Clinical Trial Protocol

Doc. No.: c02587386-05

EudraCT No.:	2014-004896-22
BI Trial No.:	1351.1
BI Investigational Product(s):	BI 836909
Title:	An open label, phase I, dose escalation study to characterize the safety, tolerability, pharmacokinetics, and pharmacodynamics of intravenous doses of BI 836909 in relapsed and/or refractory multiple myeloma patients
Clinical Phase:	Phase I
Clinical Trial Leader:	[redacted] Phone:+ [redacted] Fax: + [redacted]
Co-ordinating Investigator:	[redacted] Phone: + [redacted] Fax: + [redacted]
Status:	Final Protocol (Revised Protocol (based on global amendment 4))
Version and Date:	**Version 5.0** **Date: 26 Nov 2018**

CLINICAL TRIAL PROTOCOL SYNOPSIS

Name of company Boehringer Ingelheim		**Tabulated Trial Protocol**	
Name of finished product: Not applicable			
Name of active ingredient: BI 836909			
Protocol date: 10 Feb 2015	**Trial number:** 1351.1		**Revision date:** 26 Nov 2018
Title of trial:	An open label, phase I, dose escalation study to characterize the safety, tolerability, pharmacokinetics, and pharmacodynamics of intravenous doses of BI 836909 in relapsed and/or refractory multiple myeloma patients		
Co-ordinating Investigator:	[redacted]		
Trial site(s):	Multi-centre		
Clinical phase:	I		
Objective(s):	Primary objective: To determine the maximum tolerated dose (MTD) as well as the dose limiting toxicities (DLT) of a 6-week regimen of BI 836909 given as continuous intravenous infusion in patients with relapsed and/or refractory multiple myeloma. Secondary objectives: • Recommended dose for further development • To provide preliminary findings on the safety profile and assess pharmacokinetic profile of BI 836909 • To assess pharmacodynamic and anti-tumoral activity of BI 836909 • To evaluate immunogenicity of BI 836909		
Methodology:	• Phase I dose escalation trial of BI 836909 given as intravenous infusion. • Starting dose: 0.20 µg/day • A 6-week regimen will be tested (4 weeks of continuous intravenous administration of BI 836909 followed by a 2 weeks off-period).		

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Methodology:

For the dose levels of 0.2 to 1.6 µg/day single patient cohorts are entered. The following dose cohorts will be tested within the above-mentioned dose range:

- 0.2, 0.4, 0.8 and 1.6 µg/day
- The DLT observation period for the single patient cohorts will be 2 weeks. If a patient has been on treatment in one of the above-mentioned dose cohorts for 2 weeks without DLT or other relevant safety findings the first patient of the next higher dose cohort will be entered if agreed on by the safety committee. If a patient has reached DLT, then the safety committee recommends 3 + 3 cohorts. Patients may not proceed to the next higher dose level before completion of 6 patients.

One intra-patient dose escalation is allowed within the single patient dose cohorts if the initial dose is tolerated and no DLT occurs during 1st cycle. In case of DLT additional patients will be entered into this cohort following a 3 + 3 design.
For the dose levels ≥ 3.2 µg/day 3-6 patients will be treated per dose level and observed for 4 weeks during the first cycle before decision for dose escalation to the next dose cohort is made.
The following dose cohorts will be tested within the above-mentioned dose range:

3.2, 6.5, 13, 25, 50, 100, 200 ,400 and 800 µg/day.. Intermediate dose cohorts with 50% increments of previous dose will be entered if determined by thesafetycommittee. Increments to the next higher dose will not exceed 2-fold increases.
The DLT observation period will be extended to 4 weeks for all future cohorts before decision for dose escalation within the next dose cohort is made:

- Per dose level 1 patient will be enrolled and treated for 1 week before all remaining patients for this cohort can be entered. Additional patients should not start treatment before the previous patient has been treated for 48 hours in order to monitor initial transient toxicities due to cytokine release syndrome.
- Once the MTD of BI 836909 is determined up to 6 additional patients will be treated at the MTD or the recommended dose for confirmation of safety.

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Number of patients	
total entered:	Up to 50 patients depending on dose level reached
Each treatment:	**Dose escalation**: Number of patients will depend on the number of dose levels to be tested before MTD determination or determination of the recommended dose. Based on preclinical data, it is expected that > 5 dose levels in addition to the 4 single-patient doses will be tested. Up to 50 patients will be treated during the dose escalation phase. Up to 6 additional patients will be treated with MTD or recommended dose.
Diagnosis :	**Patients with relapsed and/or refractory multiple myeloma**
Main criteria for inclusion:	Patients with relapsed and/or refractory multiple myeloma and progression after ≥ 2 prior treatment lines (including proteasome inhibitor and immune-modulatory drugs). Patients with significant comorbidities such as impaired renal function, cardiovascular diseases (i.e. uncontrolled hypertension, unstable angina, history of infarction within past 6 months, congestive heart failure > NYHA II), active infection requiring treatment, or active autoimmune disease will be excluded.
Test product(s):	BI 836909 in vials for continuous intra-venous infusion
Comparator products:	N/A
Duration of treatment:	Treatment will continue for up to 5 cycles or until: • Disease progression or start of further anticancer treatment • Non-acceptable toxicity • Patient decision to withdraw consent • Investigator's decision In case of ongoing clinical benefit after five courses additional 5 courses may be given if considered indicated by the treating investigator.

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Criteria for efficacy:	**Efficacy evaluation will be based on the response criteria of the International Myeloma Working Group (IMWG, 2006)** **Secondary endpoints for efficacy:** Objective response rate (percentage of patients with sCR, CR, PR and VGPR) • Duration of response (DOR) • Minimal residual disease (MRD) response rate • Duration of MRD response • Progression free survival (PFS)
Criteria for pharmacokinetics:	**Pharmacokinetic endpoints are secondary or further endpoints** **Secondary endpoint:** Concentration at steady state after i.v. infusion (C_{ss})
[redacted]	
Criteria for safety:	**Primary endpoint**: • Maximum tolerated dose (MTD) of BI 836909: MTD is defined as the highest dose of the dose level tested where ≤ 1 patient out of 6 develops dose limiting toxicity (DLT). • Number of patients with dose limiting toxicities (DLTs) will be reported. The safety of BI 836909 will be assessed by a descriptive analysis of incidence and intensity of adverse events graded according to CTCAE (version 4.03), the incidence of dose limiting toxicity (DLT), laboratory data and results of physical examination. If MTD cannot be determined based on safety findings, a recommended biologically active dose for further development will be determined based on pharmacokinetic and pharmaco-dynamic data.
Statistical methods:	Patients with DLT, objective response rate, MRD will be explored and summarized by descriptive statistics. Kaplan-Meier methods will be used for time to event endpoints.

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Statistical methods:	The pharmacokinetic parameters Css, [redacted] will be descriptively explored.		

FLOW CHART: BI 836909 CONTINUOUS INTRAVENOUS INFUSION

Trial Periods	Screen	Treatment courses[1]																	EOT[2]	FU[3]
Course[1]		1						2 – 4						5 or last cycle[4]						
Week		1 - 4					5 - 6	1 - 4					5 - 6	1 - 4						
Visit [6]	Screen[5]	1	2	3	4	5	6	1	2	3	4	5	6	1	2	3	4	5		
Days[6]	-21 to -1	1-4[7]	8	15	22	29- 30	36	1	8	15	22	29	36	1	8	15	22	29	0 - 7	
Informed consent /IWRS call	X																			
Informed consent for pharmacogenetics and biomarkers	X																			
Bone Marrow Aspirate[8]	X											X							X	
Minimal residual disease assessment in bone marrow (MRD)[9]												X							X	
Bio-Banking of bone marrow	X[10]											X								
Blood for pharmacogenetics		See separate flow chart																		
Biomarker in urine		See separate flow chart																		
Demographics	X																			
Medical history	X																			
Review of in-/exclusion criteria/ IWRS call	X																			
Height	X																			
Weight	X							X						X					X	
Physical examination[16]	X	X				X	X	X						X					X	
[redacted]																				
Body temperature	X	X	X	X	X	X		X	X	X	X	X		X	X	X	X	X	X	
Blood pressure (with heart rate)	X	X	X	X	X	X		X	X	X	X	X		X	X	X	X	X	X	
12-lead ECG (local)[11]	X							X						X					X	
General safety laboratory parameters[12]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Screening for HCV, HBV, HIV	X																			
Serum pregnancy test	X							X						X					X	
Hospitalisation [7]		X				X[7]		X						X						
Home Care Support[13]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Concomitant therapy	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Adverse events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Eligibility for treatment		X						X						X						
Administration of BI 836909		X	c.i.v.			X		X	c.i.v.			X		X	c.i.v.			X		
Disease / response assessment (clinical/MRI) [14]	X							X						X					X	
Pharmacokinetics[15]		see separate flow chart																		
Reason for treatment discontinuation / IWRS call																			X	
Next line of anti-cancer therapy																				X
Patient status																				X

1 each course has a duration of 6 weeks, 4 weeks of continuous infusion of BI 836909 and 2 weeks break.

2 EOT will be performed after permanent discontinuation of trial medication or as soon as possible but no later than 1 week after discontinuation of trial drug (Section 6.2.5.1)

3 Follow up visit should be performed 30 days after the EOT (REP visit). In case of ongoing clinical benefit, patients can be followed up to collect data for duration of response. Follow-up visits for responders will be at 3, 6 and 12 months after EOT if a patient did not progress, started a new anti-cancer treatment, died, or withdrew informed consent.
Follow up visit after EOT: report all AEs, SAEs, AESIs regardless of relatedness. This includes all deaths unless due to underlying disease (Section 6.2.5.2)
Extended follow up: report related SAEs and AESIs.
Please note: Death should always be reported as SAE in this trial unless due to underlying disease.

4 in case of clinical benefit a maximum of 5 cycles is administered. In case of ongoing clinical benefit up to a maximum of 5 additional treatment cycles can be given if considered indicated by the investigator (Section 4.1.5), visit 6 at day 36 must be performed for all cycles except the last one.

5 results from routine assessments (MRI) for multiple myeloma are accepted for screening if performed no later than 28 days before start of treatment (Section 6.2.2)

6 ± 3 days

7 patients will be hospitalized in the first cycle for 3 or 4 days if first bag change will be performed in the clinic, on day 1 of cycle 2 for 24 hours, in patients within intra-patient dose escalation at the time when dose is escalated also for 24 hours and in all subsequent cycles for 8 hours on day 1 of each cycle; patients will also be hospitalized at the end of cycle 1 (day 29); hospitalization may be prolonged in case a patient experiences a cytokine release syndrome or a severe AE (Section 6.2.1).

8 within 14 days before day 1 cycle 1 or on day 1 cycle 1 before start of treatment, when M protein/ Free kappa/lambda light chain (FLC) becomes undetectable during treatment, on day 29 of cycle 3 and at EOT
Karyotyping: recent analysis will be accepted for screening before start of treatment if performed within 3 months prior to start of study medication and in case that no therapy has been given between assessment of karyotyping and study medication; otherwise, a baseline karyotype should be performed at screening; subsequent karyotyping could also be performed in subsequent marrow samples **(tests to be done locally).**
Percentage (%) of plasma cells in bone marrow should be assessed locally according to institutional standards and documented in eCRF.

9 MRD (minimal residual disease assessment): when M protein/FLC becomes undetectable during treatment; day 29 of cycle 3 and EOT (tests to be done centrally).

10 Optional collection and bio-banking of a baseline bone marrow sample and a bone marrow sample on treatment when a complete response is reached.

11 at screening and at the beginning of each cycle (except for cycle 1).

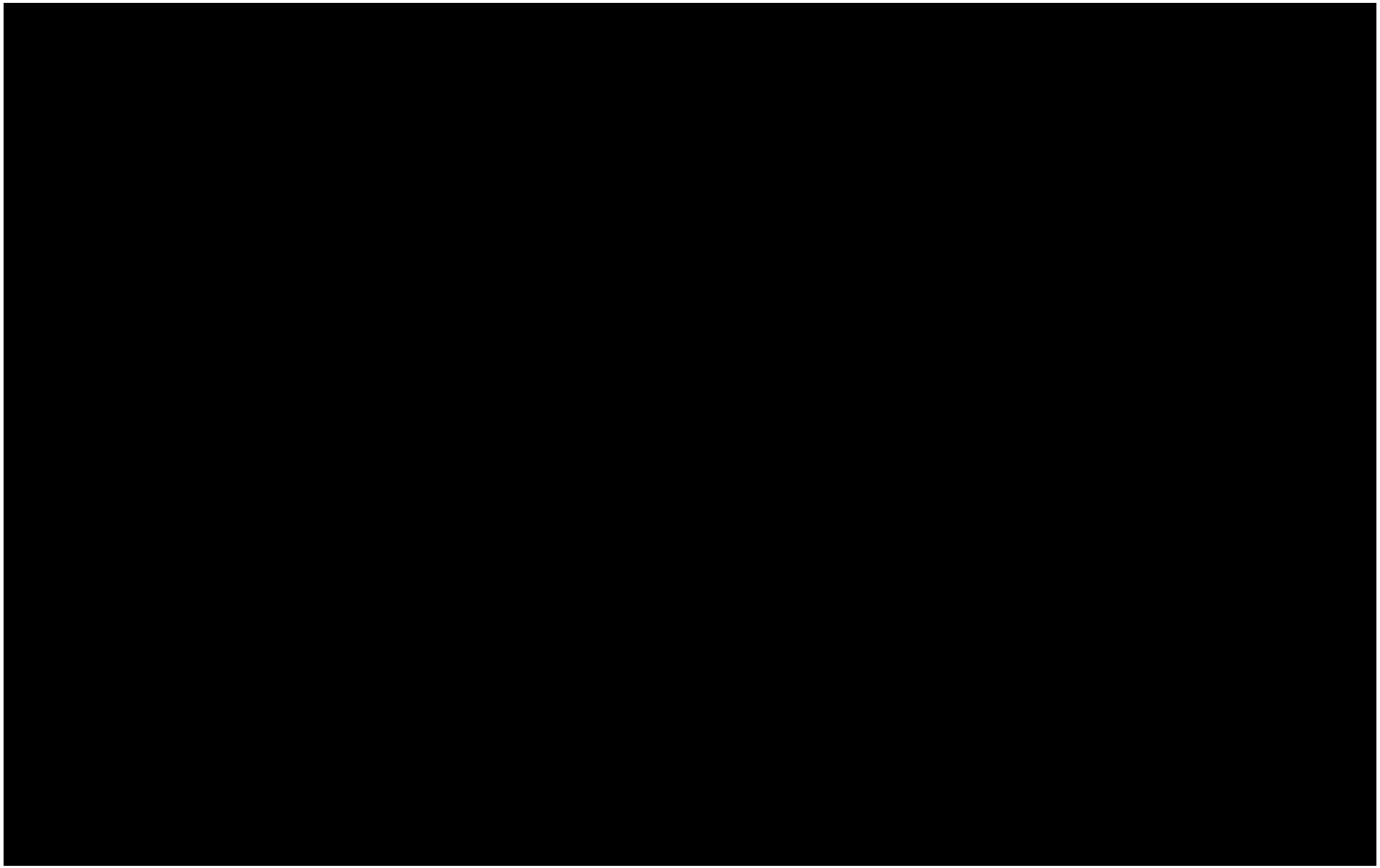
12 at screening and at each visit and at EOT; during hospitalization in cycle 1 safety lab should be done before start of treatment on day 1 and repeated in the evening of day 1 as well as in the morning of days 2 and 3; in cycle 2 safety lab should be done before start of treatment on day 1 and in the morning of day 2.
On day 29 of cycle 1 blood draw for safety lab should be done before the end of the infusion.

13 Infusion bag will have to be exchanged during continuous infusion of BI 836909 approximately every 4 days; patients should either come to the clinic or bag change will be done by a home care service.

14 Clinical disease assessment must be performed:
At screening, at start of each cycle as well as at EOT.
MRI must be performed:
At screening and at start of each other cycle at or within 14 days before day 1, cycle 3; day 1, cycle 5; day1, cycle 7; day 1… and/or at time of progression based on IMWG response criteria or start of further anticancer therapy; Results from routine assessments (MRI) for multiple myeloma are accepted for screening if performed within 28 days before start of treatment.
Clinical disease status will be assessed at screening and at the start of each new cycle (e.g, before cycle 2, 3, 4 and 5 etc.) as well as at EOT.

15 see separate Flow chart; Appendix 10.2.

16 Orienting neurological examination should be performed at screening as well as at EOT and daily during hospitalization required by the protocol.



