45. Therefore, the patient numbers are as expected and increase when moving away from the high-toxicity scenario.

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

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11. DESCRIPTION OF GLOBAL AMENDMENT(S)

11.1 GLOBAL AMENDMENT 1

Number of global amendment		1
Date of CTP revision		20 AUG 2015
EudraCT number		N/A
BI Trial number		1315.7
BI Investigational Product(s)		BI 836858
Title of protocol		A Phase I/II, Multicenter, Open-Label, Dose Escalation and Randomized Trial of BI 836858 in Patients with Low or Intermediate-1 Risk Myelodysplastic Syndromes
To be implemented only after approval of the IRB/IEC/Competent Authorities		☒
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		☐
Can be implemented without IRB/IEC/ Competent Authority approval as changes involve logistical or administrative aspects only		☐
Section to be changed		Title Page
Description of change		Status has been updated: "Trial Protocol" replaced with "Revised Protocol (based on Global Amendment 01)" Version and Date have been updated: Version 1.0 replaced with Version 2.0; Date 06Mar2014 to be replaced with 13Aug2015
Rationale for change		Update
Section to be changed		Headers
Description of change		Added the extension "-03" to the c02304070 document number.

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Number of global amendment		1
Rationale for change		The "01" and "-02" version of the document number were inadvertently omitted in the previous version of the protocol. The current amendment reflects the new document number of "-03".
Section to be changed		Synopsis -Diagnosis
Description of change		For Phase I and Phase II: Further clarify patients eligible for this trial and added "are refractory to or are not amenable or eligible for approved MDS therapy"
Rationale for change		Revised entry criteria based on FDA feedback
Section to be changed		Synopsis – Main Criteria for Inclusion
Description of change		For Phase I and Phase II: Further clarify patients eligible for this trial and added "are refractory to or are not amenable or eligible for approved MDS therapy"
Rationale for change		Revised entry criteria based on FDA feedback
Section to be changed		Synopsis – Criteria for Efficacy
Description of change		
Rationale for change		Clarification and Update
Section to be changed		Flow Chart – Introduction Treatment
Description of change		Clarified the collection of "other MDS therapies" during follow-up is for Phase II only.
Rationale for change		Updated
Section to be changed		Flow Chart – Introduction Treatment
Description of change		Revised the timing of EOT visits from 28 days (+ 7 days) to 30 days (+ 7 days) after last administration of BI 836858.
Rationale for change		Boehringer-Ingelheim Standards
Section to be changed		Flow Chart – Introduction Treatment
Description of change		Revised the Follow-up period for Phase I patients:

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Number of global amendment		1
		Follow-up starts 4 weeks after the EOT visit; Phase I patients: visits or telephone calls will occur at least every 4 weeks for 6 months. After the 6th follow-up visit, the patient will be considered off trial. Phase II patients: visits or telephone calls will occur at least every 4 weeks until 12 months after the last administration of BI 836858, after which these visits will occur every 6 months until the end of the trial
Rationale for change		Clarification and Update
Section to be changed		Flow Chart – Introduction Treatment
Description of change		Revised Footnote #4 to include an additional safety lab to be performed 24 hours after intra-patinets dose esacaltion occurs: "For details refer to Section 5.2.3.1. Urine has to be measured only at screening, EOC4 and EOT. Safety laboratory assessments may be completed up to 2 days prior to administration, or BSC treatment on trial (Phase II). An additional safety lab will be collected on day 2 (i.e., 24 hours after the first administration of BI 836858) and 24 hours after the first higher dose for patients who participate in intra-patient dose escalation. Other lab tests to be included: haptoglobin, direct Coombs test, and bilirubin (direct and indirect)"
Rationale for change		Clarification and Update
Section to be changed		Flow Chart – Introduction Treatment
Description of change		Further clarified Footnote #8 to note timing of EOT ECGs and Bone marrow aspirate to include reference to introduction Cycles 5 and 6 "ECG and bone marrow aspiration will be performed at EOT only if the patient has completed at least 2 cycles (e.g. received 4 administrations) since the EOC4 visit" (or additional introduction cycle 5 and 6).
Rationale for change		Clarification and Update
Section to be changed		Flow Chart – Introduction Treatment
Description of change		Updated Vital Assessment in flowchart to remove text on Overall survival. Clarification on Phase I vs Phase II survival data collection covered under FU: Follow-up footnote. Updated Footnote #20 to clarify overall survival to be collected from Phase II patients only. "Overall Survival for Phase II Patients only"
Rationale for change		Clarification and Update

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Number of global amendment		1
Section to be changed		Flow Chart – Maintenance
Description of change		Clarified the collection of "other MDS therapies" during follow-up is for Phase II only.
Rationale for change		Updated
Section to be changed		Flow Chart – Maintenance
Description of change		Revised the Follow-up period for Phase I patients: Follow-up starts 4 weeks after the EOT visit; Phase I patients: visits or telephone calls will occur at least every 4 weeks for 6 months. After the 6th follow-up visit, the patient will be considered off trial. Phase II patients: visits or telephone calls will occur at least every 4 weeks until 12 months after the last administration of BI 836858, after which these visits will occur every 6 months until the end of the trial Follow-up starts 4 weeks after the EOT visit; visits or telephone calls will occur at least every 4 weeks until 12 months after the last administration of BI 836858, after which these visits will occur every 6 months.
Rationale for change		Clarification and Update
Section to be changed		Flow Chart – Maintenance
Description of change		Further clarified Footnote #4 to note timing of EOT ECGs and Bone marrow aspirate to include reference to introduction Cycles 5 and 6 ECG and bone marrow aspiration will be performed at EOT only if the patient has completed at least 2 cycles (e.g. received 2 administrations) since the EOC4 visit (or additional introduction cycle 5 and 6).
Rationale for change		Clarification and Update
Section to be changed		Flow Chart – Maintenance
Description of change		Clarified Footnote#5 and collection of AEs during REP: Follow-up of AEs not recovered since the EOT. Follow-up of new AEs that occurred during REP. Concomitant therapy during FU is collected only if indicated for treatment of adverse event.
Rationale for change		Clarification and Update
Section to be changed		Flow Chart – Maintenance
Description of change		Updated Footnote #12 to clarify overall survival to be collected from Phase II patients only. Overall Survival for Phase II Patients only
Rationale for change		Clarification and Update
Section to be changed		

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Number of global amendment		1
Description of change		
Rationale for change		
Section to be changed		
Description of change		
Rationale for change		
Section to be changed		
Description of change		
Rationale for change		
Section to be changed		Abbreviations
Description of change		Added one abbreviation to distinguish between Progressive Disease and Pharmacodynamics Added: pd: Pharmacodynamics
Rationale for change		Clarification
Section to be changed		2.2 Trial Objectives
Description of change		Added additional eligibility language: "The Phase I primary objectives of the trial are to determine the maximum tolerated dose (MTD) and the Recommended Phase II Dose (RP2D) to be used in the Phase II. Secondary objectives include safety, pharmacokinetics, exploratory biomarkers and efficacy of BI 836858 monotherapy in patients with low or intermediate-1 risk MDS with symptomatic anemia, who at a minimum, experienced ESA treatment failure or do not qualify (serum erythropoietin level > 500 U) for ESA treatment and are refractory to or are not amenable or eligible for approved MDS therapy.

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		Patients with a deletion 5q cytogenetic abnormality will be allowed in Phase I who do not qualify for lenalidomide treatment (Absolute Neutrophil Count (ANC) < 500/µL or platelets <50,000/µl) or who experience primary lenalidomide failure. lenalidomide failure is defined as lack of hematological improvement after 4 months of therapy, or secondary failure defined as loss of prior lenalidomide response at any time point." And In the randomized Phase II, primary objectives are to investigate the efficacy of BI 836858 plus Best Supportive Care (BSC) vs. Best Supportive Care alone, in low or intermediate-1 risk MDS patients with symptomatic anemia without a deletion 5q cytogenetic abnormality who are previously untreated or who progressed/became resistant following ESA, and are refractory to or are not amenable or eligible for approved MDS therapy. Secondary objectives include the investigation of safety and tolerability of BI 836858 in this patient population.
Rationale for change		Revised entry criteria based on FDA feedback
Section to be changed		2.3 Benefit-Risk Assessment
Description of change		Clarified eligibility criteria by deleting 5-AZA and replacing with Hypomethylating Agents (HMA): MDS are a heterogeneous group of clonal neoplasms with a patient median age at diagnosis of > 70 years. ESA remain the first-line treatment of anemia in most lower-risk MDS patients without del 5q. Responses to ESA treatment is transient, but interestingly, approximately 70% of the relapses of anemia after initial response to EPO are not associated with progression to higher-risk MDS but simply to loss of sensitivity of erythroid progenitors to EPO. Despite considerable progress in understanding the etiology and biologic behavior of lower risk MDS, BSC is still the standard of care for patients progressing after treatment with EPO or 5-azaHypomethylating Agents (HMA) in countries where it is available.
Rationale for change		Revised entry criteria based on FDA feedback
Section to be changed		3.1 Overall Trial Design and Plan

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Description of change		Added additional eligibility language Phase I: In Phase I, patients with low to intermediate-1 risk MDS, who have, at a minimum, experienced ESA treatment failure, except for patients who do not qualify for ESA treatment and are refractory to or are not amenable or eligible for approved MDS therapy, will be assigned to a dose cohort under investigation. Treatment failure on ESAs is defined as 1) failure or ceasing to show hematologic response after at least 8 weeks of 40,000 to 60,000 IU/week of erythropoietin (EPO) or equivalent or 2) low chance/response to ESA with endogenous serum EPO>500. It is expected that approximately 50 patients will be enrolled.
Rationale for change		Revised entry criteria based on FDA feedback
Section to be changed		3.1 Overall Trial Design and Plan
Description of change		Updated stratification factor and stratification levels: Patients also must have experienced treatment failure on ESAs, except for patients who do not qualify for ESA treatment. As defined above, treatment failure on ESAs is defined as 1) failure or ceasing to show hematologic response after at least 8 weeks of 40,000 to 60,000 IU/week of erythropoietin (EPO) or equivalent or 2) low chance/response to ESA with endogenous serum EPO>500. Randomization will be stratified by number of previous lines of MDS therapy (0, 1, >=2), where previous MDS therapy also includes previous ESA therapy (refer to Section 7.5). A total of 150 patients, 75 each arm, will be enrolled in Phase II.
Rationale for change		Revised Phase II Stratification levels in response to FDA feedback on potential patients eligible for trial.
Section to be changed		3.1 Overall Trial Design and Plan
Description of change		Updated eligibility language and stratification levels for Phase II: In Phase II, patients will be enrolled in a randomized manner to investigate efficacy and safety of BI 836858 at RP2D in patients either previously untreated or following progression/resistance after the treatment with ESAs and/or approved MDS drugs such as

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		HMAs5-aza. Treatment failure on 5-azaHMA is defined as 1) no response after at least four cycles of 5-azaHMA, 2) progression of disease on 5-azaHMA or 3) Grade 3-4 non-hematologic toxicity. Patients also must have experienced treatment failure on ESAs, except for patients who do not qualify for ESA treatment. As defined above, treatment failure on ESAs is defined as 1) failure or ceasing to show hematologic response after at least 8 weeks of 40,000 to 60,000 IU/week of erythropoietin (EPO) or equivalent or 2) low chance/response to ESA with endogenous serum EPO>500. Randomization will be stratified by number of previous lines of MDS therapy (0, 1, >=2), where previous MDS therapy also includes previous ESA therapy Patients are stratified by no previous MDS therapy vs. previous ESA and/or 5-aza therapy (refer to Section 7.5). A total of 150 patients, 75 each arm, will be enrolled in Phase II.
Rationale for change		Revised Phase II eligibility and Stratification levels in response to FDA feedback on potential patients eligible for trial.
Section to be changed		3.1.1.1 Phase I
Description of change		Added additional eligibility language: Adult patients with low to intermediate-1 risk MDS, according to International Working Group (IWG) criteria, who, at a minimum, experienced ESA treatment failure, except for patients that do not qualify for ESA treatment and are refractory to or are not amenable or eligible for approved MDS therapy, will be enrolled for the Phase I. Approximately three Phase I sites in the United States will participate in the Phase I.
Rationale for change		Revised entry criteria based on FDA feedback
Section to be changed		3.1.1.1 Phase I
Description of change		Clarified what data may and will be available for the DSB meetings: The Phase I dose-escalation will be guided by a Bayesian logistic regression model (BLRM) with overdose control (refer to Section 7). The DSB will consist of the Phase I investigators, Team Member Medicine (TMM), Trial Clinical Monitor (TCM), Project Statistician, Clinical Pharmacological Project Lead (CPPL) and TransMed Expert (TME). The

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		information on the overdose risk will be presented by the trial statistician to the DSB. Additional information, such as lower grade adverse events, pharmacokinetics (PK), if available, progressive disease (PD), individual patient profiles and other relevant information will also be presented. Based on this information, the members of the DSB will reach a joint 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 DSB will also recommend the size for the next cohort. However, the final decision on the next cohort size will be made by a mutual decision between the TMM and the Coordinating Investigator (CI). Minutes of the DSB meetings and recommendations will be documented and archived by the TCM.
Rationale for change		Clarification and Update
Section to be changed		3.1.1.2 Phase II
Description of change		Updated eligibility language: Adult patients with low to intermediate-1 risk MDS, who received no prior treatment or progressed/become resistant after ESA and/or approved MDS drugs, such as HMAs 5-aza treatment will be included in the Phase II. Approximately 20 sites from United States and select European countries will participate in the Phase II.
Rationale for change		Revised entry criteria based on FDA feedback
Section to be changed		3.2 Discussion of Trial Design, Including the Choice of Control Group(s)
Description of change		Revise language on intra-patient dose escalation. Intra-patient dose escalation will not be allowed. Single intra-patient dose escalation will be permitted. See Section 4.1.4 for details.
Rationale for change		Clarification and Update
Section to be changed		3.3 Selection Of Trial Population
Description of change		Revised Phase II entry criteria based on FDA feedback: Phase II will enter approximately 150 patients with lower risk MDS who were either previously untreated or progressed/became resistant following ESA and/or approved MDS drugs such as HMAs5-aza treatment. Approximately 20 sites from United States and European countries are expected to participate in

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		Phase II.
Rationale for change		Revised entry criterion based on FDA feedback
Section to be changed		3.3.2 Inclusion Criteria
Description of change		• Revised Inclusion Criterion #1 to reflect FDA feedback: Documented diagnosis of MDS according to World Health Organization (WHO) criteria that meets International Prognostic Scoring System (IPSS) classification of low or intermediate-1 risk disease as determined by microscopic and standard cytogenetic analyses of the bone marrow and peripheral complete blood count (CBC) and who are refractory to or are not amenable or eligible for approved MDS therapy.
Rationale for change		Revised entry criterion based on FDA feedback
Section to be changed		3.3.2 Inclusion Criteria
Description of change		Revised Inclusion #3 to better clarify entry requirements based on previous ESA exposure and EPO levels. Replaced Patients must have serum erythropoietin level > 500 U/L, or, if ≤ 500 U/L, patient is non-responsive to, refractory to, or intolerant of ESAs, or ESAs are contraindicated or unavailable. With Patient is non-responsive to, refractory to, or intolerant of ESAs, or ESAs are contraindicated or unavailable, or a documented serum erythropoietin level of > 500 U/L.
Rationale for change		Clarification and Update
Section to be changed		3.3.3 Exclusion Criteria
Description of change		Removed Exclusion # 4 to be in line with FDA feedback on patients eligible for the trial: Phase II only: any previous treatment for low or intermediate-1 risk MDS with lenalidomide or decitabine.
Rationale for change		Revised exclusion criteria based on FDA feedback
Section to be changed		4.1.1 Identity of BI investigational product and comparator product(s)
Description of change		Clarfied the infusion rates for all infusions on trial and added language on stability and maximum time allowed for infusions. The first and second infusionAll infusions will be started at a rate of 10 mL/h. The infusion rate should be increased every 30 (+/-10) minutes by

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		10 mL/h to a maximum of 80 mL/h as long as tolerated by the patient. Infusion should not exceed 8 hours. If considered safe by the Investigator, the stepwise increase of infusion rate during the third and subsequent infusions may be faster or steps may be omitted, but the maximum infusion rate must not exceed 120 mL/h. If symptoms of an infusion-related reaction occur, the infusion should be temporarily stopped. Upon recovery, it should be infused at 50% of the rate at which the reaction occurred and should not be dose escalated from this dose for at least 30 minutes. Lower rates may be selected if clinically indicated. Depending on the time of occurrence and the severity of the reaction, the investigator may consider administering additional supportive medication, e.g. corticosteroids. A stepwise re-increase of the infusion rate to a maximum of 80 mL/h is possible. For medical reasons, in case a patient experiences an adverse event during the infusion, the duration of the infusion may be expanded until the use-by date and use-by time indicated on the label is reached. The actual duration of the infusions and infusion steps need to be documented in the eCRF including actual start and end time, actual time points for interruption and restart of the infusion and the actual infusion rates. Infusions should not exceed 8 hours. In cases where an infusion is ongoing at 8 hours from the time of the start of infusion, the infusion must be stopped and documented.
Rationale for change		Clarification and Updated
Section to be changed		4.1.3 Selection of Doses in the Trial – Phase I and Table 4.1.3: 1 Entry of patients into trial, by cohort
Description of change		Replaced enrollment with entry
Rationale for change		Updated based on Boehringer Ingelheim standards
Section to be changed		4.1.3 Selection of Doses in the Trial – Phase I
Description of change		Clarified the permitted timing of the start of a new patient within a cohort: A one-week observation period must be followed between the first administration of BI 836858 and the start of treatment of the subsequent patient for all patients in the 20 mg cohort.