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ABBREVIATIONS

ADA	Anti-Drug Antibody
AE	Adverse Event
ALT	Alanine Aminotransferase
AESI	Adverse Event of Special Interest
Anti-HBs	Hepatitis B Surface Antibody
Anti-HBc	Hepatistis B Core Antibody
Anti-HCV	Hepatitis C Antibody
AP	Alkaline Phosphatase
APRIL	A Proliferation inducing Ligand
aPTT	Activated Partial Thromboplastin Time
AST	Aspartate aminotransferase
[redacted]	
BAFF	B cell activating factor
BI	Boehringer-Ingelheim
BiTE	Bi-specific T-cell enhancer
BCMA	B-cell Maturation Antigen
BIRDS	Regulatory Documents for Submission
BLQ	Below the limit of quantification
[redacted]	
BSA	Body Surface Area
CA	Competent authority
CAR	Chimeric antigen receptor
CBA	Cytometric Bead Array
CD	Classification determinant
CHO	Chinese hamster ovary
COPD	Chronic obstructive pulmonary disease
CI	Confidence Interval
c.i.v.	Continuous intravenous infusion
cv	Continuous infusion
[redacted]	
C_{ss}	Concentration at steady state after i.v. infusion
CML	Local Clinical Monitor
CNS	Central nervous system
CRA	Clinical Research Associate
CRAB	CRAB criteria in MM (Hypercalcemia renal insufficiency, anemia and ostelytic lesions)
CRF	Case Report Form
CRO	Clinical Research Organisation
CR	Complete Remission
CRS	Cytokine release syndrome

CT	Computer Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTL	Cytotoxic T lymphocyte
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
dL	Deciliter
DLT	Dose Limiting Toxicity
DILI	Drug induced liver toxicity
DMC	Data Monitoring Committee
DNA	Desoxyribonucleic Acid
DOR	Duration of response
eCRF	Electronic Case Report Form
EC_{50}	Half maximal effective concentration
EDC	Electronic Data Capture
ECG	Electrocardiography
ECOG	Eastern Cooperative Oncology Group
e.g.	For example
EudraCT	European Clinical Trials Database
EOR	End of Residual Effect Period
EOT	End of Trial
FACS	Fluorescence Activated Cell Sorting
FLC	Free light chain
FS	Factor for Sex
FU	Follow up visit
GCP	Good Clinical Practice
G-CSF	Granulocte Colony Stimulating Factor
GFR	Glomerular filtration rate
GM1-antibody	Antiganglioside antibody 1
H	Hour
HBV	Hepatitis B Virus
HBsAg	Hepatitis B Surface Antigen
HCL	Hydrogen chloride
HCV RNA	Hepatitis C Ribonucleic Acid
HCV	Hepatitis C Virus
HNSTD	Highest Non-Severely Toxic Dose
HIV	Human immunodeficiency virus
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IL-2	Interleukine-2
IL6R	Interleukine -6 receptor
IMiDs	Immunomodulators
INN	International Nonproprietary Name

INR	International Normalised Ratio
ISF	Investigator Site File
IMWG	International Myeloma Working Group
IRB	Institutional Review Board
IRR	Infusion-related reactions
IUD	Intrauterine Device
ISF	Investigator Site File
i.v.	intravenous
IWRS	Interactive Web-based Response System
Kg	Kilogram
[redacted]	
LDH	Lactate Dehydrogenase
LUC	Large Unstained Count
MCP-1	Monocyte Chemoattractant Protein-1
MedDRA	Medical Dictionary for Drug Regulatory Activities
ml	Mililiter
m^2	Square meter
µg	Microgram
MM	Multiple Myeloma
MPT	Melphalan-Thalidomide-Prednisone
MRD	Minimal Residual Disease
mRNA	Messenger Ribonucleic acid
MRT/MRI	Magnet resonance tomography/ Magnet resonance imaging
MSD	Meso Scale Discovery
MTD	Maximum Tolerated Dose
n.a.	Not applicable
NaCL	Natrium Chloride
NC	Non Compliance
NCI	National Cancer Institute
NBE	New biological entity
NK	Natural Killer Cell
NOA	Not analysed
NOD	Non-obese diabetic
NOR	No valid result
NOS	No sample available
[redacted]	
NYHA	New York Heart Association
OPU	Operative Unit
OR	Overall response
OS	Overall survival
PAD	Pharmacologically active dose
PBMC	Peripheral blood mononuclear cell
PD	Progressive disease
PET	Positronen-Emissions-Tomography
PFS	Progression Free Survival
Pg	Pictogram

PI	Principle Investigator
PLT	Platelet
PK/PD	Pharmacokinetics/Pharmacodynamics
p.o.	per os (oral)
PR	Partial Response
PT	Prothrombin Time
q.d.	quaque die (once a day)
RBC	Red Blood Count
RDC	Remote Data Capturing
REP	Residual Effect Period
RNA	Ribonucleic Acid
SAE	Serious Adverse Event
SC	Safety Committee
ScFv	Single chain fragment variable
SD	Stable Disease
SCID	Severe combined immune deficiency
sCR	Stringent Sesponse
SNP	Single nucleotide polymorphism
SOP	Standard Operating Procedure
[redacted]	
T-cell	T lymphocyte
TCM	Trial Clinical Monitor
TLS	Tumour Lysis Syndrom
TNF	Tumour necrosis factor
TNFRSF17	Tumor necrosis factor receptor superfamily member 17
[redacted]	
TSL	Tumour lysis syndrome
ULN	Upper Limit of Normal
VGPR	Very Good Partial Response
VH	Heavy chain
VL	Light chain
[redacted]	
WBC	White blood count
WFI	Water for injection

1. INTRODUCTION

1.1 MEDICAL BACKGROUND

Multiple Myeloma (MM) is a malignant neoplasm of plasma cells that accumulate in bone marrow leading to bone destruction and marrow failure. The age adjusted annual incidence is increasing with approximately 6 new cases per 100,000. The incidence is twice as high in the black US population compared to Caucasians. MM is sensitive to a variety of cytotoxic drugs both as initial treatment or as treatment for relapsed disease. The 5-year survival rate for MM has improved from ~ 25% for newly diagnosed patients in 1975 to ~ 45% in 2006 (R14-3715). This is mainly attributed to new drugs such as proteasome inhibitors and immunomodulators (IMiDs). However, responses are transient and MM is not considered curable with current approaches. Patients refractory to proteasome inhibitors and IMiDs have a poor prognosis with a median overall survival of 9 months with further treatment and 3 months without (R14-3714). Outcome is particularly poor in molecularly defined populations such as the high risk subgroup del17p13 positive MM (R14-3712). New treatment options are therefore urgently required. Although many NBEs are in clinical development for MM no antibody or antibody fragment has yet been registered.

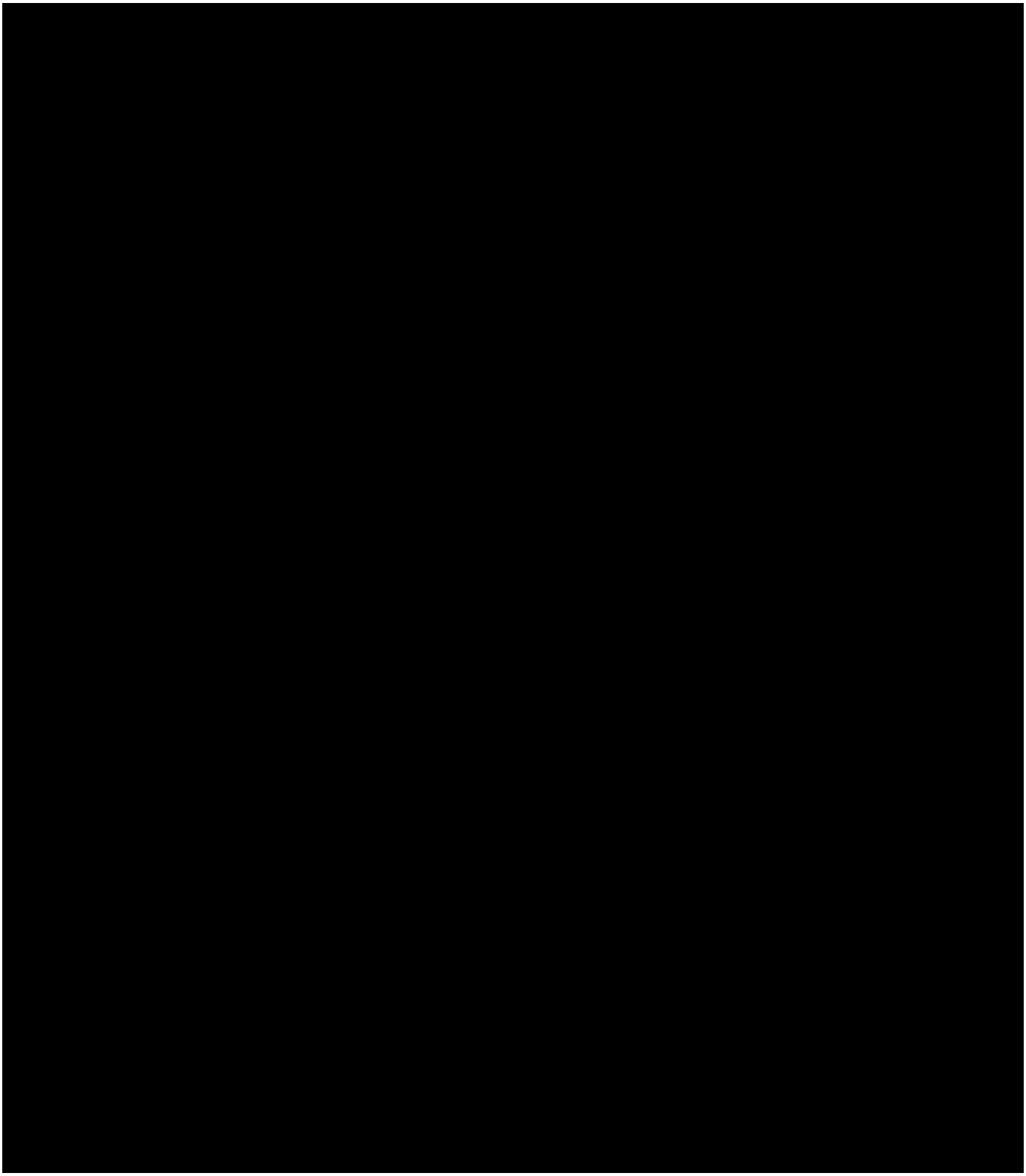
MM patients presenting with active symptomatic disease are initially treated with **primary induction therapy** followed by high dose chemotherapy with autologous stem cell support in selected patients. Patients eligible for intensive treatment are identified by age (with 65 to 75 years constituting the upper limit), lack of comorbidities and preserved renal function. Although this modality has improved survival of younger and fit patients, the median duration of response does not exceed 3 years and few patients remain free of the disease for more than 10 years (R14-3753). Relapses are due to the failure of high-dose chemotherapy to eradicate residual disease. Consolidation and maintenance approaches have been tested in order to increase the depth and duration of remission. Since maintenance approaches have been hampered by lack of efficacy or tolerability there is still the option of improving survival outcome in the transplant setting by adding novel modalities to induction, consolidation or maintenance regimens. Patients not eligible for high dose therapy usually receive similar induction regimens as the transplant candidates based on the proteasome inhibitor Bortezomib or a Melphalan based combination with Thalidomide. Median OS of Melphalan-Thalidomide-Prednisone (MPT) in elderly patients is 40 months (P11-05130). Lenalidomide in combination with Dexamethasone is the standard regimen for **relapsed/refractory MM** but may move to the first line setting in transplant ineligible patients based on recent trial results (R14-15304). Other established strategies in the relapsed setting are repeat induction regimens or bortezomib or IMiD based salvage combinations with alkylating agents. An improvement of outcome (PFS and OS) is clearly needed in the relapsed setting. The patients who have become **refractory** to established treatments and progressed on treatment or within 60 days of completing their last therapy have a dismal prognosis of 9 months OS on treatment and 3 months without (R14-3714). The unmet need is highest in this population.

1.2 DRUG PROFILE

B cell maturation antigen (BCMA, TNFRSF17, CD269) is a transmembrane protein belonging to the TNF receptor super family. BCMA expression is selectively induced during late stage plasma cell differentiation and is absent on naïve and memory B cells (R14-2907). Upon binding to its ligands, B cell activating factor (BAFF) and a proliferation inducing ligand (APRIL), the survival of the bone marrow plasma cells and plasmablasts is promoted (R14-2906). BCMA does not maintain normal B cell homeostasis but is required for the survival of long lived plasma cells. Studies in BCMA -/- mice showed that the survival of long lived bone marrow plasma cells was impaired but B cell development and early humoral immune responses were indistinguishable from wild type mice (R14-2905). The mRNA expression of BCMA is highly elevated in malignant plasma cell disorders. By contrast, mRNA expression in normal tissues is very low and restricted to lymphoid tissues where normal long lived plasma cells are located. BCMA protein expression is reported to be restricted to plasma cells only. Neither T–cells, myeloid cells (R14-4494) nor CD34+ hematopoietic stem cells (R14-2794) express BCMA. The selective expression of BCMA makes it a very attractive target for antibody-based and chimeric antigen receptor (CAR)-based therapies (R14-2794).

BI 836909 consists of two single chain variable scFv fragments (scFv) that bind to B-cell maturation antigen (BCMA) on tumor cells and CD3 on T-cells. Each of the scFv fragments consists of a VH and VL domain connected with a Glycine/Serine linker. The two scFv fragments are connected with a short Glycine/Serine linker. [redacted]

[redacted]



2. RATIONALE, OBJECTIVES, AND BENEFIT - RISK ASSESSMENT

2.1 RATIONALE FOR PERFORMING THE TRIAL

Several publications demonstrate that BCMA is universally expressed on the cell surface of MM cells (R14-2906, R14-3798, R14-3711). A recently published prevalence study showed that 12/67 MM patients had high, 52/67 patients had intermediate and only 3/67 MM patients had low to negative BCMA surface expression. There was no correlation between BCMA expression and disease stage, response to last treatment and time from diagnosis, but, there was a trend towards higher BCMA expression levels in tumors with adverse genetics (R14-3711). Expression of BCMA is restricted to plasmablasts and long lived plasma cells and is absent on normal human tissues (R14-2794, R14-2906). Pretesting for BCMA expression is not a requirement for myeloma patients to be entered into the trial.

BI 836909 is an Anti-BCMA Bi-Specific T-cell Engager (BiTE) which binds to BCMA on MM cells as well as CD3ε on T-cells. It is a bispecific new biological entity (NBE) and functions as a bridge between MM cells and cytotoxic T lymphocytes (CTLs) and directs the cytolytic activity of CTLs to MM cells. The BiTE concept has successfully been tested for the CD19xCD3 BiTE blinatumomab which is in late stage clinical development at this time (R14-3640).

BI 836909 has not yet been tested in humans.

2.2 TRIAL OBJECTIVES

The primary objective of this trial is to determine the maximum tolerated dose (MTD) of BI 836909 administered by continuous i.v. infusion in patients with relapsed and/or refractory multiple myeloma. If the MTD is not reached based on safety findings, a recommended dose for further development will be determined. This will depend on the safety data, pharmacokinetic/ pharmacodynamics data and potentially preliminary efficacy data. Secondary objectives are to document the safety and tolerability of BI 836909, to perform pharmacokinetic and pharmacodynamic analyses and to evaluate relevant biological effects in terms of parameters of efficacy. The starting dose is based on a Pharmacologically Active Dose (PAD) estimated from the EC50 of the most sensitive in vitro cytotoxicity assay and pharmacokinetic modelling. Assuming an average body surface area (BSA) of 1.7 m^2 the proposed starting dose of 0.12 µg/ m^2/day translates into a starting dose of 0.20 µg/d given by continuous intravenous injection. In the clinical trial the administered doses will not be BSA-adapted. The proposed starting dose is 4500 fold lower than the HNSTD (540 µg/m^2/day) and 1500 fold lower than the dose (180 µg/m^2/day) that did not result in cytokine release in the 4-week toxicology study in cynomolgus monkeys.

2.3 BENEFIT - RISK ASSESSMENT

Progress in understanding the biological behavior of MM has been achieved and effective treatment regimens have been developed. However, these treatments are not curative and most patients with MM still die of their disease. In particular, patients with relapsed and/or refractory multiple myeloma have a need for new therapeutic options.

BI 836909 is a Bi-specific T-cell Engager that binds to BCMA on MM cells and on CD3ε on T-cells and therefore functions as a bridge between cancer cells and CTLs and directs the cytolytic activity to the MM cells.

BI 836909 shows strong binding to human BCMA, and comparable cross reactive binding to cynomolgus BCMA. Cells of a bone marrow aspirate of a MM patient containing BCMA positive target cells as well as T autologous cells were incubated for 48 hours with BI 836909. The number of BCMA/CD38 positive cells was determined by flow cytometry over time. The number of viable BCMA/CD38 positive cells decreased in the samples incubated with BI 836909. The cell number in the untreated samples was not reduced.

At time of protocol preparation, BI 836909 has not previously been tested in humans. BCMA is not expressed on other cells than plasma cells. The anticipated side effect profile of BI 836909 based on preclinical studies comprise predominantly depletion of plasma cells and alterations of lymphatic tissues. Changes in WBC (decreases of lymphocytes and monocytes, increases of neutrophils) may occur. Lymphocytopenia may predispose to infections. Given the mode of action cytokine release syndromes may happen. Cytokine release can be associated with clinical symptoms such as fever, chills, nausea, vomiting, hypotension, dyspnoea, tachypnea, headache, tachycardia, rash, and/or hypoxia. CNS toxicities were observed with blinatumomab, the CD19xCD3 BiTE molecule. Whether this side effect is restricted to the CD19 target is still unclear. Considering the experience with other monoclonal antibodies in different indications, infusion-related reactions as well as cytokine release syndrome may occur and have to be differentiated from tumour lysis syndrome. Adverse events like these are frequently reported in patients with malignant diseases and may be due to the underlying disease, the treatment or both. Autoimmune phenomena in terms of anti-drug antibodies may occur. Prophylactic measures will be implemented in this protocol for primary prevention, supportive treatments are available (see Sections 4.1.4.1 and 4.2.1.2).

Current therapy for MM often cause remissions, but nearly all patients eventually relapse and die. There is substantial evidence of an immune-mediated elimination of myeloma cells in the setting of allogeneic hematopoietic stem cell transplantation. There is clearly a great need for new immunotherapies for multiple myeloma and targeting BCMA on MM cells and directing the cytolytic activity of CTLs to MM cells by a BCMA-BiTE might be a major advance in treating patient with refractory or relapsed MM.

Patients with MM may benefit from treatment with BI 836909 in terms of tumour cell reduction, tumour stabilisation, control of tumour-related symptoms and improved survival as BI 836909 targets an epitope of MM cells which has not previously been targeted. The potential benefit of therapy with BI 836909 is expected to outweigh the treatment-related risks.

Although rare, a potential for drug-induced liver injury is under constant surveillance by sponsors and regulators. Therefore, this trial requires timely detection, evaluation, and follow-up of laboratory alterations in selected liver laboratory parameters to ensure patients' safety, see also Section 5.2.2. Advanced and pretreated MM patients may present with elevated liver enzymes at study entry due to liver involvement or pretreatment with hepatotoxic regimen. Transaminase elevations may also occur during treatment with BI 836909 in the context of infusional reactions or cytokine release syndromes which can be managed by experienced

investigators. Therefore the definitions for hepatic injury have been modified to reflect the disease state of MM patients entering the trial. Therefore, this trial requires timely detection, evaluation, and follow-up of laboratory alterations in selected liver laboratory parameters to ensure patients' safety, see also Section 5.2.2.

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

The trial is an open-label, non-randomized phase I dose-escalation trial with modified 3+3 design to evaluate the tolerability and safety of BI 836909 given as continuous intravenous infusion as well as to determine the MTD or to establish the recommended dose for further development of BI 836909 administered as continuous intravenous infusion.

MTD is defined as the highest dose of the dose level tested where ≤ 1 patient out of 6 develops dose limiting toxicity. If MTD cannot be determined based on safety findings, a recommended dose for further development will be determined based on pharmacokinetic and pharmacodynamics data.

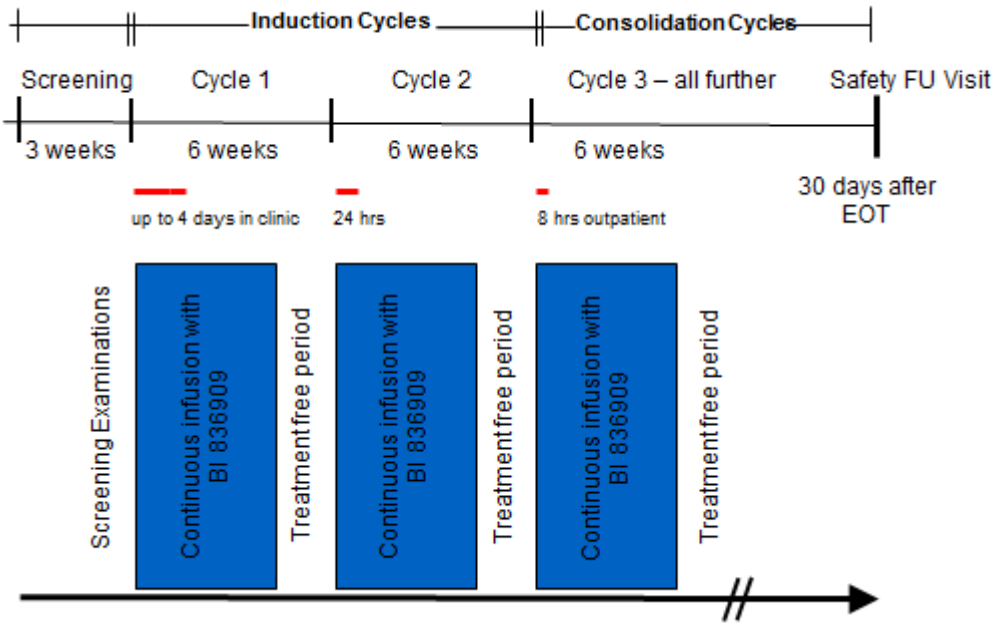


Figure 3.1: 1 Overall study design (In case of ongoing clinical benefit, patients can be followed up to collect data for duration of response. Follow-up visits for responders will be at 3, 6 and 12 months after EOT if a patient did not progress, started a new anti-cancer treatment, died, or withdrew informed consent.)

The study consists of the following phases:

- Screening period (day – 21 to day -1): baseline assessments will be performed as well as in- and exclusion criteria will be evaluated
- Treatment period: Treatment will continue for up to five 6-week cycles or until:
  - Disease progression/start of further anticancer treatment

- Non-acceptable toxicity
- Patient decision to withdraw consent
- Investigator's decision

In case of ongoing clinical benefit after five courses additional 5 courses may be given if considered indicated by the investigator.

- End of treatment (EOT): this visit will take place as soon as possible after discontinuation of study medication but no later than 1 week after discontinuation of trial drug
- Follow up visit (FU): follow up visit should be performed 30 days after the EOT (REP visit). Patients will be treated for a maximum of 10 cycles. In case of ongoing clinical benefit, patients can be followed up to collect data for duration of response. Follow-up visits for responders will be at 3, 6 and 12 months after EOT if a patient did not progress, started a new anti-cancer treatment, died, or withdrew informed consent. Last patient out is defined as the ~~REP~~last visit completed by the last patient. This will be the end of the trial.
  For patients who have entered the trial before the approval of the second revision last visit would be defined as the last follow up visit after the approval date.
  For patients who have re-consented after the approval of the fourth revision last visit would be defined as above.

The following dose levels will be tested:

Table 3.1: 1 Dose escalation scheme

Dose level	Dose µg/d	Patients per cohort	Approximate increment to next dose
1	0.2	1	2x
2	**0.4**	**1**	**2x**
3	**0.8**	**1**	**2x**
4	**1.6**	**1**	**2x**
5	**3.2**	**3 (+3)**	**2x**
6	6.5	3 (+3)	2x
7	13	3 (+3)	2x
8	25	3 (+3)	2x
9	50	3 (+3)	2x
10	100*	3 (+3)	2x
11	200*	3 (+3)	2x
12	400*	3 (+3)	2x
13	800*	3 (+3)	2x

*Intermediate dose cohorts with up to 50% increment versus the previous cohort will be entered if determined by the safety committee,in case that the dose of a cohort exceeds MTD (> 1 patient out of 6 with DLT) and the previous cohort is well tolerated.

For example:

- 75µg/day in case a dose of 100µg/day exceeds MTD
150µg/day in case a dose of 200µg/day exceeds MTD
- 300µg/day in case a dose of 400µg/day exceeds MTD
- 600µg/day in case a dose of 800µg/day exceeds MTD

The above-mentioned intermediate dose cohorts will follow the 3 (+3) design. The starting dose will be 0.20 µg/day given as a continuous intravenous infusion for 4 weeks.

An every 6-week regimen will be tested (4 weeks of continuous intravenous administration of BI 836909 followed by a 2 weeks off-period).

For the dose levels 0.2 to 1.6 µg/day single patient cohorts are entered since no clinical activity is expected at these doses.

If a patient has been on treatment in one of the above-mentioned dose cohorts for 2 weeks without DLT the first patient of the next higher dose cohort will be entered if agreed on by the safety committee. If a patient has reached DLT, then the safety committee recommends the switch to a 3 + 3 cohort for the dose level at which the DLT occurred. Patients may not proceed to the next higher dose level before completion of 6 patients.

One intra-patient dose escalation is allowed within the single patient dose cohorts if the initial dose is tolerated well and no DLT occurs during 1st cycle. In case of DLT additional patients will be entered into this cohort following a 3+3 design.

For the dose levels ≥ 3.2 µg/day 3-6 patients will be treated per dose level and observed for 4 weeks during the first cycle before decision for dose escalation to the next dose cohort is made.

Per dose level 1 patient will be enrolled and treated for 1 week, then further patients will be enrolled. Patients should be entered sequentially. Additional patients should not start treatment before the previous patient has been treated for 48 hours in order to monitor initial transient toxicities due to cytokine release syndrome.

In the dose escalation part the trial safety committee (for details see Section 3.1.1) can determine to enter additional and intermediate dose cohorts at any time e.g. if DLTs or other safety events, pharmacodynamics activity or antitumor efficacy occur. The safety committee will also determine to switch from single patient cohorts to a 3+3 design at doses below **3.2µg/d** if DLTs, pharmacodynamic activity or antitumor efficacy occur.

PK/PD data might be taken into account for dose escalation decisions if available.

Patients should be entered sequentially. Treatment initiation of more than 1 new patient per day will not be permitted during the dose escalation phase.

Once the MTD or the recommended dose for better characterization of safety and early evaluation of anti-tumour activity is determined up to 6 additional patients will be treated with MTD or the recommended dose.

3.1.1 Administrative structure of the trial

This study is sponsored by Boehringer Ingelheim. A Coordinating Investigator as specified on the cover page of this protocol will be nominated and will be responsible to coordinate investigators at different centres participating in this multicentre trial. Tasks and responsibilities for the Coordinating Investigator will be defined in a contract. Documents on participating (Principal) Investigators and other important participants, especially their curricula vitae, will be filed in Boehringer Ingelheim Regulatory Documents for Submission (BIRDS). Details on handling of the trial supplies including responsible institutions are given in Section 4 of this protocol. The target group of Principal Investigators will be haemato-oncologists experienced and specialized in the treatment of MM and in the conduct of phase I trials. The Principal Investigator (PI) at each site will be responsible for assuring the proper conduct of the trial, patient care, and safety at the site. The investigator or in some cases one or more sub-investigators will be responsible for the daily conduct of the trial, patient visits, eCRF completion, and for assisting the CRAs in site monitoring.

Site personnel authorized by the Investigator must enter the information required by the protocol into the eCRF. A Study Monitor will visit each site in accordance with the monitoring plan and review the eCRF data against the source data for completeness and accuracy. Discrepancies between the source data and those entered onto the eCRF will be addressed by qualified site personnel. When a data discrepancy warrants a correction, that correction will be made by authorized site personnel. Data collection procedures will be discussed with the study site at the site initiation visit and/or at the Investigator's Meeting.

The study sites will use a validated electronic data capture (EDC) system to enter subjects' data from source documents onto electronic eCRFs. Password-protected access to the EDC system will be via a secure website. Data clarification forms and data corrections will be handled through the same system. All transactions within the EDC system must be fully documented within an electronic audit trial. Each set of completed eCRFs must be reviewed and electronically signed and dated by the Investigator. In compliance with remote data retention requirements, the study sites will be provided with a CD-ROM containing the eCRFs and the complete audit trail in PDF format, subsequent to database lock.

A complete list of investigators and other persons whose participation materially will affect the conduct of the trial will be filed in BIRDS and provided in the Clinical Trial Report (CTR).

The study may be outsourced for responsibilities that include site monitoring, study medication logistics and processing of safety reports, among others.

Boehringer Ingelheim has appointed a Trial Clinical Monitor (TCM), responsible for coordinating all required activities to

- Manage the trial in accordance with applicable regulations and internal SOPs,
- Direct the clinical trial team in the preparation, conduct and reporting of the trial,
- Order the materials as needed for the trial
- Ensure appropriate training and information of local monitors (CML), Clinical Research Associates (CRAs) and Investigators of participating countries.

The safety laboratory investigations (haematological, biochemical, coagulation, and urine) and specific biomarkers (Section 5.1.2, 5.2.4 and 5.3.3) will be performed at the investigator site and no central laboratory will be used for these parameters. Only standard laboratory investigations are required by the protocol for safety laboratory investigations. The certification and/or accreditation for each laboratory or evidence that it participates in an established quality program must be provided by the investigator and filed at the Sponsor and the local ISF of the site, as well as the normal ranges of each test performed.

[redacted]

All trial relevant documentation will be stored in BIRDS. Trial relevant documentation which has to be at the trial site will be filed in the ISF at the investigator site. The ISF document will be kept in print-out version at the sites as far as required by local regulation and BI-SOP.

A safety committee (SC) of the investigators in cooperation with the responsible trial monitor and the medical project leader of the sponsor as well as medical representatives from Amgen will be implemented to analyse ongoing safety information and decide on further steps in dose finding. Prior to escalating the dose to the next higher dose cohort there will be a safety teleconference or meeting between trial investigators and the medical project leader of the sponsor to discuss any findings in the ongoing and already recruited cohorts, this means that all available clinical and safety data including repeated cycles of prior dose cohorts will be taken into consideration for assessments and decision making. Participation of the coordinating investigator or [redacted] deputy is a mandatory requirement for this committee to establish a quorum. After the defined observation period of each cohort this safety committee will discuss the need to enter additional patients or dose cohorts or release the next dose cohort and dose increment as per protocol. The same is true for the decision to switch from single patient cohorts to the 3+3 design. Step dosing may be implemented based on cytokine release syndrome qualifying for DLT following the following guidance:

- Restart with previous dose level for 4 days (one bag) and then escalate to current dose level until the end of the cycle.

The composition of the SC will be documented in BIRDS. The tasks and responsibilities will be agreed in contracts between the SC members and the Sponsor. SC will decide on the switch from single patient cohorts to the 3+3 design independently from defined dose cohorts based on clinical activity (antitumor response) and/or clinically relevant safety or pharmacodynamics findings.

Data Management and Statistical Evaluation will be done by BI according to BI SOPs.

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

Summary of assessments (see corresponding Flow charts):

At screening, blood samples are drawn, a physical examination and a routine MRI scan are performed, and the patient is evaluated for eligibility in the trial. Bone marrow aspirate/biopsy will be performed. In case karyotyping of bone marrow aspirate/biopsy has been performed after the latest therapy within 3 months before start of trial medication, it should be recorded.

Clinical disease status will be assessed at screening and at the start of each new cycle (e.g, before cycle 2, 3, 4 and 5 etc.) as well as at EOT with physical examination and clinical assessment of the multiple myeloma. MRI scans in this trial will be performed prior to treatment, at screening and every other cycle at day 1, cycle 3, day 1, cycle 5, day1, cycle 7, day 1 and/or at time of progression or start of further anticancer therapy.
Results from routine assessments (MRI) for multiple myeloma are accepted for screening if performed no later than 28 days before start of treatment.
Bone marrow examination, MRI scan and additional CT scans will be performed at time points outlined in the Flow chart. Results of MRI scans, additional CT scans, optional PET scan or bone marrow examination performed during the conduct of the trial should be reported in the eCRF. After the EOT visit which must occur immediately at time of permanent discontinuation of study medication but no later than 7 days after last drug administration, the patient will have a follow up visit within 30 days after EOT (REP visit) for assessment of AEs /SAEs, patient status and further anti-cancer treatment. In case of ongoing clinical benefit, patients can be followed up to collect data for duration of response. Follow-up visits for responders will be at 3, 6 and 12 months after EOT if a patient did not progress, started a new anti-cancer treatment, died, or withdrew informed consent and will assess related SAEs and AESIs.