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Rationale for change		Clarification and Updated
Section to be changed		4.1.4 Drug assignment and administration of doses for each patient
Description of change		Added language on allowance of intra-patient dose escalation and required tests: Intra-patient dose escalation may be considered after agreement between investigator and sponsor for selected patients. It is restricted to patients who have completed and received a minimum of 8 administrations of BI 836858 and tolerate the treatment well at the time of dose escalation. Intra-patient dose escalation can only be performed at a time when the next higher dose cohort has been reviewed and considered safe by the DSB. The dose escalation step is limited to the dose which has been administered to the next higher cohort. Only one dose escalation will be permitted for a patient. Dose escalations can only occur on Day 1, or Visit 1 of a cycle. After the first dose at the higher dose level, patients have to be monitored for at least 24 hours after the end of the infusion, including a safety laboratory 24 hours after the first administration of the escalated dose of BI 836858. Patients who have escalated to a higher dose and who experience toxicities may be permitted to reduce back to a lower dose, following the criteria described above. Intra-patient dose escalation of BI 836858 will not be allowed in this trial.
Rationale for change		Clarification and Updated
Section to be changed		4.1.4 Drug assignment and administration of doses for each patient
Description of change		A log of all patients pre-screened and enrolled into the study (i.e. having given informed consent) will be maintained in the Investigator Site File (ISF) at the investigational site irrespective of whether they have been treated with investigational drug or not.
Rationale for change		Updated based on Boehringer Ingelheim standards
Section to be changed		4.2.1 Rescue medication, emergency procedures, and additional treatment(s)
Description of change		Clarified use of Growth factors does not include ESAs while on trial. “Rescue medication to reverse the action of BI

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		836858 is not available. Potential side effects of BI 836858 have to be treated symptomatically. Patients should receive supportive care according to the local guidelines regarding treatment of infusion-related reactions, blood product support, antibiotics, antivirals, analgesics, skin and mouth care, etc. The use of growth factors such as granulocyte colony stimulating factor (G-CSF) will be allowed (other than ESAs), but growth factors should be avoided during the first four administrations (2 cycles) for better assessment of safety and response parameters. G-CSF should not be given prophylactically."
Rationale for change		Clarification and Updated
Section to be changed		4.2.2.1 Restrictions regarding concomitant treatment
Description of change		Clarified use of Growth factors does not include ESAs while on trial. "Patients must not be receiving any concurrent treatment for MDS while on study. Exceptions will be made for supportive therapies such as transfusions or use of growth factors. The use of colony stimulating factor (G-CSF) will be allowed (other than ESAs), but growth factors should be avoided during the first four administrations (2 cycles) of BI 836858 for better assessment of safety and response parameters. G-CSF should not be given prophylactically."
Rationale for change		Clarification and Updated
Section to be changed		
Description of change		
Rationale for change		
Section to be changed		5.1.2.1 Bone marrow aspirate and peripheral blood
Description of change		Clarification that a "fresh" bone marrow sample is required. Historical samples will not be permitted for submission for analysis. "At baseline a BM aspirate is required. A BM

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		biopsy will be required if aspiration is inadequate. If these assessments were done prior to the patient's participation in the trial, they will be acceptable as long as they were obtained within 4 weeks prior to start of treatment with the trial drugs, otherwise, new samples will need to be obtained for the purpose of the study."
Rationale for change		Clarification and Updated
Section to be changed		
Description of change		
Rationale for change		
Section to be changed		5.2.1 Endpoint(s) of safety
Description of change		Revised DLT definition based on FDA feedback to consider events that are non disease-related events as possible DLTs: "The safety of BI 836858 in the Phase I and II will be assessed by a descriptive analysis of incidence and intensity of adverse events graded according to CTCAE (version 4.0), the incidence of non disease-related adverse events qualifying for dose limiting toxicity (DLT), laboratory data and results of physical examination."
Rationale for change		Revised DLT definition based on FDA feedback
Section to be changed		5.2.1.1 Dose Limiting Toxicity (DLT)
Description of change		Revised DLT definition based on FDA feedback to consider events that are non disease-related events as possible DLTs: "The Dose Limiting Toxicity is defined as follows: • Grade ≥ 3, according to CTCAE version 4.0, drug non disease-related, non-hematologic toxicity adverse events, with the following exceptions: • Any laboratory abnormality, which is not considered clinically significant by the investigator or resolves spontaneously or can be recovered with appropriate treatment within 5 days

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		• For patients with neutrophils <500 /µL (0.5 x 109/L) at start of treatment febrile neutropenia with neutrophils <500 /µL (0.5 x 109/L) or infection with neutrophils <500 /µL (0.5 x 109/L) will not constitute a DLT if they can be recovered with appropriate treatment within 14 days."
Rationale for change		Revised DLT definition based on FDA feedback
Section to be changed		5.2.2.2 Adverse Event and Serious Adverse Event Reporting
Description of change		Revised the timing of EOT visits from 28 days (+ 7 days) to 30 days (+ 7 days) after last administration of BI 836858. "The Residual Effect Period (REP) for BI 836858 is 2830 days. Therefore all events reported within 2830 days after the last trial medication will be considered on drug. All adverse events will be reported up until the last per protocol visit (EOT) which is 2830 days after the last dose of trial medication. The investigator does not need to actively monitor patients for adverse events once the clinical trial has ended. However, if the investigator becomes aware of an SAE(s) that occurred after the patient has completed the clinical trial (including any protocol required REP and / or follow-up), it should be reported by the investigator to the sponsor if considered relevant by the investigator."
Rationale for change		Boehringer Ingelheim Standards
Section to be changed		Table 5.2.2.2:1 AE/SAE Reporting Requirements
Description of change		Clarfication on the reporting of death after the REP: "Please note: The event(s) leading to death (other than progressive disease) should always be reported as SAE in this trial"
Rationale for change		Clarification and Updated
Section to be changed		5.2.2.2 Adverse Event and Serious Adverse Event Reporting and Table 5.2.2.2: 1 AE/SAE reporting requirements
Description of change		Clarified SAE reporting relative to deaths that occur after REP that are due to progressive disease: "Exemption to SAE Reporting Disease progression/relapse of the underlying condition is a study endpoint for analysis of

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		efficacy. Disease progression/relapse is exempted from reporting as a (S)AE. Progression/relapse of the subject's underlying condition will be recorded in the appropriate pages of the (e)CRF as part of efficacy data collection. Death due to disease progression/relapse is to be recorded on the appropriate (e)CRF page and not on a SAE form. Examples of exempted events of disease progression/relapse are: • Progression/relapse of underlying condition (Progressive disease PD): if PD is clearly consistent with the suspected progression as defined by the respective response criteria. • Hospitalization/Procedures due solely to the progression/relapse of underlying condition Clinical symptoms and/or signs of progression/relapse (with or without confirmation by objective criteria), if the symptom can exclusively be determined to be due to the progression/relapse of the underlying condition and meets the expected pattern of progression/relapse for the disease under study. If the observed event is not unequivocally due to progression/relapse of the underlying condition and there is a reasonable possibility for a causal relationship to administration of study medication, the event must be reported as (S)AE on both the SAE form and the (e)CRF. Exempted events are collected and tracked following the protocol-specified monitoring plan. Exempted events are monitored at appropriate intervals preferably by an independent committee such as a Data Monitoring Committee."
Rationale for change		Clarification and Updated
Section to be changed		5.2.3.1 General Safety Laboratory Parameters
Description of change		Updated Hematology panel to clarify type of tests and frequency. "Hemoglobin, red blood cell count (RBC), white blood cell count (WBC) with differential

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		(neutrophils, basophils lymphocytes, monocytes, eosinophil), platelets (PLT) Reticulocytes have to be measured only at Visit 1 of every second cycle, EOC4, EOT. Visit 1 of every second cycle after EOC4 and EOT."
Rationale for change		Clarification and Updated
Section to be changed		5.2.3.1 General Safety Laboratory Parameters
Description of change		Updated Biochemistry panel to clarify type of tests and frequency. "Glucose, sodium, potassium, calcium, inorganic phosphate, creatinine, AST, ALT, alkaline phosphatase (AP), lactate dehydrogenase (LDH), bilirubin, urea (preferred) or BUN, total protein, albumin, uric acid Serum immunoglobulin levels (IgG, IgM, IgA) and direct antiglobulin (direct Coombs) test have to be measured only every 8 weeks2 cycles, EOC4 and EOT."
Rationale for change		Clarification and Updated
Section to be changed		5.2.3.1 General Safety Laboratory Parameters
Description of change		Added clarification and language that additional safety tests are required 24 hours after a patient dose escalates. "An additional Additional safety labs will be collected on day 2 of Cycle 1 (i.e., 24 hours after the first administration of BI 836858) and after the first infusion of a higher dose, following intra- patient dose escalation (i.e. 24 hours after the first administration of the higher dose). Other lab tests to be included for these visits: haptoglobin, direct antiglobulin/Coombs test, bilirubin (direct and indirect) and free hemoglobin. Non pre-existing abnormal laboratory values (CTCAE Grade 3 or higher) will be followed up every 48 hours until these laboratory values are back to at least CTCAE Grade 1 or baseline."
Rationale for change		Clarification and Updated
Section to be changed		
Description of change		

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Number of global amendment		1
Rationale for change		
Section to be changed		
Description of change		

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Rationale for change		
Section to be changed		
Description of change		
Rationale for change		
Section to be changed		
Description of change		
Rationale for change		
Section to be changed		6.2.1 Screening and Run-in Period(s)
Description of change		Clarified the collection of Molecular genetics and cytogenetics. Phase I patients will only require historical and available data. Phase II patients are required to have tests performed as part of