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

The primary objective of this trial is to determine the MTD. The most important secondary objective is to assess the safety of BI 836909 given as continuous intravenous infusion.

For the first 4 doses up to and including 1.6µg/d dose cohorts single patient cohorts have been chosen since no clinical benefit is expected at these low doses.

For the remaining dose cohorts a standard 3+3 design has been chosen as this is an established standard approach in phase I studies in oncology:

The following dose cohorts will be tested as single patient cohorts: 0.2, 0.4, 0.8 and 1.6 µg/day.

If a patient has been on treatment in one of the above-mentioned dose cohorts for 2 weeks without DLT the first patient of the next higher dose cohort will be entered. In case that a DLT has been observed in the single patient cohorts 5 additional patients will be entered on this actual dose level.

Intra-patient dose escalation is allowed once to the next higher dose within the first 4 above-mentioned dose cohorts up to 1.6µg/d.

In case that no DLTs have been observed during the first cycle within the single patient dose cohorts the patient can be treated at the next higher dose level in subsequent cycles. Only one

intra-patient dose escalation step is allowed. This approach of intra-patient dose escalation reduces the number of patients treated at pharmacologically inactive doses to a minimum and increases the likelihood of treatment benefit for patients entered at low dose.

Prior to treatment of a patient at the next higher cohort a safety committee quorum needs to be obtained to oversee the observation period of this dose level to make sure that no additional patients must be entered at that dose level and that a patient can be entered at the next higher dose level. If the safety committee recommends treatment of additional patients at the lower dose level 2 additional patients must be entered at the lower dose level first. The 3 + 3 design will then be followed.

For the dose levels **≥ 3.2 µg/day** 3-6 patients (3+3 design) will be treated per dose level and observed for 4 weeks before decision for dose escalation to the next dose cohort is made.

If one patient of the cohort of three patients experiences a dose limiting toxicity (DLT) (for definition see 5.2.1.1) within the first cycle (4 weeks of continuous infusion), three additional patients will be treated at the same dose level according to a standard 3+3 design.

If at least two out of up to six patients at a dose level experience a DLT, the MTD has been exceeded and the dose will be de-escalated until a dose level is reached in which at most one DLT out of six patients is observed (R01-0028).

3.3 SELECTION OF TRIAL POPULATION

A total number of approximately 50 patients is expected to be entered into the trial. The number of patients depends on the number of dose escalation steps. A total of 5 sites will participate; this means that a total number of approximately 6 to 10 patients should be entered per site.

A comprehensive review of all relevant medical factors including patient characteristics (e.g. age, performance score, concomitant diagnoses, organ dysfunctions) as well as disease characteristics will be the basis for the decision of the investigator on whether a patient is eligible or not.

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

3.3.1 Main diagnosis for study entry

The eligible patients for the trial are patients with relapsed and/or refractory multiple myeloma who have progression of disease after at least 2 prior treatment lines (including proteasome inhibitors and at least one regimen containing an immune - modulatory drug [IMiD]). Patients must have measurable disease at time of screening as defined in Section 3.3.2.

Please refer to Section 8.3.1 (Source Documents) for the documentation requirements pertaining to the in-and exclusion criteria.

3.3.2 Inclusion criteria

1. Patients with a documented diagnosis of relapsed and/or refractory multiple myeloma who progressed after at least two prior treatment regimens, including both a proteasome inhibitor as well as an immune - modulatory drug at time of screening
2. Must have measurable disease, defined by one or more of following at time of screening:
   - a serum M protein > 0.5 g/dl measured by serum protein electrophoresis
   - urinary M protein excretion > 200 mg/24 hours
   - serum free light chain (FLC) measurement > 10 mg/dl, provided that the serum FLC ratio is abnormal
3. Relapse or progression of disease with an indication for therapy as per investigator`s judgment at time of screening
4. Life expectancy of at least 6 months as per investigator`s judgment at time of screening
5. ECOG Performance Status 0, 1 or 2 at time of screening
6. Age ≥ 18 years at time of screening
7. Written informed consent which is consistent with ICH-GCP guidelines and local legislation.
8. Able to adhere to the study visit schedule e.g. ability to come to the clinic and adhere to other protocol requirements
9. Indwelling central venous catheter or willingness to undergo intra venous central line placement

3.3.3 Exclusion criteria

1. Plasma cell leukemia
2. Extramedullary relapse of multiple myeloma
3. Known central nervous system involvement by multiple myeloma
4. Last anticancer treatment < 2 weeks prior to visit 1
5. Last treatment with a therapeutic antibody less than 6 weeks prior to visit 1
6. Prior allogeneic stem cell transplantation or solid organ transplantation
7. Autologous stem cell transplantation < than 90 days at time of treatment start
8. Last corticosteroid < 2 weeks prior to visit 1 unless the dose is ≤ 10 mg/day prednisolone or equivalent
9. AST or ALT >3 x upper limit of normal (CTCAE version 4.03 grade 2 or higher) at time of screening
10. Total conjugated bilirubin >1.5 x upper limit of normal (CTCAE version 4.03 grade 2 or higher) at time of screening
11. Absolute neutrophil count <1.0 x 10^9/L (without growth factor support) at time of screening
12. Platelets <25 x 10^9/L (without transfusions) at time of screening
13. Calculated GFR <30 mL/min (Cockroft-Gault Formula; see Appendix 10.4) at time of screening
14. Clinical relevant concurrent medical disease or condition which according to the investigator's judgment would either compromise patient safety or interfere with the evaluation of the safety of the test drug, e.g. symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia requiring therapy at time of screening

15. Clinically not controlled chronic or ongoing infectious disease requiring treatment at the time of enrolment or within the previous two weeks
16. Active hepatitis B or hepatitis C, or laboratory evidence for a chronic infection with hepatitis B or C (see Section 5.2.4.3.1) at time of screening; HIV infection at time of screening
17. Women of childbearing potential not using a highly effective method of birth control during the trial until one year after the last dose. Highly effective methods of birth control are defined as those which result in a low failure rate (i.e. less than 1% per year) when used consistently and correctly used such as implants, injectables, combined oral contraceptives, intrauterine devices (IUDs), sexual abstinence or vasectomised partner. Barrier methods of contraception are accepted if condom or occlusive cap is used together with spermicides (e.g. foam, gel). Female patients will be considered to be of childbearing potential unless surgically sterilized by hysterectomy or bilateral tubal ligation/salpingectomy, or postmenopausal (12 months with no menses without an alternative medical cause)
18. Male patients with partners of childbearing potential who are unwilling to use condoms in combination with a second medically acceptable method of contraception during the trial and for a minimum of 6 months after treatment.
19. Pregnancy or breast feeding
20. Known or suspected active alcohol or drug abuse as per investigator's judgment
21. Treatment with another investigational drug within the past four weeks before start of therapy or concomitantly with this trial
22. Patients with a known hypersensitivity to any component of the study drug
23. Patients with other malignancies within 5 years at time of screening (except basal cell or squamous cell carcinoma of the skin or carcinoma in situ treated with curative therapy)
24. Known autoimmune diseases requiring systemic treatment in past 5 years and interfering with evaluation of study drug.
25. Pre-existing disorders of the central nervous system.

3.3.4 Removal of patients from therapy or assessments

3.3.4.1 Removal of individual patients

The investigator or patient themselves may stop treatment at any time for safety or personal reasons.

- The patient withdraws consent for study treatment or study participation, without the need to justify the decision.
- The patient needs to take concomitant drugs that interfere with the investigational product (See Section 4.2).
- The patient can no longer be treated with trial medication for other medical reasons (such as surgery, adverse events, other diseases, or pregnancy)
- Relapse or Progressive Disease (PD), including deterioration of general condition due to disease progression or relapse (for definition see Appendix 10.1) or start of further anti-cancer therapy
- The patient fails to follow protocol requirements/directions and represent a safety issue for patient

- Eligibility criteria are violated and represent a safety issue for patient
- AEs that cannot be managed by dose reduction or adequate treatment
- Further dose reductions considered necessary but not allowed according to the protocol (see Section 4.1.4.3)
- The patient is found to be pregnant during program participation (please refer to Section 5.2.3)
- A change in the patient's status creating an unfavourable risk/benefit in favour to stop study medication.

Given the patient's agreement, the patient will undergo the procedures for early treatment discontinuation and follow up as outlined in the Flow chart and Section 6.2. For all patients the reason for withdrawal (e.g. adverse event) must be recorded in the eCRF. These data will be included in the trial database and reported.

For safety reasons it is recommended that the patient is encouraged to return for at least the follow-up visit.

When discontinuation is due to a serious AE (SAE) the treating investigator must follow the event until it is resolved, becomes chronic, or remains stable with no resolution expected.

If a woman becomes pregnant after having taken study medication, the treating investigator must report immediately any drug exposure during pregnancy to the sponsor. Drug exposure during pregnancy has to be reported immediately (within 24 hours) to the defined unique entry point for SAE forms of the respective BI OPU (country-specific contact details will be provided on the fax cover page).

For cases of paternal exposure to the BI product during the clinical trial, the pregnancy (mother is not a participant in the clinical trial) has also to be reported to BI, if the father (participant in the clinical trial) voluntarily reports it to the investigator.

In both cases 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 the clinical trial and not the SAE form is to be completed.

The Pregnancy Monitoring Form for the clinical trial (Part A and Part B) will be provided by the sponsor with the clinical trial documentation.

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:

- Failure to meet expected enrolment goals overall or at a particular trial site
- Emergence of any efficacy/safety information invalidating the earlier positive benefit-risk-assessment that could significantly affect the continuation of the trial
- Violation of GCP, the CTP, or the contract disturbing the appropriate conduct of the trial
- Discontinuation or modification of the clinical development program with BI 836909 for any reason.

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

4. TREATMENTS

4.1 TREATMENTS TO BE ADMINISTERED

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

Substance (INN):	**BI 836909**
Pharmaceutical form:	Powder for solution for infusion after dilution in water plus 5 ml bag-diluent
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Unit strength:	75 µg lyophilisate
Daily dose:	See Section 4.1.5
Duration of use:	BI 836909 will be administered as a continuous 4-week infusion followed by a 2-week break for 5 cycles or until progression, unacceptable adverse events or other reason necessitating withdrawal. In case of ongoing clinical benefit a maximum of 5 additional treatment cycles can be given if considered indicated by the treating investigator. This means that a maximum of 10 cycles can be given to a patient.
Route of administration:	Intravenous infusion
Posology:	Rate controlled infusion; the flow rate is set to 2.6 ml/h (250 ml in 96 hours).
Substance (INN):	**Bag Diluent for BI 836909**
Pharmaceutical form:	5 ml diluent [redacted]
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Unit strength:	N.A.
Daily dose:	N.A.
Duration of use:	5 ml bag diluent will be added to each bag independent of dose given and will be administered as a continuous 4-week infusion followed by a 2-week break for 5 cycles or until progression, unacceptable adverse events or other reason necessitating withdrawal.
Route of administration:	Intravenous infusion

Posology:	Rate controlled infusion; the flow rate is set to 2.6 ml/h (250 ml in 96 hours).

4.1.1.1 Description of portable pump for continuous intravenous infusion of BI 836909

BodyGuardTM 323 Multi-Therapy Ambulatory Infusion Pump (Ceasarea Medical Electronics GmbH; 72805 Lichtenstein; Germany) will be used in the trial for the 4 –week continuous rate controlled intravenous infusion. Site personnel will be trained on the use of the pump by the vendor. Detailed instructions will be available in the ISF.

4.1.2 Method of assigning patients to treatment groups

This is a single arm, open-label, dose-escalation trial. Assignment of a patient to a dose has to be confirmed by the investigator with the clinical monitor of the sponsor as described below in Section 4.1.4.

4.1.3 Selection of doses in the trial

This is the first in man study with BI 836909 and the starting dose will be a Pharmacologically Active Dose (PAD) estimated from the EC50 of the most sensitive in vitro cytotoxicity assay and pharmacokinetic modelling. Based on this modelling, the starting dose for Phase I for continuous intravenous injection is 0.20µg/d. The proposed starting dose is 4500 fold lower than the HNSTD (540 µg/m^2/day) and 1500 fold lower than the dose (180 µg/m^2/day) that did not result in cytokine release in the 4-week toxicology study in cynomolgus monkeys. For planned dose cohorts see Table 4.1.4.1.

4.1.4 Drug assignment and administration of doses for each patient

Dose allocation will be controlled by the sponsor to ensure safety monitoring and the dose-escalation schedule is adhered to in the interest of the safety of the patients.

Each investigational site must notify the sponsor when an eligible patient is identified. Prior to inclusion of a new patient during the dose-escalation phase the investigator has to confirm the actual dose tier of BI 836909 for the patient with the clinical monitor of the sponsor who oversees the dose-escalation steps and the safety data of patients from all trial sites. Enrolment will only be possible after the sponsor has notified the site by written confirmation of the dose and earliest possible date of first administration. Drug assignment to a patient will be done via the inter-active Webb response system (IWRS).

BI 836909 will be administered as a continuous intravenous infusion.

An every 6 week regimen will be tested (4 weeks of continuous intravenous administration of BI 836909 followed by a 2-week off-period).

Start of infusion of BI 836909 may be at any time during the day. However, to facilitate blood sampling for pharmacokinetic (PK) and pharmacodynamic analyses, it is recommended to start the infusion during the morning hours.

Preparation of solution for infusion will be done by the pharmacist at the site (for details, see ISF and pharmacy file). Pre-filled 250 ml bags with 0.9% NaCl will be used for the 4-day infusion. In a first step 5 ml bag diluent will be added to the normal saline containing bag and then the diluted solution of BI 836909 in a concentration according to actual dose level will be added.

Bag exchange must occur every 4 days either in the hospital or at patient`s home by the home care service (for details see corresponding manuals). Once the infusion line has been disconnected from patient`s implanted port the port should be flushed with normal saline before a new catheter will be accessed. Catheter must be flushed at the beginning of the infusion with normal saline.

Table 4.1.4: 1 Dose escalation scheme

Dose µg/day	Patients per cohort	Observation time of ongoing patients before enrolment/entry of next patient/cohort
0.2	1	2 weeks, then enrol next cohort
0.4	1	As in previous cohort
0.8	1	As in previous cohort
1.6	1	As in previous cohort
3.2	3 (+3)	1 week for first patient, then enter next two patients; additional patients should not start treatment before the previous patient has been treated for 48 hours in order to monitor initial transient toxicities due to cytokine release syndrome. All 3 must have completed 4 weeks before enrolling next cohort
6.5	3 (+3)	As in previous cohort
13	3 (+3)	As in previous cohort
25	3 (+3)	As in previous cohort
50	3 (+3)	As in previous cohort
100	3 (+3)	As in previous cohort
200	3 (+3)	As in previous cohort
400	3 (+3)	As in previous cohort
800	3 (+3)	As in previous cohort

*Intermediate dose cohorts may be added based on decision of the safety committee (see table 3.1:1) and will follow the above-mentioned rules.

For details see Section 3.1.

During the dose-escalation phase, each patient will receive a continuous infusion of BI 836909 given for 4 weeks followed by observation for 2 weeks after termination of the continuous

infusion. Treatment is given until progression according to IMWG response criteria (see Appendix 10.1), non-acceptable toxicity, patient decision to withdraw consent, investigator's decision. In case of clinical benefit a maximum of 5 cycles is administered. In case of ongoing clinical benefit additional 5 treatment cycles can be given if considered indicated by the treating investigator.

4.1.4.1 Prophylactic measures

4.1.4.1.1 Premedication

Premedication is mandatory 30-120 minutes prior to start of administration of BI 836909 to prevent/reduce severity of infusion-related reactions and before increasing the dose in case of an intra-patient dose escalation, unless a contraindication for premedication exists. The premedication for before start of each cycle should include

- Acetaminophen/paracetamol 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 or 16 mg dexamethasone

If BI 836909 has been well tolerated without signs of infusion-related reactions during the first cycle, glucocorticoid premedication may be reduced to 50% of the administered dose before first cycle, i.e. glucocorticoid i.v., equivalent to prednisolone 50 mg at start of second cycle. If tolerated well the investigator may decide to further reduce or do without premedication in repeated treatment cycles.

4.1.4.1.2 Monitoring for infusion-related reactions and cytokine release syndromes

Close monitoring of the patient during and after the infusion of BI 836909 is required for evaluation of infusion-related risks. The measures of monitoring include:

- Hospitalization of patients with access to intensive care days 1–4 of cycle 1 and in case of intra-patient dose escalation within the first cycle of dose escalation.
- Hospitalization of patients with access to intensive care on day 1 of cycle 2 (for a total of 24 hours) and in case of intra-patient dose escalation within the first cycle of dose escalation.
- Frequent measurements and documentation of blood pressure and heart rate (see Section 5.2.6.1).