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		Screening. • "Molecular genetics and cytogenetics of MDS (Historical/available data for Phase I patients and required at screening for Phase II patients)"
Rationale for change		Clarification and Updated
Section to be changed		6.2.2 Treatment Period(s)
Description of change		Clarify the frequency and timing of Physical exams. "Physical examination and ECOG performance score completed Day 1 of every second cycle beginning with cycle 1. Physical exam may be completed up to 2 days prior to administration and ECOG must be completed on the day of the administration. Height only at Day 1 of first cycle. If the first administration of BI 836858, or BSC treatment on trial (Phase II) is completed within 3 days of the screening visit, these examinations do not need to be repeated" Removal of erroneous text. • - Bone marrow aspiration (Required before the 9th administration of BI 836858 or by EOC4 and at the discretion of the Investigator) Clarification on timing of PGx sample Blood for pharmacogenomics (Day 1 of Cycle 1. If not obtained at C1D1, a sample may be collected anytime during Cycle 1)
Rationale for change		Clarification and Updated
Section to be changed		6.2.2.2 Visit 2 and Visit 4 (+ 1 day window allowed beginning in Cycle 3), following administration of BI 836858 (Phase II: these visits will also occur for BSC patients,
Description of change		Correct text in header as visits 2 and 4 are not dosing days
Rationale for change		Clarification and Updated
Section to be changed		6.2.2.2 Visit 2 and Visit 4
Description of change		Updated language to remove erroneous text as Visit 2 and 4 and not dosing days: In Cycles 1 and 2, visits will occur at Day 8 and

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		Day 22 after the administration. Beginning in Cycle 3 and thereafter, patients will come to the clinic only for infusions and will not be required to complete the visits on Day 8 and Day 22 unless medically indicated. On the Visit 2 and Visit 4 days, the following parameters and investigations will be obtained and / or performed:
Rationale for change		Clarification and Updated
Section to be changed		6.2.2.3 End of Cycle 4 (EOC4)
Description of change		Clarify that testing is only required for patients enrolled in Phase II • "Molecular genetics and cytogenetics of MDS (Phase II patients only)"
Rationale for change		Clarification and Updated
Section to be changed		6.2.2.5 Maintenance Cycles (Visit 1)
Description of change		Correct typographical error. PEs starting with Cycle 1 of the maintenance phase and not Cycle 5. • "Physical examination every other cycle starting with cycle 51 (may be completed up to 2 days prior) and ECOG performance score
Rationale for change		Clarification and Updated
Section to be changed		6.2.3 End of trial Treatment and Follow-up Period
Description of change		Revised and clarified header of section refers to end of treatment and not trial
Rationale for change		Clarification and Updated
Section to be changed		6.2.3.1 End of Treatment (EOT)
Description of change		Revised timing of EOT visit to be in line with Boehringer-Ingelheim standards. "The EOT visit is to occur 2830 days (+7 days) after the last administration of BI 836858. " Clarified that Molecular/cytogenetic testing only required for Phase II patients • "Molecular genetics and cytogenetics of MDS (Phase II patients only)" Clarified text and fixed error. • End of trial treatment. This will include the reason for conclusion of trial treatment if applicable, premature discontinuation of trialtreatment, and date of last administration of the trial drug

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Number of global amendment		1
Rationale for change		Clarification and Updated
Section to be changed		6.2.3.2 Follow-up
Description of change		Clarify and revised follow-up period for Phase I and Phase II patients. "Follow-up visits or telephone calls will be performed after the patient has completed or discontinued treatment according to protocol or is not eligible for further treatment cycles. Follow-up visits or telephone calls will begin 4 weeks after the EOT visit. Follow-up will end in case the patient is lost to follow-up or in case the Investigator and Sponsor agree not to pursue further follow-up visits. In phase I, Follow-up visits should be performed at 4 week intervals for 6 months. After the 6 month assessment, patients will be considered off trial. In Phase II, Follow-up visits should be performed at 4 week intervals for the first 12 months or earlier if appropriate as determined by the Investigator, and thereafter in 6 month intervals.
Rationale for change		Clarification and Updated
Section to be changed		7.3 Planned Analyses
Description of change		Clarified definition that the intent to treat population as randomized set and not treated. "For the Phase II the full analysis set (Phase II) is defined, in analogy to the intention to treat population as the treated randomized set with respect to Phase II; i.e. all patients randomized."
Rationale for change		Clarification and Updated
Section to be changed		7.3.3 Safety Analysis
Description of change		Revised definitions. "All treated patients of the full analysis set (both Phase I and Phase II) will be included in the safety analyses. Two analyses will be performed. The first analysis of safety will be performed for the first part of the trial (determination of the MTD, first cycle only, treatment regimen = initial dose at the start of the treatment, full analysistreated set (Phase I only)). This descriptive analysis will evaluate the MTD for the monotherapy of BI 836858 in MDS patients. The second analysis will be performed with respect to all cycles and will act as a support for the

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Number of global amendment		1
		determination of the MTD (full analysistreated set (both Phase I and Phase II)).”
Rationale for change		Clarification and Updated
Section to be changed		7.5 Randomization
Description of change		Randomization will be performed in the phase II part of this trial only. In Phase I, doses will be assigned based on the decision made by the DSB (see Section 7.3.4.). In Phase II, the randomization ratio is 1:1 for the two treatment arms, i.e. BI 836858 plus BSC vs. BSC alone, per investigator’s choice. Randomization will be stratified by number of previous lines of MDS therapy (0, 1, ≥ 2), where previous MDS therapy also includes previous ESA therapy. Randomization will be performed using IVRS/IWRS. Boehringer Ingelheim Pharma GmbH & Co. KG, Clinical Trial Support Group or a CRO appointed by the Sponsor will provide the randomization lists using a validated randomization number generating system. Access to the randomization codes will be controlled and documented.
Rationale for change		Revised Phase II Stratification levels in response to FDA feedback on potential patients eligible for trial.
Section to be changed		
Description of change		
Rationale for change		

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11.2 GLOBAL AMENDMENT 2

Number of global amendment		2
Date of CTP revision		16 JUN 2017
EudraCT number		N/A
BI Trial number		1315.7
BI Investigational Product(s)		BI 836858
Title of protocol		A Phase I/II, Multicenter, Open-Label, Dose Escalation and Randomized Trial of BI 836858 in Patients with Low or Intermediate-1 Risk Myelodysplastic Syndromes
To be implemented only after approval of the IRB/IEC/Competent Authorities		☒
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		☐
Can be implemented without IRB/IEC/ Competent Authority approval as changes involve logistical or administrative aspects only		☐
Section to be changed		1.2.1 BI 836858
Description of change		*The following has been added:* There are two combination studies for patients diagnosed with AML ongoing, one with azacytidine (ClinicalTrials.gov Identifier: NCT03013998) and another one with decitabine (ClinicalTrials.gov Identifier: NCT02632721). Only limited pharmacokinetic, pharmacodynamic and tumor response data are not available at this point.
Rationale for change		Update on BI 836858 clinical program
Section to be changed		2.1 Rationale for Performing The Trial

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Number of global amendment		2
Description of change		*The following text in bold below is added*: It has been described that previous treatments with HMAs or lenalidomide reduce the number and activity of NK cells. [R17-1502, R17-1503, R17-1510]. BI 836858 mediated ADCC depends on functional NK cells. Therefore, it is hypothesized that Lower-Risk MDS patients it without previous HMA or lenalidomide treatments may respond better to BI 836858, providing the rationale for an MTD expansion cohort targeting this group of patients. Low to intermediate-1 risk MDS patients comprise around 70% of the entire MDS populations. In clinical practice, lower-risk patients are those with expected median survival measured in years, and those who have a lower chance to progress to AML. The main clinical burden in this group of patients is symptomatic cytopenias and their associated complications, such as bleeding, risk of infection and iron overload. The goal of treatment is to alleviate symptomatic cytopenias and abrogate or reduce RBC transfusion requirements leading to better quality of life. This rationale is supported by FDA and EMA approval of lenalidomide in MDS patients with a del 5q. Overall treatment options for patients with lower risk MDS, especially for those without a 5q deletion, are limited and benefit to available treatment is not satisfactory. Rates of RBC TI for at least 8 weeks for patients with Low to Intermediate-1 risk MDS with treatment of HMAs or lenalidomide are 15 to 30% without improvement in overall survival. Furthermore the outcomes for those patients who failed treatment with HMAs or lenalidomide are poor with an estimated 3 year overall survival rate of 27% [R11-1106, R17-1501, R17-1504, R17-1505, R17-1506, R17-1507, R17-1508, R17-1509, R17-1521].
Rationale for change		Rationale and justification for enrolling treatment naïve patients in the expansion cohort
Section to be changed		2.2 Trial Objectives

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Number of global amendment		2
Description of change		*The following text in bold below is added:* The Phase I primary objectives of the trial are to determine the maximum tolerated dose (MTD) and the Recommended Phase II Dose (RP2D) to be used in the Phase II. Secondary objectives include safety, pharmacokinetics, exploratory biomarkers and efficacy of BI 836858 monotherapy. The trial will enroll patients with low or intermediate-1 risk MDS with symptomatic anemia, who at a minimum, experienced ESA treatment failure or do not qualify (serum erythropoietin level > 500 U) for ESA treatment and are refractory to or are not amenable or eligible for approved MDS therapy in the dose escalation phase and for one of the MTD expansion cohorts. The second MTD expansion cohort will enroll patients with low or intermediate-1 risk MDS with symptomatic anemia, experienced ESA treatment failure or do not qualify (serum erythropoietin level > 500 U) for ESA treatment and who have not received prior HMA and/or lenalidomide (this cohort is referred to as "untreated"). Patients with a deletion 5q cytogenetic abnormality will be allowed in Phase I who do not qualify for lenalidomide treatment (Absolute Neutrophil Count (ANC) < 500/µL or platelets <50,000/µl) or who experience primary lenalidomide failure (not for untreated expansion cohort). lenalidomide failure is defined as lack of hematological improvement after 4 months of therapy, or secondary failure defined as loss of prior lenalidomide response at any time point.
Rationale for change		Updated to reflect new expansion cohort
Section to be changed		Figure 3.1:1 Structure of the 1315.7 Phase I/II
Description of change		Figure updated
Rationale for change		Update to reflect additional expansion cohort
Section to be changed		3.1 Overall Trial Design and Plan
Description of change		*Added:* The second expansion cohort will enroll patients with low or intermediate-1 risk MDS with symptomatic anemia, who at a minimum, experienced ESA treatment failure or do not qualify (serum erythropoietin level > 500 U) for ESA treatment and who have not received prior HMA and/or lenalidomide.
Rationale for change		New language for additional expansion cohort

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Number of global amendment		2
Section to be changed		3.1 Overall Trial Design and Plan
Description of change		*The following text below in bold is added:* In Phase I dose escalation part, patients with low to intermediate-1 risk MDS, who have experienced ESA treatment failure, except for patients who do not qualify for ESA treatment and are refractory to or are not amenable or eligible for approved MDS therapy will be assigned to a dose cohort under investigation. After determination of the MTD/RP2D the same group of patients as for the dose escalation will be enrolled in the first expansion cohort (referred to as "pre-treated" patients). The second expansion cohort will enroll patients with low or intermediate-1 risk MDS with symptomatic anemia, who at a minimum, experienced ESA treatment failure or do not qualify (serum erythropoietin level > 500 U) for ESA treatment and who have not received prior HMA and/or lenalidomide (referred to as "untreated" patients). Treatment failure on ESAs is defined as 1) failure or ceasing to show hematologic response after at least 8 weeks of 40,000 to 60,000 IU/week of erythropoietin (EPO) or equivalent or 2) low
Rationale for change		New language for additional expansion cohort
Section to be changed		3.1 Overall Trial Design and Plan
Description of change		*The following text has been added:* two expansion cohorts (untreated and pre-treated with HMA and/or lenalidomide) will recruit up to 12 patients per cohort. Overall a minimum of 12 patients (including both expansion cohorts and the last escalation cohort) will
Rationale for change		New language for additional expansion cohort
Section to be changed		3.1.1.1 Administrative structure of the trial
Description of change		*The text below in bold below has been added:* Adult patients with low to intermediate-1 risk MDS, according to International Working Group (IWG) criteria, who, at a minimum, experienced ESA treatment failure, except for patients that do not qualify for ESA treatment and are refractory to or are not amenable or eligible for approved MDS therapy, will be enrolled for the Phase I dose escalation part. After determination of the MTD/RP2D, the same group of patients as for the dose escalation will be enrolled in the first expansion cohort (referred to as "pre-treated" patients)

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Number of global amendment		2
		The second expansion cohort will enroll patients with low or intermediate-1 risk MDS with symptomatic anemia, who, experienced ESA treatment failure or do not qualify (serum erythropoietin level > 500 U) for ESA treatment and who have not received prior HMA and/or lenalidomide (referred to as "untreated" patients).Approximately three Phase I sites in the United States will participate in the dose escalation portion of Phase I. An additional 2-3 sites in the United States will participate during the cohort expansion portion of Phase I. The Phase I dose-escalation will be guided by a Bayesian logistic regression model (BLRM) with overdose control (refer to Section 7). The DSB will consist of the Phase I investigators, Team Member Medicine (TMM), Trial Clinical Monitor (TCM), Project Statistician, Clinical Pharmacological Project Lead (CPPL) and TransMed Expert (TME). The information on the overdose risk will be presented by the trial statistician to the DSB. Additional information, such as lower grade adverse events, pharmacokinetics (PK), if available, progressive disease (PD), individual patient profiles and other relevant information will also be presented. Based on this information, the members of the DSB will reach a joint 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 DSB will also recommend the size for the next cohort. However, the final decision on the next cohort size will be made by a mutual decision between the TMM and the Coordinating Investigator (CI). Minutes of the DSB meetings and recommendations will be documented and archived by the TCM. Two expansion cohorts (untreated or pre-treated with HMA and/or lenalidomide) will recruit up to 12 patients per cohort and receive treatment at the RP2D prior to start of Phase II. Prior to the initiation of Phase II, a Phase I safety analysis report will be prepared based on the Phase I data. A summary of safety and efficacy from the dose escalation cohorts and from either one or both

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Number of global amendment		2
		of the expansion cohorts and RP2D will be included in the Phase I safety analysis report. The Phase I safety analysis report will be made available for all investigators who participate in the Phase II.
Rationale for change		New language for additional expansion cohort
Section to be changed		3.2 Discussion of Trial Design, Including The Choice of Control Group(s)
Description of change		*The text in bold below has been added:* The Phase I is designed to determine the dose of BI 836858 monotherapy in patients with low to intermediate-1 MDS with symptomatic anemia. The study will be conducted in an open label, single arm dose escalation trial design. Dose escalation and cohort size will be determined based on the recommendation by the DSB, according to a Bayesian Model with overdose control. An escalation with overdose control design will increase a chance of treating patients at efficacious doses while reducing the risk of overdosing. This design is based on practical experience and is a preferable algorithmic method due to its superior ability to identify the dose with the 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). Expansion cohorts will enroll at the RP2D defined during the dose escalation portion of Phase I.
Rationale for change		New language for additional expansion cohort
Section to be changed		3.3 Selection of Trial Population
Description of change		*The text in bold below has been added:* Phase I will enter approximately 50 patients from approximately 3-5 sites in the United States. In the Phase I dose escalation part, the trial will recruit patients with lower risk MDS who were either previously untreated or progressed/became resistant following ESA treatment. After determination of the MTD/RP2D, the same group of patients as for the dose escalation will be enrolled in the first expansion cohort. The second expansion cohort will enroll patients with low or intermediate-1 risk MDS with symptomatic anemia, who experienced ESA treatment failure or do not qualify for ESA treatment and who have not received prior HMA and/or lenalidomide.
Rationale for change		New language for additional expansion cohort
Section to be changed		3.3.2 Inclusion criteria

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Number of global amendment		2
Description of change		• The text in bold below has been added: • 1.Documented diagnosis of MDS according to World Health Organization (WHO) criteria that meets International Prognostic Scoring System (IPSS) classification of low or intermediate-1 risk disease at screening as determined by microscopic and standard cytogenetic analyses of the bone marrow and peripheral complete blood count (CBC) and who are refractory to or are not amenable or eligible for approved MDS therapy. The second expansion cohort will enroll patients with low or intermediate-1 risk MDS with symptomatic anemia, experienced ESA treatment failure or do not qualify (serum erythropoietin level > 500 U) for ESA treatment and who have not received prior HMA and/or lenalidomide. • • -Phase I (dose escalation and "pre-treated" expansion cohort only): refractory to or not amendable or eligible for established MDS therapy (HMA, lenalidomide) • -Phase I ("untreated" expansion cohort only): no [prior HMA and/or lenalidomide treatment • 2. Patient has the evidence of symptomatic anemia according to the following criteria: • -Phase I only: Patients must have mean haemoglobin concentration <10.0 g/dL of 2 measurements (not influenced by RBCs within 8 weeks prior to start of treatment OR, • -Phase I/II: Patients must have received ≥ 2 units of RBCs for hemoglobin ≤ 9.0 g/dL within 8 weeks prior to start of treatment.
Rationale for change		• New language for additional expansion cohort

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Number of global amendment		2
Section to be changed		• 3.3.3 Exclusion criteria
Description of change		• The following text has been removed: • 7. Prothrombin time (PT) > 1.5x ULN for patients not on therapeutic vitamin K antagonists (phenprocoumon, warfarin) • • The following text has been modified: • Known human immunodeficiency virus (HIV) infection and / or active hepatitis B infection (defined as presence of Hep B DNA), active hepatitis C infection (defined as presence of Hep C RNA) ~~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.~~
Rationale for change		• Update and clarify exclusion criterion
Section to be changed		• 3.3.3 Exclusion criteria
Description of change		14. Female patients of childbearing potential who are sexually active and unwilling to use a medically acceptable method of contraception during the trial and for 6 months after the last administration of BI 836858, i.e. combination of two forms of effective contraception (defined as hormonal contraception, intrauterine device, transdermal patch, implantable or injectable contraceptive, bilateral tubal ligation 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 sterilized (e.g. hysterectomy, bilateral oophorectomy or bilateral salpingectomy
Rationale for change		• Update and Clarification
Section to be changed		• 3.3.4 Removal of patients from therapy or assessments