In courses 2 and higher the patients are required to be hospitalized under close surveillance with access to intensive care days 1-3 again in case of infusion related events in earlier treatment courses. If no infusion related events occurred in earlier treatment courses an observation period of 4 - 8 hours in the hospital will suffice at start of each continuous infusion of BI 836909 in courses 3 and higher.

4.1.4.1.3 Tumour lysis syndrome

All patients have to be monitored for clinical or laboratory evidence of tumour lysis syndrome (see Appendix 10.3). To prevent tumour lysis syndrome, all patients should receive appropriate

hydration and supportive measures (e.g. rasburicase) according to local standards or available guidelines (R10-4517). In addition, close monitoring of laboratory parameters to allow for early diagnosis of a possible tumour lysis syndrome is recommended, for details please refer to Section 5.2.4.2 CTCAE version 4.03 classifies TLS in grade 3 (present), grade 4 (life threatening consequences; urgent intervention indicated) and grade 5 (death). Presence of TLS is not clearly defined by CTCAE version 4.03 (R10-4848). For this trial the Cairo-Bishop classification will be used to define presence of TLS, i.e. presence of clinical TLS (R10-4517).

4.1.4.1.4 Handling of infusion-related reactions or cytokine release syndromes

In case of an infusion-related reaction or cytokine release syndrome, appropriate measures depending on the type and severity of the reaction should be taken by the investigator according to best medical judgement and local guidelines. Supportive therapy including steroids may be used as clinically indicated. For supportive treatment of severe CRS interleukin 6 receptor (IL6R) antagonists may be used (R15-0031).

Changes of the infusion rate and temporary interruptions of the infusion have to be recorded in the eCRF.

Infusion-related reactions or cytokine release syndromes CTCAE version 4.03 grade 3 and 4 are defined to be adverse events of special interest and have to be reported according to the rules defined for SAE-reporting (see Section 5.2.2.1).

The following recommendations for the management of infusion-related reactions or cytokine release syndromes (Table 4.1.4.1.4: 1) should be considered by the investigator as guidance:

- In the case of an infusion-related reaction CTCAE version 4.03 grade 1 or 2, the infusion of BI 836909 should be temporarily interrupted and resumed as soon as considered clinically manageable by the investigator.
- In the case of an infusion-related reaction CTCAE version 4.03 grade 3 or 4, the infusion has to be stopped immediately. These patients should not be re-exposed to BI 836909.

Table 4.1.4.1.4: 1 Grading and management of cytokine release syndrome

CRS grade	Description of severity[a] (CTCAE v4)	Interruption	Minimum expected intervention	Re-start guidance	Permanent discontinuation
1	Mild reaction; infusion interruption not indicated; intervention not indicated	n/a	Administer symptomatic treatment (e.g. paracetamol/ acetaminophen for fever). Monitor for CRS symptoms including vital signs and pulse oximetry at least Q2 hours for 12 h or until resolution, whichever is earlier.	n/a	n/a
2	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g. antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for ≤24 h	Immediately interrupt BI 836909 until event has improved to CRS grade ≤1, but for no less than 72 h.	Administer: • Symptomatic treatment (e.g. paracetamol/ acetaminophen for fever) • Supplemental oxygen when oxygen saturation is <90% on room air • Intravenous fluids or low dose vasopressor for hypotension when systolic blood pressure is <85 mmHg. Persistent tachycardia (e.g. >120 bpm) may also indicate the need for intervention for hypotension. Monitor for CRS symptoms including vital signs and pulse oximetry at least Q2 hours for 12 hours or until resolution to CRS grade ≤1, whichever is earlier. Investigators may also use tocilizumab[c] as an additional therapy in this setting at a dose of 4-8 mg/kg as a single dose, particularly if CRS does not improve to grade ≤1 within 4 h after dose interruption. For subjects with extensive co-morbidities or poor performance status, manage per grade 3 CRS guidance below.	• Re-start possible, if successfully managed and improvement to CRS grade ≤1 within 7 days, • Consult with Boehringer Ingelheim medical monitor first. • Hospitalization: 48 h • In the event of 2 consecutive cases of CRS of grade 2, consider reducing dose to 200 µg/d for subjects originally receiving 400 µg/d • Additional measures: additional assessments and premedication as indicated in CTP	• If there is no improvement to CRS ≤grade 1 within 7 days • If interruption is >14 days • In case of repeat grade 2 event despite dose reduction

Table 4.1.4.1.4: 1 (cont'd) Grading and management of cytokine release syndrome

3	Prolonged (e.g. not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae (e.g. renal impairment, pulmonary infiltrates)	Immediately interrupt/ delay BI 836909 until event has improved to CRS grade ≤1.	Admit to intensive care unit for close clinical and vital sign monitoring per institutional guidelines. Administer dexamethasone (or equivalent) IV at a dose maximum of 3 doses of 8 mg (24 mg/d). The dose should then be reduced step-wise. AND/OR Investigators should also consider use of tocilizumab[c] as an additional therapy in this setting at a dose of 4-8 mg/kg as a single dose.	As for CRS grade 2	• If there is no improvement to CRS ≤grade 2 within 5 days and CRS ≤grade 1 within 7 days. • In case of 2 separate grade 3 CRS events. • If interruption is >14 days
4	Life-threatening symptoms • Requirement for ventilator support OR • Grade 4 organ toxicity (excluding transaminitis) per CTCAE criteria	n/a	Admit to intensive care unit for close clinical and vital sign monitoring per institutional guidelines. Administer dexamethasone (or equivalent) IV at a dose maximum of 3 doses of 8 mg (24 mg/day). Further corticosteroid use should be discussed with the Boehringer Ingelheim medical monitor. Additionally, tocilizumab[c] should be administered at a dose of 4-8 mg/kg as a single dose and may be repeated once within 24 to 48 h based on clinical assessment.	n/a	Immediately stop the infusion (if applicable) and permanently discontinue BI 836909 therapy.

CRS = cytokine release syndrome; CTCAE = Common Terminology Criteria for Adverse Events; IV = intravenous
[a] CTCAE v4 grading used, therapy adapted using the revised grading system for cytokine release syndrome (R16-2323)
[b] High dose vasopressors (all doses are required for ≥3 h): norepinephrine monotherapy ≥20 µg/min, dopamine monotherapy ≥10 µg/kg/min, phenylephrine monotherapy ≥200 µg/min, epinephrine monotherapy ≥10 µg/min; if on vasopressin, vasopressin + norepinephrine equivalent of ≥10 µg/min; if on combination vasopressors (not vasopressin), norepinephrine equivalent of ≥20 µg/min.
[c] All sites will ensure that CRS rescue medications are available on-site, including corticosteroids and 2 doses of tocilizumab per study subject.

4.1.4.2 Continuation of Treatment during a Course

Adverse events and laboratory values will be evaluated continuously by the investigator and the sponsor. Prior to start of each new cycle of BI 863909, adverse events and safety laboratory will be assessed. To continue treatment with a further infusion of BI 863909 all of the following criteria must be met:

(1) Neutrophils ≥500 /µL (0.5 x 10^9/L) and platelets ≥25 000 /µL (25 x 10^9/L), with or without growth factor support or transfusions.

(2) Acceptable tolerability (in case of an adverse event at the planned start of a treatment course, patients may continue therapy only after recovery to a level which would allow further therapy, i.e. CTCAE version 4.03 grade 1 or pre-treatment value.)

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

4.1.4.3 Dose reductions and dose delays

Related SAEs/AEs of ≥ grade 2 or non-drug related SAEs/AEs of ≥ grade 2 deemed intolerable by the patient or the treating physician and not responding to appropriate medical management will result in a pause until resolution to baseline or grade 1. A pause of a maximum duration of 14 days and a dose reduction to the next lower dose level is allowed if clinically indicated. Only one dose de-escalation step is allowed.

DLT events in any cycle, cases meeting the pre-defined hepatic injury criteria (ref. 5.2.2.1) and infusion related reactions or cytokine release syndromes ≥ grade 3 will lead to permanent discontinuation in the dose escalation phases. After recovery to baseline or grade 1 continuation of the cycle at the next lower dose tier is allowed. Only one dose de-escalation step is allowed.

CNS events ≥ grade 2 irrespective of relatedness that have not resolved to baseline or grade 1 within one week despite treatment interruption will lead to permanent discontinuation in the dose escalation phase. CNS events that have resolved to baseline or grade 1 within one week can be continued at the next lower dose level. Only one dose de-escalation step is allowed.

In case of dose reductions all future courses will also be at the reduced dose level.

4.1.4.4 Permanent discontinuation of BI 836909

Patients treated at the initial dose cohort of 0.2µg/d who require a dose reduction will be permanently discontinued.

A pause of treatment or delayed start of treatment of more than 2 weeks or several interruptions exceeding a total of 14 days of treatment per cycle due to SAEs/AEs will lead to permanent treatment discontinuation.

4.1.4.5 Temporary treatment interruption of BI 863909

If a pause of treatment < 14 days occurs within a cycle then the cycle will be restarted at the same or the next lower dose (if clinically indicated) and continued until the pre-scheduled end of the cycle. This dose will be continued in subsequent cycles.

If a pause of treatment occurs and less than 7 days of treatment would remain after restart of the cycle there is an option to skip the last treatment days and continue with the next course as scheduled. However, treatment should not be given for less than 14 days per cycle.

Patients who permanently discontinue treatment for reasons other than DLT will be replaced. Only patients who will receive at least 14 days of treatment in the first course will be evaluable for the primary analysis unless they develop DLT.

For dose levels 2 and higher the trial safety committee may decide to start the subsequent cycles of the affected patient and potentially new patients at this and higher dose cohorts in a stepwise fashion: treatment will be started at 10-30% of the target dose for the first week (but not earlier than 4 days after the stop of infusion in retreated patients). On day 9 the dose may be escalated to the target dose.

The re-start of the infusion should be performed in the hospital under supervision of the investigator.

4.1.5 Blinding and procedures for unblinding

4.1.5.1 Blinding

This phase I trial will be performed according to an open-label, single arm design. It will recruit patients with relapsed and/or refractory MM. This open-label trial will be handled in an open fashion by the sponsor throughout, i.e. also for the purpose of data cleaning and preparation of the analysis. The eCRF will contain information on the treatment and the dose.

4.1.5.2 Procedures for emergency unblinding

Not applicable.

4.1.6 Packaging, labelling, and re-supply

BI 836909 will be supplied in lyophilized vials containing 75µg BI 836909 to be reconstituted with 1ml water for injection (WFI). Water for injection will not be provided. One pack of medication contains 1 vial of lyophilized BI 836909 and 1 vial of 5 ml bag diluent. For details of packaging and the description of the label, refer to the ISF.
Medication will be delivered to the investigator's pharmacy where the total dose per patient will be prepared upon request from the investigator.
Re-supply will be managed by IWRS system.

4.1.7 Storage conditions

BI 836909 which will be provided by the sponsor must be kept in a secure, limited access storage area under the storage conditions defined by the sponsor and at the temperature indicated on the trial drug label. BI 836909 as well as the bag diluent must be stored in a refrigerator at 2 – 8°C and should not be frozen. Drug supplies will be kept in their original packaging. A temperature log must be maintained for documentation.

If the storage conditions are found to be outside the specified range, immediately contact the local clinical monitor or the CRA as provided in the list of contacts. For more details on BI 836909, please refer to the IB (c02942358) and the ISF.

In-use stability of BI 836909 and Bag Diluent refers can be found in the "Instruction for Pharmacists". These will be provided within the ISF and pharmacy file.

4.1.8 Drug accountability

The pharmacist will receive the investigational drugs delivered by the sponsor when the following requirements are fulfilled:

- approval of the study protocol by the IRB / ethics committee,
- availability of a signed and dated clinical trial contract between the sponsor and the Head of the investigational site,
- approval/notification of the regulatory authority, e.g. competent authority,
- availability of the curriculum vitae of the principal investigator,
- availability of a signed and dated clinical trial protocol
- Reference ranges for local laboratory values.

The Investigator/pharmacist/investigational storage drug manager will receive the investigational drugs delivered by the sponsor after the IRB/ethics committee approval of the trial and completion of a clinical trial contact between the Sponsor and the Head of Trial Center.

The Investigator and/or pharmacist and/or investigational drug storage manager must maintain records of the product's delivery to the trial site, the inventory at the site, the use by each patient, and the alternative disposition of unused products.

These records will include dates of receipt, quantities, batch/serial numbers, expiry ('use by') dates, and the unique code numbers assigned to the investigational products and trial patients. The investigator/pharmacists/investigational drug storage manager will maintain records that document adequately that the patients were provided the doses specified by the CTP and reconcile all investigational products received from the sponsor. At the time of return to the sponsor and/or appointed CRO, the investigator/pharmacists/investigational drug storage manager must verify that all unused or partially used drug supplies have been returned by the patient or homecare service to the trial site and that no remaining supplies are in the investigator's possession.

The Investigator/pharmacist/investigational storage drug manager will receive the investigational drugs delivered by the sponsor after the IRB/ethics committee approval of the trial and completion of a clinical trial contact between the Sponsor and the Head of Trial Center.

4.2 CONCOMITANT THERAPY, RESTRICTIONS, AND RESCUE TREATMENT

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

4.2.1.1 Rescue medication

Rescue medication in term of an antidote to reverse the action of BI 836909 is not available. Potential side effects of BI 836909 have to be treated symptomatically.

All concomitant or rescue treatment(s) taken during the course of the trial must be recorded in the source documents (e.g. patient files) and in eCRF.

4.2.1.2 Supportive care

Patients should receive supportive care according to local guidelines regarding treatment of infusion-related reactions (Section 4.1.4.1.2), blood product support, antibiotics, antivirals, analgesics, etc. In the case of a tumour lysis syndrome, supportive therapy including rasburicase may be used as clinically indicated at the investigator's discretion.

4.2.1.2.1 Treatment of Myeloma Bone Disease, Hypercalcemia, Pain and Renal Failure

Treatment of myeloma bone disease, hypercalcemia, pain and renal failure should be done according to institutional standards.

4.2.1.2.2 Growth factors

The use of growth factors such as Erythropoiesis-Stimulating Proteins as well as granulocyte colony stimulating factor (G-CSF) will be allowed during therapy. However, growth factors are not allowed at inclusion and should be avoided, if patient`s condition allows, in the first treatment course for better assessment of safety parameters.

4.2.1.2.3 Infections

Prophylactic antibiotics, antifungal and antivirals are allowed and should be given according to institutional standards. Pneumocystis prophylaxis should also be given according to institutional standards. For patients who are considered to have an increased risk for herpes infections, the prophylaxis is mandatory unless medically contraindicated. Subjects who may experience neutropenia for 7 days or longer are at a high risk for infectious complications. As appropriate, these subjects will be administered prophylactic antibacterial, antifungal, and antiviral medications. These subjects will be monitored for early signs of breakthrough infections after the initiation of antibacterial therapy to prompt additional evaluation and possible therapy modification.

Patients who develop fever >38.3°C or a sustained temperature of >38°C ≥1 h will be hospitalised, undergo the following diagnostic work-up and started on empirical treatment with broad spectrum i.v. antibiotics according to institutional standards:

- Blood cultures from central line and peripheral veins
- Urine culture
- CT-Thorax low dose
- Respiratory virus by pharyngeal wash (Parainfluenza 1-4, Influenza A + B, Adenovirus, Metapneumovirus, Echovirus, Rhinovirus, Bocavirus, Coronavirus, Entrovirus und RSV by multiplex PCR)

Subjects with active systemic infections requiring IV antibiotics, antivirals, or antifungals should not be dosed with BI 836909 until infection has resolved and if being treated with an anti-infectious therapy, the course of such therapy should have been completed.

Patients requiring interruption of treatment for >14 days due to active infection will be permanently discontinued.

4.2.1.3 Concomitant medication

All concomitant therapies to provide adequate care may be given as clinically necessary, unless given as anti-myeloma therapy. Bis-phosphonates can be given as clinically indicated. All concomitant treatments should be recorded in the eCRF except for vitamins or nutrient supplements. Trade names, indication and dates of administration of concomitant therapies will be documented. For parenteral nutrition during the trial, the components not need to be specified in detail. It should just be indicated as “parenteral nutrition”. If a patient needs general anaesthesia, it will be sufficient to indicate “general anaesthesia” without specifying the details.