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Number of global amendment		2
Description of change		*The text below has been added:* • Delay in start of subsequent treatment cycle of more than 8 weeks due to a drug-related event (e.g. delay in recovery of blood counts). Refer to section 4.1.4.
Rationale for change		Update and Clarification
Section to be changed		4.1.3 Section of doses in the trial
Description of change		*The text below has been added:* If no DLT is observed at a dose that efficacy is considered sufficient, the DSB may decide to include additional number of patients at the same dose level and to declare this dose level as the RP2D. Before the conclusion of Phase I and prior to initiating the Phase II, two expansion cohorts (untreated or pre-treated with HMA and/or lenalidomide) will recruit up to 12 patients per cohort (overall a minimum of 12 patients – inclusive of the lase dose escalation cohort) and receive treatment at RP2D. In the expansion cohorts new patients may be enrolled at any time without observation period.
Rationale for change		New language for additional expansion cohort
Section to be changed		4.1.4 Drug assignment and administration of doses for each patient
Description of change		*The text in bold below has been added:* Before the administration of BI 836858, adverse events and safety laboratory will be assessed. To start or continue treatment with further administrations, all of the following criteria must be met
Rationale for change		Clarify start of treatment
Section to be changed		5.1.1 Endpoints of efficacy
Description of change		*The text below has been added:* • Mean hemoglobin increase ≥ 1.5 g/dL
Rationale for change		Additional endpoint
Section to be changed		5.1.2.3 Assessment and definition of response criteria
Description of change		*The text below has been added:* • Mean hemoglobin increase ≥ 1.5 g/dL — Time Frame: Up to approximately 48 weeks. Proportion of subjects achieving hemoglobin (Hgb) increase from baseline ≥ 1.5 g/dL over any consecutive 56-day period in absence of

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Number of global amendment		2
		Red blood cell (RBC) transfusions.
Rationale for change		Additional endpoint
Section to be changed		5.2.1.3 Recommended Phase 2 Dose (RP2D)
Description of change		*The text in bold below has been added:* Before the conclusion of Phase I and prior to initiating the Phase II, two expansion cohorts (untreated or pre-treated with HMA and/or lenalidomide) will recruit up to 12 patients per cohort (overall minimum of 12 patients – inclusive of the last dose escalation cohort) and receive treatment at RP2D. *The following text has been removed from this section:* Based on the ~~overall~~ Phase I data, the DSB will make a final determination of the RP2D, which must not exceed the MTD. The Phase I safety analysis report, including the rationale of RP2D determination will be made available to all investigators prior to the initiation of Phase II.
Rationale for change		New language for additional expansion cohort
Section to be changed		
Description of change		
Rationale for change		
Section to be changed		6.2.3.1 End of treatment (EOT)
Description of change		*The following text has been removed from this section*: • Physical examination including weight (~~may be completed up to 2 days prior)~~ and ECOG performance score
Rationale for change		Remove timing of Physical Assessment at EOT
Section to be changed		7.1 Statistical Design- Model
Description of change		*The text below has been added:* The DSB may recommend stopping the dose finding phase after the criterion for MTD 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 DSB may decide to include additional number of patients at

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Number of global amendment		2
		this dose level and to declare this dose as the recommended dose for phase 2 (RP2D).
Rationale for change		Update DSB Dose finding definition
Section to be changed		7.3.3 Safety analyses
Description of change		*The text in bold below has been added:* All treated patients (both Phase I and Phase II) will be included in the safety analyses. Two analyses will be performed. The first analysis of safety will be performed for the first part of the trial (determination of the MTD, first cycle only, treatment regimen = initial dose at the start of the treatment, treated set (Phase I only)). This descriptive analysis will evaluate the MTD for the monotherapy of BI 836858 in MDS patients. The second analysis will be performed with respect to all cycles and will act as a support for the determination of the MTD (treated set (both Phase I and Phase II)). In addition a sensitivity analysis for the second expansion cohort will be conducted. Further details will be described in the TSAP.
Rationale for change		Update for additional expansion cohort

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11.3 GLOBAL AMENDMENT 3

Number of global amendment		**3**
Date of CTP revision		**12 DEC 2018**
EudraCT number		**2018-002177-21**
BI Trial number		**1315.7**
BI Investigational Product(s)		**BI 836858**
Title of protocol		**A Phase I/II, Multicenter, Open-Label, Dose Escalation and Randomized Trial of BI 836858 in Patients with Low or Intermediate-1 Risk Myelodysplastic Syndromes**
To be implemented only after approval of the IRB/IEC/Competent Authorities		☒
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		☐
Can be implemented without IRB/IEC/ Competent Authority approval as changes involve logistical or administrative aspects only		☐
Section to be changed		**Title Page**
Description of change		*Add* EudraCT No. **2018-002177-21**
Rationale for change		Added European Country to Trial
Section to be changed		**Clinical Trial Protocol Synopsis**
Description of change		*Objectives: Deleted text:* Phase II: To investigate safety and efficacy of BI 836858 plus Best Supportive Care (BSC) compared to Best Supportive Care alone in low or intermediate-1 risk MDS patients with symptomatic anemia. ~~without a deletion 5q cytogenetic abnormality.~~
Rationale for change		Definition of Phase II patient population was further clarified
Section to be changed		**Clinical Trial Protocol Synopsis**
Description of change		*Diagnosis section: Phase I patient population updated with bold text and Phase II patient*

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Number of global amendment		**3**
		population deleted: ~~**Phase I:**~~ Patients with MDS with symptomatic anemia due to low or intermediate-1 risk (i.e., **International Prognostic Scoring System** (IPSS) score 0-1) ~~who at a minimum~~ have experienced Erythropoiesis-Stimulating Agent (ESA) treatment failure or low chance of response to ESAs **and are refractory to or are not amenable or eligible for approved MDS therapy.** ~~Phase II: Patients with MDS with symptomatic anemia due to low or intermediate-1 risk (i.e., International Prognostic Scoring System (IPSS) score 0-1) without a deletion 5q cytogenetic abnormality who at a minimum have experienced ESA treatment failure or low chance of response to ESAs and are refractory to or are not amenable or eligible for approved MDS therapy~~.
Rationale for change		Definition of Phase I patient populations was further clarified and Phase II patient population was removed
Section to be changed		**Clinical Trial Protocol Synopsis**
Description of change		*Main criteria for Inclusion section was updated for Phase I (added bold text) and revised for Phase II (deleted text):* Phase I: Adult patients with low or intermediate-1 risk MDS who, experienced ESA treatment failure, except for those who have a low chance to respond to ESA treatment **and are refractory to or are not amenable or eligible for approved MDS therapy.** Phase II: Adult patients with low or intermediate-1 risk MDS ~~either previously untreated or following progression/resistance after ESA and are refractory to or are not amenable or eligible for approved MDS therapy~~.
Rationale for change		Definitions of Phase I and Phase II patient populations inclusion criteria further clarified as requested by German Health Authority
Section to be changed		**Clinical Trial Protocol Synopsis**
Description of change		*Duration of treatment section was further clarified with added bold text:* Patients **with clinical benefit, PR or CR after the 4th (or 6th) Cycle** will receive repeated cycles

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Number of global amendment		**3**
		until relapse after Complete Response (CR), Partial Response (PR), erythroid response (HI-E), Red Blood Cell transfusion independency or Marrow Complete Response (mCR), Progressive Disease (PD), or unacceptable adverse event(s), in the absence of other withdrawal criteria.
Rationale for change		Clarify point at which patients can transition to Maintenance phase
Section to be changed		**Section 1.2.1 BI 836858**
Description of change		*Reference for unpublished data was updated:* Reference **P17-02032** was added. References section 9.1 updated with citation
Rationale for change		Supporting Data was published, reference updated
Section to be changed		**Section 2.1 Rationale for Performing the Trial**
Description of change		*Reference for unpublished data was updated:* Reference **P17-02032** was added. References section 9.1 updated with citation
Rationale for change		Supporting Data was published, reference updated
Section to be changed		**2.2 Trial Objectives**
Description of change		*Deleted text:* In the randomized Phase II, primary objectives are to investigate the efficacy of BI 836858 plus Best Supportive Care (BSC) vs. Best Supportive Care alone, in low or intermediate-1 risk MDS patients with symptomatic anemia ~~without a deletion 5q cytogenetic abnormality who are previously untreated or~~ who progressed/became resistant following ESA, and are refractory to or are not amenable or eligible for approved MDS therapy. Secondary objectives include the investigation of safety and tolerability of BI 836858 in this patient population
Rationale for change		Definition of Phase II patient population further clarified as requested by German Health Authority
Section to be changed		**2.3 Benefit – Risk Assessment**
Description of change		*Added bold text:* Considering these data and the experience with other monoclonal antibodies in hemato-oncology indications, infusion-related reactions are likely. Prophylactic measures will be stipulated for primary prevention, and supportive treatments are available (Section 4.1.4). Although rare, a potential for drug-induced liver injury is under constant surveillance by sponsors and regulators.