Concomitant therapy should 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 EOT visit, only concomitant therapy indicated for treatment of an adverse event has to be reported or if given as anti-myeloma therapy.

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

Previous therapies for multiple myeloma must have been discontinued at least two weeks before the first administration of trial drug (see exclusion criteria Section 3.3.3 for details) and patient must have recovered from all clinically relevant toxicities. A time interval of at least four weeks must have elapsed from the last administration of any other investigational treatment for multiple myeloma to the first administration of BI 836909.
No anti-neoplastic therapy concomitantly is allowed.

No other investigational therapy concomitantly is allowed.

Additional glucocorticoid medications may be used as clinically indicated to treat infusion-related reactions at any dose. Short term systemic glucocorticoid for lung disease (for example asthma or COPD) may be used. Daily oral steroid treatment may be administered at doses equivalent to prednisolone 10 mg per day. All other indications for steroids have to be discussed and agreed upon between investigator and sponsor.

4.2.2.2 Restrictions on diet and life style

No restrictions apply with regards to diet or life style unless based on restrictions due to the portable pump used within the study.

4.3 TREATMENT COMPLIANCE

BI 836909 will be administered as a continuous intravenous infusion (c.i.v.) via infusion pump over a period of 4 weeks. Infusion bags will have to be exchanged approximately every 4 days either at site or by a trained care provider. Persons involved in exchange of the bag will document compliance. Compliance may also be verified by pharmacokinetic assessments. Any discrepancies will be explained in the eCRF by the investigator or his/her deputy.

5. VARIABLES AND THEIR ASSESSMENT

5.1 EFFICACY - CLINICAL PHARMACOLOGY OR PHARMACODYNAMICS

5.1.1 Endpoint(s) of efficacy

The efficacy endpoints will be assessed at the time points specified in the flowcharts. Efficacy endpoints will be secondary or further endpoints in the trial and will be evaluated according to the response criteria of the International Myeloma Working Group (IMWG, 2006; Appendix 10.1).

Secondary endpoints of efficacy are:

- Objective response rate (percentage of patients with stringent complete response (sCR), complete response (CR), partial response (PR) and very good partial response (VGPR))
- Duration of response (DOR)
- Minimal residual disease (MRD) response rate
- Duration of MRD response.
- Progression-free survival (PFS)

[redacted]

5.1.2 Assessment of Efficacy

5.1.2.1 Laboratory parameters

The following laboratory parameters must be evaluated to assess response of treatment:

- Multiple myeloma (MM) cells in bone marrow
  Analysis of myeloma cells in bone marrow will be conducted using a diagnostic FACS panel including markers for CD45, CD38, CD19, CD138, CD56 and kappa/lambda chains. Scheduled sampling time points will be as follows (see flow charts): within 14 days before day 1 cycle 1or in cycle 1, day 1 before start of treatment, when M protein/FLC becomes undetectable during treatment, on day 29 of cycle 3 and at EOT. **The analysis will be performed centrally.**
  Percentage (%) of plasma cells in bone marrow should be assessed locally according to institutional standards and documented in eCRF at each timepoint.

- M protein will be measured in serum at the beginning and at the end of each treatment period, i.e. at baseline (screening or Cycle 1 Day 1) and at Cycle 1 Day 29, Cycle 2 Day 1 and Cycle 2 Day 29 and Cycle X Day 1, Cycle X Day 29 and at EOT. M protein measurements in urine will only be followed up if positive for M protein in serum at

baseline (Cycle 1 Day 1). Time points for urine analysis for M protein will be the same as for serum. **Measurements will be performed locally**.

- Free Light Chains (FLC)
  In case of free kappa/lambda light chain (FLC) multiple myeloma (M protein negative cases) FLC will be analysed in serum and urine at the same time points as for M protein described above. Measurements will be performed locally. Levels of involved/uninvolved FLC, ratio of monoclonal lambda FLC / kappa FLC and ratio of monoclonal kappa FLC /lambda FLC will be determined. **Measurements will be performed locally.**

- The analysis of immunoglobulins (IgG, IgA, IgM) will be performed at baseline, followed by intervals of two weeks and at EOT. **Measurements will be performed locally.**

- ß2-microglobulin will be measured in serum as recommended for M protein described above. In urine, measurements will be done at baseline and every 6 weeks and at EOT. **Measurements will be performed locally.**

- Total calcium levels will be investigated at baseline, before start of treatment and at the end of each treatment cycle, i.e.: Cycle X Day 1, Cycle X day 29 and EOT**.**
  Measurements will be performed locally.

5.1.2.2 Objective response rate

Objective response rate is defined as the percentage of patients achieving a sCR, CR, PR and VGPR and will be evaluated according to the response criteria of the International Myeloma Working Group (IMWG, 2006; Appendix 10.1).

- Stringent complete response (sCR)
  CR as defined below plus normal FLC ratio and absence of clonal cells in bone marrow by immunohistochemistry or immunofluorescence.

- Complete response (CR)
  Complete response is defined as negative immunofixation on the serum and urine and disappearance of any soft tissue plasmacytomas and < 5% plasma cells in bone marrow.

- Very good partial response (VGPR)
  Serum and urine M-protein detectable by immunofixation but not on electrophoresis or > 90% reduction in serum M-protein plus urine M-protein level < 100 mg/24 h.

- Partial response (PR)
  Partial response is defined as a > 50% reduction of serum M-protein and reduction in 24 hours urinary M-protein by >90% or to < 200 mg/24 h.

If the serum and urine M-protein are unmeasurable a > 50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria.

If serum and urine M-protein are not measurable, and serum free light assay is also not measureable, a > 50% reduction in plasma cells is required in place of M-protein, provided baseline bone marrow plasma cell percentage was > 30%.

In addition to the above listed criteria, if present at baseline, a > 50% reduction in the size of soft tissue plasmacytomas is also required.

5.1.2.3 Duration of response (DOR)

The duration of response (DOR) is calculated from the time of first recorded achievement of a response level, that is sCR, CR, PR and VGPR until documented progression or death.

5.1.2.4 Minimal Residual Disease (MRD) response

MRD Response is defined as < 1 tumour cell within 10^4 normal cells in bone marrow using FACS analysis.

MRD response rate is calculated by the percentage of patients achieving MRD response.

5.1.2.5 Duration of MRD response

Duration of MRD response is calculated from the time of first recorded achievement of a MRD response to progression or death.

5.1.2.6 Progression

Progression is defined as an increase of > 25% from lowest response value in any one or more of the following:

- Serum M-component and/or (the absolute increase must be > 0.5 g/dL)
- Urine M-component and/or (the absolute increase must be > 200 mg/24 h)

Only in patients without measurable serum and urine M-protein levels; the difference between involved and uninvolved FLC levels. The absolute increase must be > 10 mg/dL

- Bone marrow plasma cell percentage; the absolute percentage must be > 10%
- Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas
- Development of hypercalcaemia (corrected serum calcium > 11.5 mg/dL or 2.65 mmol/L) that can be attributed solely to the plasma cell proliferative disorder

5.1.2.7 Progression free survival (PFS)

PFS is defined as the time from first treatment with BI 836909 until disease progression or death.

[redacted]

5.2 SAFETY

5.2.1 Endpoint(s) of safety

The primary objective is to assess the safety of the drug in humans and to determine the MTD of BI 836909.

Primary Endpoints are the following:

- Maximum tolerated dose (MTD) of BI 836909
  MTD is defined as the highest dose level tested where ≤ 1 patient out of 6 develop dose limiting toxicity. If MTD cannot be determined based on safety findings, a recommended dose for further development will be determined based on pharmacokinetic and pharmacodynamic data.
  The MTD will be defined on the basis of DLT observed during cycle 1. However, for those patients who receive more than one cycle of BI 836909, all adverse events corresponding to the definition of DLT (Section 5.2.1.1) will be considered for the purpose of confirming the MTD and for the selection of the recommended dose for further development. In regular intervals, all available safety data including adverse events qualifying for DLT will be reviewed by the safety committee.

- Number of patients with dose limiting toxicities

The safety of BI 836909 will be assessed by a descriptive analysis of incidence and intensity of adverse events graded according to CTCAE (version 4.03), the incidence dose limiting toxicity (DLT), laboratory data and results of physical examination.

Further endpoint of safety is

- Immunogenicity of BI 836909 (frequency of patients developing anti-drug antibodies)

The safety data will be reviewed in regular intervals as well as ad hoc if needed.

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

5.2.1.1 Dose limiting toxicity

Dose limiting toxicity (DLT) is defined as any drug-related non-haematological adverse event CTCAE version 4.03 grade 3 or higher. The following grade 3 events will not be considered

DLT: febrile neutropenia and infection responding to antibiotic/anti-infective treatment within 48 hours, fatigue, headache, insomnia, fever, hypotension.

Laboratory parameters of grade ≥ 3 but not considered clinically relevant and/or responding to routine medical management, will not be considered dose limiting toxicities.

Additional events that are considered DLT include:

- Persistent grade 4 neutropenia or thrombocytopenia until day 56 in the absence of detectable Multiple Myeloma as it may reflect a marrow toxic effect of BI 836909.

If infusion related reactions (IRR) or cytokine release syndromes (CRS) ≥ grade 2 occur or constitute DLT events the safety committee may decide to switch to step dosing for the respective and any higher dose cohort. In that case the infusion will be started at 10(-30)% of the target dose on day 1 of the course and will be escalated to the full target dose from day 9 of course 1 on for the remainder of the course. Patients will be hospitalized and pre-medicated for the dose increase the same way they are for start of treatment. Once the safety committee decides to switch to step dosing patients that may have developed DLT due to IRR or CRS events may be replaced at the respective cohort by additional patients who will receive treatment with the adapted administration schedule (step dosing).
Although hematological adverse events (e.g. anemia, thrombocytopenia, neutropenia, lymphopenia) will not be considered DLT, complications resulting from hematological events, e.g. bleeding due to thrombocytopenia or grade 4 infection due to neutropenia are classified as non-hematological adverse events and are covered by the above definition of DLT. Nevertheless, hematological adverse events will be considered for definition of the dose for further development.

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 in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment.

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

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

- results in death,
- is life-threatening,
- requires inpatient hospitalization or prolongation of existing hospitalization,

- results in persistent or significant disability or incapacity,
- is a congenital anomaly/birth defect,

or

- is to be deemed serious of any other reason it is an important medical event when based upon appropriate medical judgement which may jeopardize the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions.

Life-threatening in this context refer to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if more severe.

AEs considered "Always Serious"

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

The latest list of "Always Serious AEs" can be found in the RDC system. These events should always be reported as SAEs as described in Section 5.2.3.

Adverse Events of special interest (AESIs)

The term AESI relates to any specific AE that has been identified at the project level as being of particular concern for prospective safety monitoring and safety assessment within this trial, e.g. the potential for AEs based on knowledge from other compounds in the same class. AESI need to be reported to the Sponsor's Pharmacovigilance Department within the same timeframe that applies to SAE, see Section 5.2.3.

The following are considered AESIs:

- Infusion-related reactions and cytokine release syndromes (CTCAE version 4.03 grade 3 or higher)
- Tumour lysis syndrome
- CNS adverse events grade 2 or higher
- Any event that qualifies for DLT (refer to Section 5.2.1.1)
- Hepatic Injury

A hepatic injury is defined by the following alterations of hepatic laboratory parameters (Appendix 10.6):

- an elevation of AST and/or ALT ≥5 fold ULN combined with an elevation of total bilirubin ≥2 fold ULN (if ratio of conjugated/total bilirubin is > 0.5) measured in the same blood draw sample, and/or
- Marked peak aminotransferase (ALT, and/or AST) elevations ≥10 fold ULN

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

Work-up as outlined in the "DILI-checklist" will serve to confirm the initial abnormality, obtain a comprehensive history and medical assessment, assess the severity of liver injury, evaluate data for potential alternative causes and decide on management of trial drug. When performing all of the required examinations, the investigator is encouraged to use clinical judgement, based on the patient's disease, comorbidities, clinical situation, past viral infections and risk for reactivation, exposure, prior therapy for malignant disease, co-medications and other factors as applicable. The sequence of tests in the DILI checklist may be used as guidance. The findings from the hepatic imaging (including comparison to prior imaging if available) must be made available as soon as possible as part of the adverse event reporting process and/or on the respective CRF pages. In the event the aetiology of the abnormal liver test results is not identified based on the imaging (e.g. biliary tract, pancreatic or intrahepatic pathology), the "DILI checklist" must be completed. Virus reactivation should be assessed by viral load and PCR testing where possible. Diagnostics for auto-immune hepatitis, Wilson's disease and haemochromatosis can be completed at the end of all assessments, as these examinations will not change within a short time period but can be considered proof of a long persisting chronic condition. In case a laboratory parameter of the DILI checklist cannot be performed, the investigator should provide a comment including a brief assessment of the relevance of this parameter for the overall evaluation of DILI.

Intensity of adverse event

The intensity of the AE should be judged based on the following:

Mild: Awareness of sign(s) or symptom(s) which is/are easily tolerated

Moderate: Enough discomfort to cause interference with usual activity

Severe: Incapacitating or causing inability to work or to perform usual activities

The intensity of adverse events should be classified and recorded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 in the (e)CRF.

Causal relationship of adverse events

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.

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.

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 (such as any active comparator or placebo and for trial procedure).

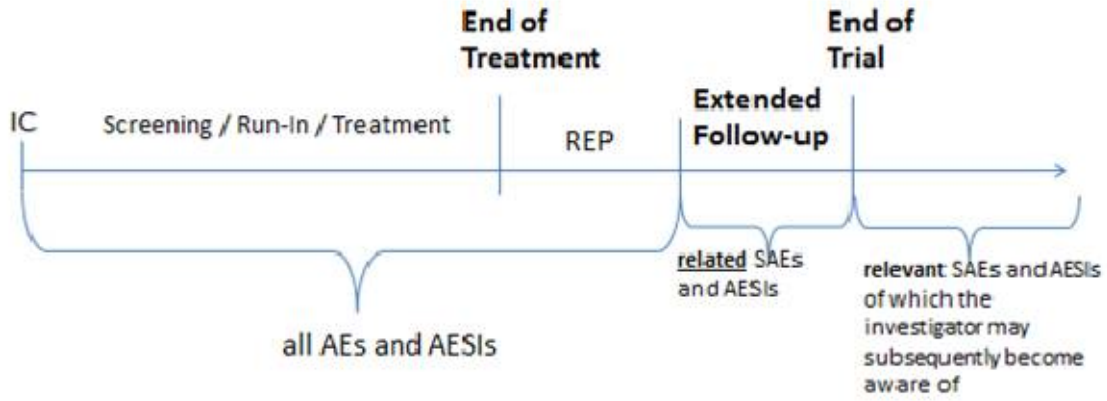
5.2.3 Adverse event collection and reporting

AE Collection

The following must be collected and documented on the appropriate eCRF by the Investigator:

- From signing the informed consent onwards through the Residual Effect period (REP) which is 30 day after EOT until the end of REP all AEs (serious and non-serious) and AESIs must be reported
- After the end of REP until trial completion all related SAEs and related AESIs must be reported.

The REP is defined as 30 days after the last administration of study medication. All AEs which occurred through the treatment phase and throughout the REP will be considered as on treatment please. Events which occurred after the REP will be considered as post treatment events.



After the last per protocol contact the Investigator does not need to actively monitor patients for AEs. However, if the Investigator becomes aware of SAEs or AESIs that occurred after the last per protocol contact, the SAEs and AESIs should be reported by the Investigator to the Sponsor if considered relevant by the investigator.

Patients may be hospitalized during selected phases of the study as required per protocol, e.g., monitoring of trial drug administration, collection of blood for pharmacokinetic purposes, or for administrative reasons. Hospitalizations for administrative reasons and other hospitalizations already planned at the screening visit need not be reported as a SAE in case they are performed "as planned".

The investigator must report the following events via telephone/fax using the SAE form immediately (within 24 hours) to the sponsor: SAEs and non-serious AEs occurring at the same time as an SAE and/or which are medically related to the SAE(s), and Protocol-specified adverse event of special interest. With receipt of any further information to these events, a follow-up SAE report has to be provided. SAEs and non-serious AEs must include a causal relationship assessment made by the investigator.

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) or by using the electronic submission process. 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.

AE reporting to sponsor and timelines

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

Information Required

For each AE, the investigator will provide information requested on the appropriate eCRF pages and the BI SAE form, e.g. onset, end date, intensity, treatment required, outcome, seriousness, and action taken with the investigational drug(s). The investigator should determine the causal relationship to the trial medication, the trial procedures outlined under Section 6.2.

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

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

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

Screening Failures

SAEs occurring in patients having discontinued the trial due to screening failures, i.e. after the screening period and who did not receive any trial medication, are to be reported if the Investigator considered the SAE related to the screening procedure. SAEs which occurred during the screening period are to be reported according to standard procedures.

Pregnancy

In the rare case that a female subject participating in this clinical trial becomes pregnant after having taken trial medication, the Investigator must report immediately (within 24 hours) the drug exposure during pregnancy (DEDP) to the Sponsor's unique entry point (country-specific contact details will be provided in the ISF). The Pregnancy Monitoring Form for Clinical Trials (Part A) should be used.

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

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

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

Exemption to SAE Reporting

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

Examples of exempted events of PD are:

- Progression of underlying malignancy (Progressive disease PD): if PD is clearly consistent with the suspected progression of the underlying malignancy as defined by the respective response criteria.
- Hospitalization/Procedures due solely to the progression of underlying malignancy (PD)

Clinical symptoms and/or signs of progression (with or without confirmation by objective criteria e.g. imaging, clinical measurement): if the symptom can exclusively be determined to be due to the progression of the underlying malignancy and does meet the expected pattern of progression for the disease under study.

Please note, when there is evidence suggesting a causal relationship between the drug and the progression of the underlying disease, the event must be reported as (S)AE.
Exempted events are monitored at appropriate intervals by an independent committee such as the Safety Monitoring Committee. All SAEs, including those persisting after trial completion must be followed up until they have resolved, have been sufficiently characterized, or no further information can be obtained.

5.2.4 Assessment of safety laboratory parameters

5.2.4.1 General safety laboratory parameters

Blood samples and urine have to be collected at the time points specified in the flowchart. Safety laboratory examinations will include haematology, biochemistry, coagulation and qualitative urine analysis. **The measurements will be performed locally.**

Haematology	Haemoglobin, red blood cell count (RBC), white blood cell count (WBC) with differential, platelets (PLT)
Biochemistry	Glucose, sodium, potassium, total calcium, inorganic phosphate, creatinine, aspartate amino transferase (AST), alanine amino transferase (ALT), alkaline phosphatase (AP), lactate dehydrogenase (LDH), total bilirubin (if elevated provide direct bilirubin), urea, total protein, albumin, uric acid, Ferritin (at baseline of cycle 1 only). Serum immunoglobulin levels (IgG, IgM, IgA) at baseline, day 15 and day 29 of each cycle only
Coagulation	Activated partial thromboplastin time (aPTT), prothrombin time (PT)/international normalised ratio (INR), fibrinogen and D-Dimers in cycle 1 and 2; thereafter on day 1 of each of the following cycles only.
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.

A serum pregnancy test needs to be obtained at the time points indicated in the flowchart in patients of childbearing potential.

In case a treatment course is delayed due to an adverse event, the patient should visit the site at least once a week for assessment of safety laboratory and adverse events. More frequent visits may be appropriate as assessed by the investigator.

5.2.4.2 Screening for laboratory evidence of tumour lysis syndrome

Tumour lysis syndrome (TLS) is characterized by metabolic derangements caused by the massive and abrupt release of cellular components into the blood after rapid lysis of malignant cells. The release of the intracellular metabolites can overwhelm normal homeostatic mechanisms, potentially leading to hyperuricemia, hyperkalemia, hyperphosphatemia, hypocalcemia, and uremia. This can result in impaired renal function, and in some cases, in acute renal failure and even death (R10-4517). To allow for early treatment in case TLS develops, vigilant monitoring is recommended if clinically indicated. During the first 48 hours after the start of the first infusion/injection of BI 836909 in course 1, and during the first 24

hours after the start of the first infusion/injection in course 2, the below listed laboratory parameters need to be determined to screen for evidence of a tumour lysis syndrome monitored frequently, i.e. every 4-8 hours between the time points at which a complete safety laboratory has to be performed. The actual date and time of the blood samples should be recorded in the eCRF.

Haematology	haemoglobin, haematocrit, red blood cell count (RBC), white blood cell count (WBC),+ differential, platelets (PLT)
Biochemistry	uric acid, potassium, calcium, inorganic phosphate, lactate dehydrogenase (LDH), creatinine, urea, ferritin.
Coagulation	Activated partial thromboplastin time (aPTT), prothrombin time (PT)/international normalised ratio (INR)**,** fibrinogen, D-dimer.

5.2.4.3 Virology

5.2.4.3.1 Screening for hepatitis B, hepatitis C and human immunodeficiency virus

Patients with active hepatitis B (HBV), hepatitis C (HCV) or laboratory evidence of a chronic infection have to be excluded from the trial, i.e. antigen or antibody positive. The same applies to patients with a human immunodeficiency virus (HIV) infection.

The following laboratory parameters have to be determined at the screening visit and reported in the eCRF: hepatitis B surface antigen (HbsAg), hepatitis B surface antibody (anti-HBs), hepatitis B core antibody (anti-HBc), hepatitis C antibody (anti-HCV), HCV RNA.

Screening for HIV infection should be performed according to local standards. The result of the HIV assessment has to be reported in the eCRF.

5.2.5 Electrocardiogram

A 12-lead resting electrocardiogram (ECG) will be performed in **all patients** at the screening visit and at the beginning of each cycle (except for cycle 1) and at the EOT visit. The ECG will be assessed for pathological results (to be recorded as either baseline condition, concomitant disease or AE) by the investigator. Additional examinations should be done whenever the investigator deems necessary.

For safety monitoring 12-lead ECGs (I, II, III, aVR, aVL, aVF, V1 - V6) will be recorded using an electrocardiograph.

All ECGs will be recorded for a 10 second duration after the subjects have rested for at least 5 min in a supine position.

5.2.6 Assessment of other safety parameters

5.2.6.1 Vital signs

Vital signs (blood pressure, pulse rate and body temperature) will be recorded at every visit during screening, treatment and EOT. Additional time points for blood pressure, heart rate and body temperature at the day of start of administration of BI 836909 are: prior to the start of premedication and infusion, then every 30 (±10) minutes after start of the infusion of BI 836909 for a total of 4 hours and thereafter 3 times a day during hospitalisation or in case of cytokine release syndrome and at each visit. In case of an infusion-related reaction, the investigator should decide whether to intensify or prolong monitoring of vital signs of the patient. Continuous cardiac monitoring should be performed during the hospitalisation for administration of BI 836909, patient surveillance may be modified by the investigator according to tolerability of the infusion during subsequent applications.

5.2.6.2 Physical examination

A physical examination including height (screening only), weight and ECOG performance score including an orienting neurological examination will be performed at screening and at the time points specified in the Flow Chart. The orienting neurological examination should be performed at screening as well as at EOT and daily during hospitalisation (see Flow charts).

During the physical examination, the patient should be assessed for possible adverse events.

5.3 OTHER

[redacted]

5.3.2 Other assessment(s)

5.3.2.1 Demographics and history

Demographics (sex, birth date, race), and baseline conditions will be collected during the screening visit. A detailed cancer history will be obtained. The date of first diagnosis of MM (month and year may be sufficient) will be recorded in the eCRF. The stage at diagnosis according to the response criteria of the International Myeloma Working Group (IMWG, 2006) at screening should be recorded (see Appendix 10.1). Previously administered chemo- and immunotherapy will be documented, including start and end dates (year and month may be sufficient), the treatment regimen/protocol with the number of courses (chemo-, immunotherapy), the best response obtained and the date of progression after each prior therapy (year and month may be sufficient). If the patient has received chemotherapy with autologous stem cell support, procedural details, including the treatment regimen prior to stem cell support should be collected. Documentation of previous radiotherapy should include the total radiation dose and radiation field(s). Any myeloma-related previous surgeries which may affect tumour

assessment in this trial according to the investigator within the past five years should be documented in the eCRF.

5.3.2.2 Concomitant diagnoses

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

[redacted]

5.4 APPROPRIATENESS OF MEASUREMENTS

Determination of MTD is based on toxicities graded according to CTCAE 4.03 (R10-4848). The CTCAE criteria are commonly used in the assessment of adverse events in cancer patients. The criteria to be used for evaluation of response (Appendix 10.1) are well established and scientifically accepted.

5.5 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

Blood samples during and at the end of infusion must be taken from the arm opposite to the infusion arm. For patients having a central venous access, PK samples obtained from either forearm. In order not to confound ECG recording, PK samples should be taken after performing the ECG.

If the infusion duration deviates from the scheduled time, the exact start and end times should be recorded in the eCRF. If the infusion stops in between, the stop time and the time when it is started again need to be documented in the eCRF. If the duration of infusion is prolonged or shortened, all following time points of PK and biomarker sampling should be adapted to the time when the i.v. infusion or s.c. injections has ended. Any changes in the rate of infusion should be documented in the eCRF.

Blood for pharmacokinetic analysis will be collected at specified time points during the corresponding treatment cycles (see corresponding Flow Charts; Appendix 10. 2) to determine the concentration of BI 836909. The blood samples for PK analysis will be processed to serum the same way as the ADA samples. The actual sampling date and time for blood samples should be documented in the eCRF. These actual sampling times will be used for determination of pharmacokinetic parameters. The exact clock time of trial medication administration and blood sampling as well as timing of any changes to the infusion flow rate will be documented in the eCRF.

Generally, PK serum samples for BI 836909 determination will be labelled with the study number, subject number, cycle number, visit number, protocol (planned) time and the sample number (according to Flow Charts; Appendix 10.2).

Detailed handling instructions for serum samples are provided in the ISF as well as the lab-manual.

5.5.1 Pharmacokinetic endpoint(s)

If data allow, the following pharmacokinetic parameters will be evaluated using non-compartmental analysis methods according to the internal BI Standard Operating Procedure (SOP).

Secondary pharmacokinetic endpoint is:

- Serum concentration at steady state (C_{ss}) for c.i.v.

[redacted]

[redacted]

5.5.2 Methods of sample collection and storage

5.5.2.1 Blood sampling for pharmacokinetic analysis

2,5 mL blood will be taken from a forearm vein or a central venous access in a vacutainer tube containing SSTII separation gel. The vacutainer should be carefully inverted 5 times after sample collection (an inversion is one complete turn of the wrist, 180 degrees and back). Tubes should stand upright for minimum 30 minutes but for a maximum of 2 hours at ambient temperature. The tube should be centrifuged for 10 min at 3,500-4,500 rpm. The specimen has been sufficiently centrifuged when the solid blood components and the liquid are approximately equally separated. The serum must be transferred with a pipette into a cryovial with colored cap (blue cap for PK) and immediately frozen at -20°C until shipment.

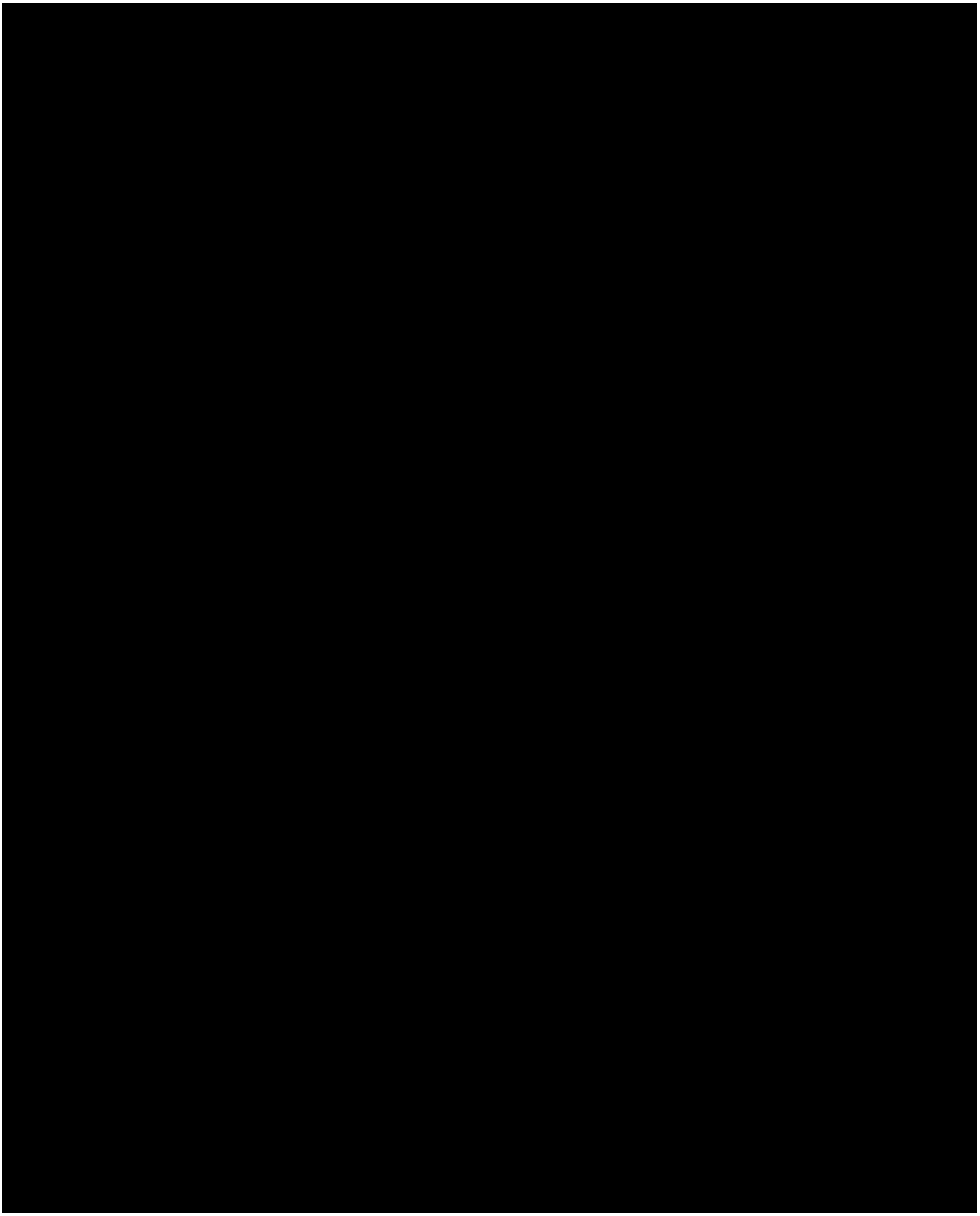
After the analysis has been performed the samples will be stored for 5 years and then destroyed.

5.5.2.2 Analytical determinations of samples

A detailed description of the validated assay will be available prior to the start of sample analysis.

The remainder samples may be used for immunogenicity assessment if needed.