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Number of global amendment		**3**
		Therefore, this study requires timely detection, evaluation, and follow-up of laboratory alterations of selected liver laboratory parameters to ensure patients´ safety. A Phase I safety analysis report will be prepared based on the Phase I data and made available to **regulatory authorities, ethics committees/IRBs** and all investigators, **and the protocol will be amended** prior to initiating Phase II **as defined in detail in Section 3.1.1.1.** In addition, this study will utilize a Data Safety Board to oversee safety, review dose limiting toxicities and determine dose escalations.
Rationale for change		German Health Authority required Phase I safety report and Phase II protocol amendment to be finalized and distributed before start of Phase II
Section to be changed		**3.1 Overall Trial Design and Plan**
Description of change		*The following text was deleted/added (in bold):* Phase I: In Phase I dose escalation part, patients with low to intermediate-1 risk MDS, who have experienced ESA treatment failure, except for patients who do not qualify for ESA treatment and are refractory to or are not amenable or eligible for approved MDS therapy will be assigned to a dose cohort under investigation. After determination of the MTD/RP2D the same group of patients as for the dose escalation will be enrolled in the first expansion cohort (referred to as "pre-treated" patients). The second expansion cohort will enroll patients with low or intermediate-1 risk MDS with symptomatic anemia, who ~~at a minimum~~ experienced ESA treatment failure or do not qualify (serum erythropoietin level > 500 U) for ESA treatment and who have not received prior HMA and/or lenalidomide (referred to as "untreated" patients). Treatment failure on ESAs is defined as 1) failure or ceasing to show hematologic response after at least 8 weeks of 40,000 to 60,000 IU/week of erythropoietin (EPO) or equivalent or 2) low chance/response to ESA with endogenous serum EPO>500. It is expected that approximately 50 patients will be enrolled. Phase II

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Number of global amendment		**3**
		In Phase II, patients will be enrolled in a randomized manner to investigate efficacy and safety of BI 836858 at RP2D in patients ~~either previously untreated or following progression/resistance after the treatment with ESAs and/or approved MDS drugs such as HMAs. Treatment failure on HMA is defined as 1) no response after at least four cycles of HMA, 2) progression of disease on HMA or 3) Grade 3-4 non-hematologic toxicity. Patients also must~~ **who** have experienced treatment failure on ESAs, except for patients who do not qualify for ESA treatment. As defined above, treatment failure on ESAs is defined as 1) failure or ceasing to show hematologic response after at least 8 weeks of 40,000 to 60,000 IU/week of erythropoietin (EPO) or equivalent or 2) low chance/response to ESA with endogenous serum EPO>500. **For further details regarding inclusion of patients in Phase II please see inclusion criteria (section 3.3.2).** Randomization will be stratified by number of previous lines of MDS therapy (0, 1, >=2), where previous MDS therapy also includes previous ESA therapy (refer to Section 7.5). A total of 150 patients, 75 each arm, will be enrolled in Phase II.
Rationale for change		Definition of Phase I and Phase II patients updated to align with updated inclusion criteria
Section to be changed		**3.1.1.1 Phase I**
Description of change		*The bolded text was added:* Adult patients with low to intermediate-1 risk MDS, according to International Working Group (IWG) criteria, who experienced ESA treatment failure, except for patients that do not qualify for ESA treatment and are refractory to or are not amenable or eligible for approved MDS therapy, will be enrolled for the Phase I dose escalation part. After determination of the MTD/RP2D, the same group of patients as for the dose escalation will be enrolled in the first expansion cohort (referred to as “pre-treated” patients) The second expansion cohort will enroll patients with low or intermediate-1 risk MDS with symptomatic anemia, who experienced ESA treatment failure

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Number of global amendment		**3**
		or do not qualify (serum erythropoietin level > 500 U) for ESA treatment and who have not received prior HMA and/or lenalidomide (referred to as "untreated" patients). Approximately three Phase I sites in the United States will participate in the dose escalation portion of Phase I. **An additional 2-3 sites in the United States and/or European country(ies) are expected to participate during the cohort expansion portion of Phase I.**
Rationale for change		Per German Ethics Committee, paragraph was revised to include language stating other countries, in addition to the United States will be participating in Phase Ib
Section to be changed		**3.1.1.1 Phase I**
Description of change		*Paragraph updated and includes additional information in bold text.* Prior to the initiation of Phase II, a Phase I safety analysis report will be prepared based on the Phase I data. A summary of safety and efficacy from the dose escalation cohorts and from either one or both of the expansion cohorts and RP2D will be included in the Phase I safety analysis report. The Phase I safety analysis report will be made available for all investigators who participate in the Phase II. Revised: Prior to the initiation of Phase II, a Phase I safety analysis report will be prepared **and the protocol will be amended based on Phase I results to update the benefit-risk assessment, stipulate the BI 836858 dose to be used in the Phase II part and define details of the patient population to be enrolled in phase II**. A summary of safety and efficacy from the dose escalation cohorts and from the expansion cohorts and RP2D will be included in the Phase I safety analysis report. The Phase I safety analysis report **and amended protocol will be made available for Health Authority and Ethics Committee/IRB review and approval (where applicable) and to all investigators** who participate in Phase II. **Phase II is not allowed by regulatory authority yet, and Phase II will not**

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Number of global amendment		**3**
		be started prior to regulatory approval as required in attending countries. Patients must not be recruited to Phase II until local Health Authority and ethics committee/IRB approvals (where applicable) are granted.
Rationale for change		German Health Authority required Phase I safety report and Phase II protocol amendment to be finalized and distributed before start of Phase II
Section to be changed		**3.3 Selection of Trial Population**
Description of change		*New text added in bold. And text deleted* Phase I will enter approximately 50 patients from **approximately 3-7 sites in the United States and/or European country(ies).** In the Phase I dose escalation part, the trial will recruit patients with lower risk MDS who were either previously untreated or progressed/became resistant following ESA treatment. After determination of the MTD/RP2D, the same group of patients as for the dose escalation will be enrolled in the first expansion cohort. The second expansion cohort will enroll patients with low or intermediate-1 risk MDS with symptomatic anemia, who experienced ESA treatment failure or do not qualify for ESA treatment and who have not received prior HMA and/or lenalidomide
Rationale for change		Per German Ethics Committee, paragraph was revised to include language stating other countries, in addition to the United States will be participating in Phase Ib
Section to be changed		**3.3 Selection of Trial Population**
Description of change		*Text deleted:* Phase II will enter approximately 150 patients ~~with lower risk MDS who were either previously untreated or progressed/became resistant following ESA and/or approved MDS drugs such as HMAs~~. Approximately 20 sites from United States and European countries are expected to participate in Phase II.
Rationale for change		Definition of Phase II patients updated to align with updated inclusion criteria
Section to be changed		**3.3.2 Inclusion Criteria**
Description of change		*Inclusion 1 updated with bold text:* • Documented diagnosis of MDS according to World Health Organization (WHO) criteria that

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		meets International Prognostic Scoring System (IPSS) classification of low or intermediate-1 risk disease at screening as determined by microscopic and standard cytogenetic analyses of the bone marrow and peripheral complete blood count (CBC). - Phase I dose escalation: patients who experienced ESA treatment failure or do not qualify (serum erythropoietin level > 500 U) for ESA treatment, and are refractory to or not amenable or eligible for established MDS therapy (HMA, lenalidomide) - Phase I expansion: • - Expansion cohort 1 ("pre-treated"): patients who experienced ESA treatment failure or do not qualify (serum erythropoietin level > 500 U) for ESA treatment and are refractory to established MDS therapy (HMA and /or lenalidomide) • - Expansion cohort 2 ("untreated"): patients who experienced ESA treatment failure or do not qualify (serum erythropoietin level > 500 U) for ESA treatment and who have not received prior HMA and/or lenalidomide (because not amenable or eligible for these treatments). Phase II: patients who experienced ESA treatment failure or do not qualify (serum erythropoietin level > 500 U) for ESA treatment. For definition of further details of the phase II patients to be included the protocol will be amended based on Phase I results
Rationale for change		To further clarify the inclusion criteria between Phase I dose escalation, expansion and Phase II
Section to be changed		**Section 3.3.3 Exclusion Criteria**
Description of change		*Added Criterion #6:* • Neutrophils <1000 /μL (1.0 x 10^9/L).
Rationale for change		Per German Health Authorities neutrophil

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Number of global amendment		**3**
		criterion was added
Section to be changed		**Section 3.3.3 Exclusion Criteria**
Description of change		*Corrected formatting of exclusion criterion #14. Move bold text under #14 criterion* • Female patients of childbearing potential who are sexually active and unwilling to use a medically acceptable method of contraception during the trial and for 6 months after the last administration of BI 836858, i.e. combination of two forms of effective contraception (defined as hormonal contraception, intrauterine device, transdermal patch, implantable or injectable contraceptive, bilateral tubal ligation 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 sterilized (e.g. hysterectomy, bilateral oophorectomy or bilateral salpingectomy
Rationale for change		Corrected formatting error to include definition of women of childbearing potential under exclusion criterion #14.
Section to be changed		**4.1.2 Method of Assigning Patients to Treatment Groups**
Description of change		*Added bold text:* In Phase I of the trial, patients will be assigned into escalating dose cohorts **and Phase I Expansion cohorts** using IRT. After determination of the MTD/RP2D, ~~and~~ Phase I safety analysis **report and protocol amendment (see section 3.1.1.1),** Phase II enrollment will be initiated.
Rationale for change		Clarification made to note end of Phase I report and protocol amendment to be made available and submitted before start pf Phase II
Section to be changed		**4.1.3 Selection of Doses in the Trial**