[redacted]



[redacted]

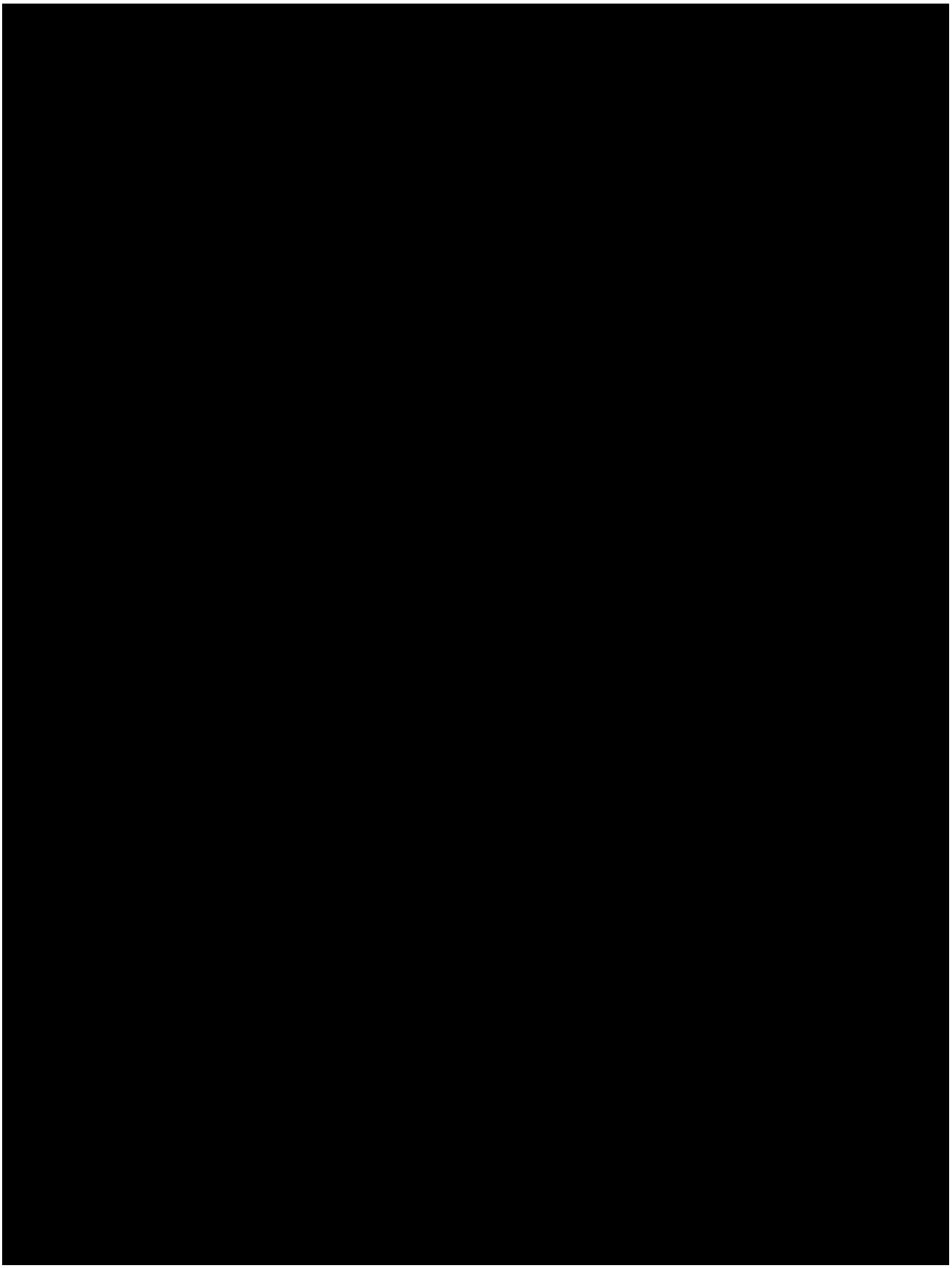
5.6.1.4 Immunophenotyping

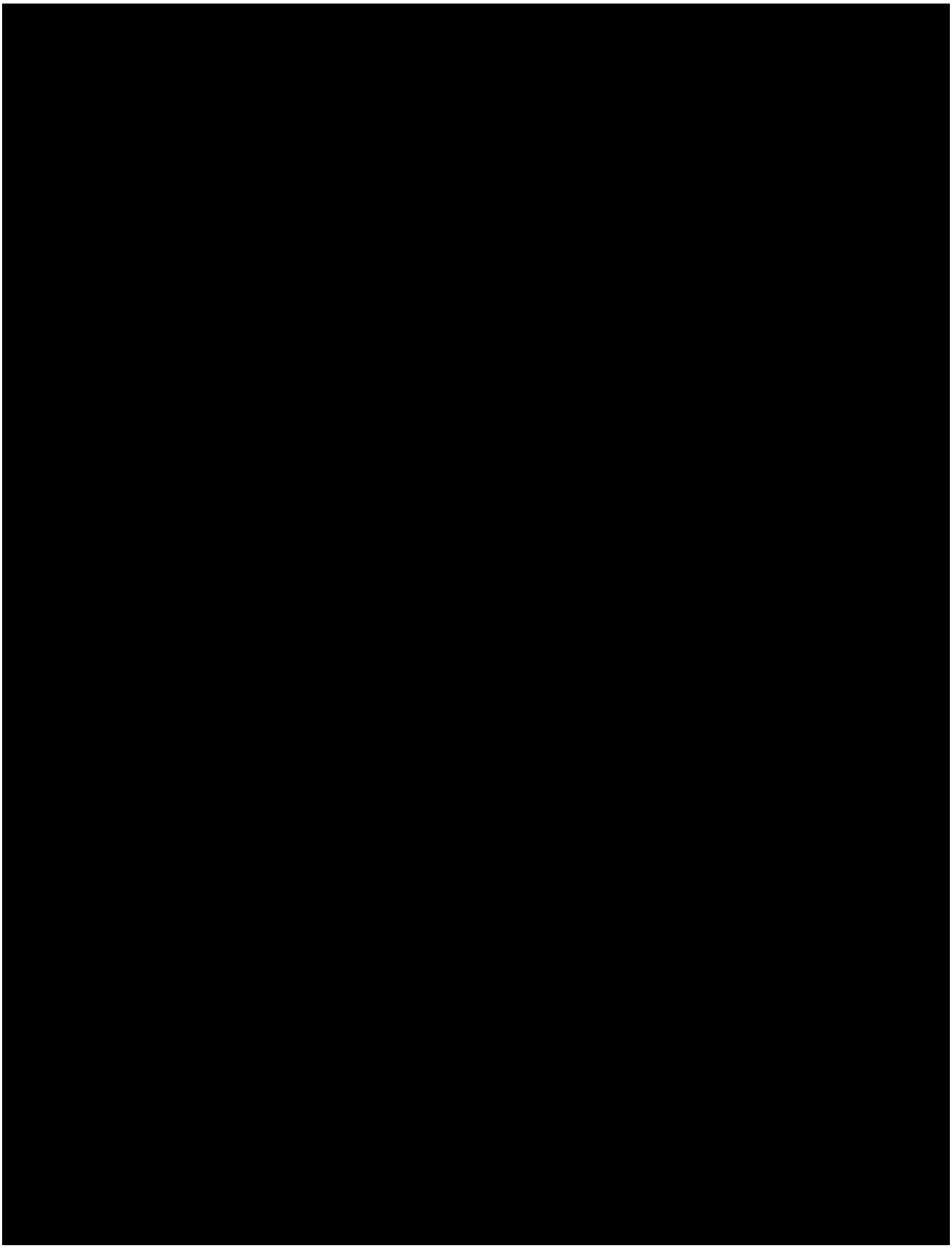
Diagnostic multiple myeloma flow cytometry including MRD

Analysis of myeloma cells in bone marrow will be conducted using a diagnostic flow cytometry panel including markers for CD45, CD38, CD19, CD138, CD56 and kappa/lambda chains. The analysis will be performed centrally. In order to assess minimal residual disease the flow cytometric panel may include 6-color-analysis such as cytIgλ /cytIgκ/CD19/CD56/CD38/CD45 and cytIgλ/CD19/cytIgκ/CD138/CD38/CD45 (R14-4637). Modifications according to updated guidance are possible.

[redacted]

[redacted]





6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

Patients must comply with all inclusion and exclusion criteria prior to the patient enters the study (see Section 3.3).

All patients should adhere to the visit schedule as specified in the Flow chart. However, in case a patient misses a visit and the patient reports to the investigator between the missed and the next scheduled visit, the procedures that were planned at the missed visit should be done and the actual date and the reason for the delay should be documented in the eCRF. Subsequent visits should follow the original visit schedule of the ongoing cycle unless a treatment pause > one week occurred. Then the next scheduled cycle should be started.

Some flexibility is allowed in scheduling the visits according to the time window specified in the Flow chart (± 3 days).

If pathological laboratory values or other issues require an additional unscheduled visit, a new eCRF page will be created for the unscheduled visit. At the unscheduled visit, it is sufficient to record only the clinical relevant labs/examinations performed.

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

6.2.1 Hospitalisation

Patients will be hospitalised for 3 – 4 days during cycle 1 as well as in the cycle when dose is escalated within one patient (single patient cohorts). In case that a step dosing approach is applied patient will also be hospitalised when dose is escalated to the normal dose (see Section 5.2.1). Patients will be hospitalised at start of cycle 2 for 24 hours and in all subsequent cycles for 8 hours in an outpatient setting.

6.2.2 Disease and Response Assessments for Multiple Myeloma

Clinical disease status for multiple myeloma will be assessed at screening, at the start of each cycle as well as at EOT.

At screening and subsequently the evaluation of multiple myeloma will be done according to IMWG (2006).

If a patient has clinical symptoms of multiple myeloma at screening, they should be recorded as baseline conditions.

Biomarkers in blood and urine will be done according to specific Flow chart for biomarkers.

Total body MRI should be performed within 14 days before day 1, cycle 1; results from routine assessments (MRI) for multiple myeloma are accepted if performed no later than 28 days before start of treatment.

Total body MRI should be performed at or within 14 days before day 1, cycle 3; day 1, cycle 5; day 1, cycle 7 as well as every other cycle thereafter and at time of EOT.

Bone marrow aspirates will be done within 14 days before day 1 cycle 1 or at cycle 1, day 1 before start of treatment, when M protein/FLC becomes undetectable during treatment, at day 29 of cycle 3 and at EOT.

For karyotyping the recent analysis will be accepted if performed within 3 months prior to start of study medication in case that no therapy has been given between assessment of karyotyping and study medication; otherwise, a baseline karyotype should be performed at screening; subsequent karyotyping could be performed in subsequent marrow samples.

The biomarker assessments will be performed as specified in the Flow charts. A bone marrow biopsy should be performed if aspirate could not be obtained (punctio sicca).

One sample of bone marrow will be provided for DNA banking in case that the patient has given consent for pharmacogenetic testing (baseline bone marrow, a bone marrow sample on treatment when a complete response is reached).

6.2.3 Screening and run-in period(s)

The examinations required for the screening visit may be conducted within a time interval of 21 days prior to the first study drug administration.

If for administrative or medical reasons, the patient is not entered within the defined screening period, it is allowed to re screen a patient. There is no maximum time period defined for re-screening.

If the patient has been determined eligible by the investigator to enter the trial (refer to Section 3.3), the investigator will assign one or more medication number(s) to the patient through the IWRS system at Visit 1 (Section 4.1.2). First dose of BI 836909 will be administered at the beginning of Visit 1 at the trial site (Day 1, cycle 1).

Table 6.2.3: 1 Screening Visit (Day -21 to -1)

Informed consent	Obtain written informed consent prior to enrolment in the trial and before any study-specific screening assessments are performed. Separate consent is required for none pre-specified pharmacogenetics and biomarker testing in bone marrow and blood.
Demographic data	Demographics and patient characteristics including detailed documentation of co-morbidities/concomitant diagnoses. Gender, date of birth/year of birth, race if allowed by local law will also be recorded.
Medical History	Oncological and relevant non-oncological baseline conditions will be recorded.
Physical examination (Section 5.2.6.2)	A general physical examination including blood pressure, heart rate and temperature as well as an orientated neurological examination will be performed, preferably by the same investigator throughout the study to enable comparability.
ECOG performance score (Section 5.2.6.2)	ECOG performance score will be assessed and documented.
Weight and Height (Section 5.2.6.2)	Height is measured at screening only. Weight is measured: preferably, the same weight scale should be used throughout the study to ensure consistency of data collected.
12-lead ECG (Section 5.2.5)	Resting 12-lead ECG (digital) is performed and analysed locally.
Safety laboratory as well as screening for HCV, HBV and HIV (Section 5.2.4)	Haematology (including differential), biochemistry, coagulation parameters and urinalysis (dipstick), as well as screening for HCV, HBV and HIV

Table 6.2.3: 1 (cont'd) Screening Visit (Day -21 to -1)

Bone marrow aspirate for disease assessment and DNA banking of bone marrow (Section 5.6.1)	Karyotyping: recent analysis will be accepted if performed within 3 months prior to start of study medication in case that no therapy has been given between assessment of karyotyping and study medication; otherwise, a baseline karyotype should be performed at screening; subsequent karyotyping could be performed in subsequent marrow samples. The following assessments will be performed (see Flow charts): • MM cells in bone marrow; percentage (%) of plasma cells in bone marrow should be assessed locally according to institutional standards and documented in eCRF. • BCMA expression by myeloma cells in bone marrow Obtain bone marrow biopsy if aspirate could not be obtained (*punctio sicca*). One sample of bone marrow will be provided for DNA banking.
Disease assessment: Clinical/MRI and blood/urine (Section 5.6.1)	Evaluation of multiple myeloma according to IMWG (2006) Clinical: if patient has clinical symptoms of Multiple Myeloma, they should be recorded as baseline conditions. Total body MRI should be performed; results from routine assessments (MRI) for multiple myeloma are accepted if performed no later than 28 days before start of treatment. [redacted]
Adverse events (Section 5.2.2)	Occurrence of AEs since signing the Informed Consent Form will be documented. For patients who become screen failures, if an AE occurs during this period, the patient should be followed until the PI determines the patient is a screen failure.

Table 6.2.3: 1 (cont'd) Screening Visit (Day -21 to -1)

Concomitant therapies (Section 4.2)	All concomitant therapies (including transfusions and anti-infectives) at trial entry and/or during screening will be recorded in the eCRF.
Review of inclusion/ exclusion criteria (Section 3.3.2 & 3.3.3)	Patient eligibility for the trial according to in- and exclusion criteria. In case of ineligibility, documentation of the reason(s) in patients source data why the patient is not eligible for the trial.
Serum pregnancy test (Section 5.2.4.1)	Serum pregnancy test in women of childbearing potential

6.2.4 Treatment period(s)

The first study drug dose should occur at the latest at Day 21 after the first screening procedure has been performed. A treatment cycle is defined as 6 weeks of duration. If initiation of a subsequent cycle is delayed due to medical reasons, additional visits beyond Day 36 may be necessary and may be performed at investigator's discretion, and should be recorded in the eCRF.

Patients may continue treatment in case of clinical benefit for 5 cycles. In case of ongoing clinical benefit up to a maximum of 5 additional treatment cycles can be given if considered indicated by the treating investigator.

6.2.4.1 Cycle 1

Patients will be hospitalized for the first 3 – 4 days.

Table 6.2.4.1: 1 Visit 1 (Day 1-3 or 4)

Physical examination (Section 5.2.6.2)	A general physical examination will be performed, preferably by the same investigator through the study to enable comparability. This includes blood pressure, heart rate and temperature. Additional time points for blood pressure, heart rate and body temperature at the day of start of administration of BI 836909 are: prior to the start of premedication and infusion, then every 30 (±10) minutes after start of the infusion of BI 836909 for the first 4 hours and additionally 3 times during hospitalisation (in the evening of day 1 as well as in the morning of day 2 and 3). Orienting neurological examination daily during hospitalisation.
[redacted]	
Weight (Section 5.2.6.2)	Weight is measured; preferably, the same weight scale should be used throughout the study to ensure consistency of data collected.
PK samples (Section 5.5 and 5.2.5)	For PK sampling, see separate Flow chart as well as section 5.5
Safety laboratory (Section 5.2.4)	Haematology, biochemistry, coagulation parameters and urinalysis (dipstick).
Adverse events (Section 5.2.2)	Occurrence of AEs since last visit.
Concomitant therapies (Section 4.2)	Any new or any change in concomitant therapies since the last visit, will be recorded in the eCRF.

Table 6.2.4.1: 1 (cont'd) Visit 1 (Day 1-3 or 4)

Disease assessment: clinical and blood and urine markers (Section 5.6.1)	Clinical: if patient has any new clinical symptoms of multiple myeloma, these should be recorded in the "disease assessment" page and as an AE when applicable (see Section 5.2.2.1). 
Administration of BI 836909 (Section 4.1)	4 weeks continuous intravenous infusion via infusion pump. Infusion bags must be exchanged approximately every 4 days.
Call IWRS/ Administer BI 836909	The IWRS system needs to be accessed (see Section 4.1.4) before any BI 836909 is administered to the patient. Dispense medication for the first course of treatment (see Section 4.1.4), as directed by the IWRS system.

Table 6.2.4.1: 2 Visit 2 – Visit 4 (Day 8 to day 22)

Home care service will be provided for bag exchange.

Assessments to be performed at start of each cycle:

Body temperature, Blood pressure, heart rate (Section 5.2.6.2) Serum pregnancy test (Section 5.2.3)	This examination includes blood pressure, heart rate and temperature. Serum pregnancy test in women of childbearing potential
Safety laboratory (Section 5.2.4)	Haematology, biochemistry, coagulation parameters and urinalysis (dipstick). Immunoglobulins will be measured at visit 3 (day 15)
[redacted]	
Adverse events (Section 5.2.2)	Occurrence of AEs since last visit.
Concomitant therapies (Section 4.2)	Any new or any change in concomitant therapies since the last visit, will be recorded in the eCRF.
Administration of BI 836909 (Section 4.1)	4 weeks continuous intravenous infusion via infusion pump. Infusion bags must be exchanged approximately every 4 days
Call IWRS/ Administer BI 836909	The IWRS system needs to be accessed (see Section 4.1.4.2) before any BI 836909 is administered to the patient. Dispense medication for the first course of treatment (see Section 4.1.4), as directed by the IRT system.

Table 6.2.4.1: 3 Visit 5 (Day 29 and day 30)

Physical examination and [redacted] (Section 5.2.6.2)	A general physical examination will be performed, preferably by the same investigator through the study to