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Number of global amendment		**3**
Description of change		*Deleted text:* The dose is planned to be escalated in cohorts at pre-defined dose levels based on a maximum escalation of 100%. The provisional dose levels are 20mg, 40mg, 80mg, 160mg, and 320mg. Intermediate or lower dose levels, depending on the number of DLTs observed in the study, ~~and dose levels higher than 320 mg~~ may be investigated if agreed upon between Investigator and Sponsor
Rationale for change		Paragraph was updated indicating that doses above 320 mg of BI 836858 will not be tested in this trial
Section to be changed		**4.1.4 Drug Assignment and Administration of Doses for Each Patient**
Description of change		*Text was re-bulleted (split to create 3 bullets from 2) and text deleted:* Before the administration of BI 836858, adverse events and safety laboratory will be assessed. To start or continue treatment with further administrations, all of the following criteria must be met: 1) Neutrophils ≥1000 /µL (1.0 x 10^9/L) ~~and~~ 2) Platelets ≥50,000 /µL (50 x 10^9/L), unless CTCAE Grade 3 or 4 ~~neutropenia or~~ thrombocytopenia was preexistent prior to trial entry. ~~Patients who go from Grade 3 neutropenia to Grade 4 neutropenia after treatment may continue on study provided there is no evidence of infection or febrile neutropenia.~~ Patients who go from Grade 3 to Grade 4 thrombocytopenia after treatment may continue on study provided that post-transfusion platelet count is at least 20,000/uL before therapy is given. 3) Acceptable tolerability (in case of an AE at the planned start of a further administration, patients may continue therapy only after recovery to a level which would allow further therapy, i.e. CTCAE grade 1 or baseline value.)
Rationale for change		In response to German Health Authority, the on study dosing requirements were updated and clarified
Section to be changed		**4.1.8 Drug Accountability**

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Number of global amendment		**3**
Description of change		*Bold text added.* Each Investigator and/or pharmacist will receive the investigational drugs delivered by the Sponsor when the following requirements are fulfilled: • approval of the study protocol by the Institutional Review Board (IRB) / Independent Ethics Committee (IEC), • availability of a signed and dated clinical trial contract between the sponsor and the Head of Trial Center, • approval/notification of the regulatory authority, e.g. competent authority, • availability of the curriculum vitae of the principal Investigator, • availability of a signed and dated CTP or immediately imminent signing of the CTP, • availability of the proof of a medical licence for the principal investigator, • availability of the FDA Form 1572, **if applicable.**
Rationale for change		Updated to reflect global requirements
Section to be changed		**5.2.1.3 Recommended Phase 2 Dose (RP2D)**
Description of change		*Deleted text and updated with bold text:* Based on the Phase I data, the DSB will make a final determination of the RP2D, which must not exceed the MTD. The Phase I safety analysis report, including the rationale of RP2D determination will be ~~made available to all investigators~~ **prepared** prior to the initiation of Phase II.
Rationale for change		Added clarification on the preparation of the end of Phase I report
Section to be changed		**6.2.3.3 End of the Whole Trial**
Description of change		*Added bold text:* 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 **provided that treatment continuation is in the best interest of the patient, based on clinical trial results and the investigator´s benefit risk assessment for an individual patient**. Those patients will then be reported in a revised report

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Number of global amendment		**3**
		and it will be noted in the original report that such a revised report will be written. At least one Follow-up visit is requested whenever feasible for all patients who discontinue study treatment due to the trial termination by the sponsor.
Rationale for change		Further clarification made to section on ongoing participation of patients who are receiving benefit at trial closure
Section to be changed		**7.3.4.1 Phase I**
Description of change		*Updated paragraph with additional bold text:* A Phase I safety analysis report will be prepared prior to the initiation of Phase II. A summary of safety and efficacy from the dose escalation cohorts and from the expansion cohorts will be included in the Phase I safety analysis report. Results of this evaluation will be documented, archived and made available for Health Authority and Ethics Committee/IRB review and approval (where applicable) and to all investigators who participate in the Phase II. Such an analysis will be defined in more detail in the TSAP.
Rationale for change		Statistical section was updated to align with protocol changes on availability of end of Phase I report prior to starting Phase II
Section to be changed		**9.1 Published References**
Description of change		*Added:* P17-02032 Eksioglu, E A, Chen, X, Heider, K-H, Rueter, B, McGraw, K L, Basiorka, A A, et al. Novel therapeutic approach to improve hematopoiesis in low risk MDS by targeting MDSCs with the Fc-engineered CD33 antibody BI 836858. Leukemia 2017; 31(10), 2172-2180.
Rationale for change		Updated references list with new publication

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11.4 GLOBAL AMENDMENT 4

Number of global amendment		**4**
Date of CTP revision		**11 Sep 2019**
EudraCT number		**2018-002177-21**
BI Trial number		**1315.7**
BI Investigational Product(s)		**BI 836858**
Title of protocol		**A Phase I/II, Multicenter, Open-Label, Dose Escalation and Randomized Trial of BI 836858 in Patients with Low or Intermediate-1 Risk Myelodysplastic Syndromes**
To be implemented only after approval of the IRB/IEC/Competent Authorities		☒
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		☐
Can be implemented without IRB/IEC/ Competent Authority approval as changes involve logistical or administrative aspects only		☐
Section to be changed		**Title Page**
Description of change		Change of Trial Clinical Monitor from to
Rationale for change		New Trial Clinical Monitor assignment
Section to be changed		After the Sponsor's decision to discontinue development of BI 836858 and to stop further recruitment of patients into study 1315.7, trial participants still on treatment and with clinical benefit from BI 836858 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 and assessments are reduced for all patients in treatment cycles ≥5.

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Number of global amendment		**4**
		Changes made in the following sections will be effective after approval of CTP version 5.0: **Synopsis – section "Number of patients"** Actual number of patients entered/treated in Phase I Dose Escalation (21 patients) and in Phase I Expansion (6 patients) was added. **One new sentence added:** Recruitment in this trial was discontinued prematurely during the Phase I expansion cohort • **Flow Chart and Footnotes:** Section amended to clarify visits, assessments and procedures that are mandatory/not mandatory at visits ≥5. • **Flow Chart – Maintenance and Footnotes:** Sections amended to clarify visits, assessments and procedures that are mandatory/not mandatory at visits ≥5. • **Table 1 and Footnotes:** Section amended to clarify visits, assessments and procedures that are mandatory/not mandatory at visits ≥5. • **Table 3 and Footnotes:** Section amended to clarify assessments and procedures that are mandatory/not mandatory at visits ≥5. • **3.1 Overall Trial Design and Plan** Clarification added about premature discontinuation of recruitment to this trial. • **3.3.4.2 Discontinuation of the trial by the Sponsor** Clarification added about premature discontinuation of recruitment to this trial. • **4.2.1 Rescue medication, emergency procedures, and additional treatment(s)**

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Number of global amendment		**4**
		New Text: After implementation of CTP version 5.0 collection of Concomitant Therapy information only if the indication is treatment of an (S)AE. • **5.2 Safety** **New text:** Recruitment in this trial was discontinued prematurely during the Phase I expansion cohort. With the aim to minimize the burden for trial participants, after implementation of CTP version 5.0, the mandatory protocol procedures described below in section 5.2.2, Assessment of adverse events, 5.2.3, Assessment of safety laboratory parameters, 5.2.4, Electrocardiogram, 5.2.5, Assessment of other safety parameters, and 5.3.1 Physical Examinations are reduced for all patients who continue to receive trial medication in treatment cycles ≥5. 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 5.2.2, which remains unchanged). • **5.2.2.2 Definition of adverse events (Pregnancy)** **New Text** After implementation of CTP version 5.0, pregnancy test results will not be documented by default in the eCRF. Only positive pregnancy tests will be documented via the Pregnancy Monitoring Form (and reported as an AE if applicable). • **5.2.5.1 Vital Signs** **New text:** After implementation of CTP version 5.0, vital signs are mandatory only at the day of administration of BI 836858. Results will be

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Number of global amendment		**4**
		documented in the eCRF only if qualifying for an adverse event. • **6.2 Details of trial procedures at selected visits** Clarifications added about reduced mandatory protocol procedures for treatment cycles ≥5 with reference to updated Flow chart. **New text:** With the aim to minimize the burden for trial participants, after implementation of CTP version 5.0, the mandatory protocol procedures are reduced for all patients who continue to receive trial medication in treatment cycles ≥5. Instead, safety 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. Findings during safety assessments are documented in the eCRF only if qualifying for an adverse event (see sections 5.2.2, which remain unchanged). • **6.2.3.2 Follow-up** **New text**: After implementation of CTP version 5.0, no further follow-up visits after EoR, unless follow-up is for S(AE) that occurred before EoR period. • **6.2.3.3 End of the whole trial** Clarification added about the definition of the end of the whole trial. • **7.1 Statistical Design - Model** **New text:** Recruitment in this trial was discontinued prematurely during the dose expansion cohort
Description of change		Recruitment in this trial was discontinued prematurely during the Phase I expansion cohort.
Rationale for change		To minimize the burden for trial participants,

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Number of global amendment		**4**
		the mandatory protocol procedures and assessments are reduced for all patients in treatment cycles ≥5.

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APPROVAL / SIGNATURE PAGE

Document Number: c02304070 **Technical Version Number:7.0**

Document Name: clinical-trial-protocol-version-5

Title: A Phase I/II, Multicenter, Open-label, Dose Escalation and Randomized Trial of BI 836858 in Patients with Low or Intermediate-1 Risk Myelodysplastic Syndromes

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Approval-Clinical Trial Leader		12 Sep 2019 20:34 CEST
Approval-Therapeutic Area		12 Sep 2019 22:41 CEST
Approval-Biostatistics		13 Sep 2019 17:50 CEST
Approval-Team Member Medicine		17 Sep 2019 10:12 CEST
Author-Trial Clinical Pharmacokineticist		20 Sep 2019 17:36 CEST
Approval-Clinical Trial Leader		20 Sep 2019 18:09 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed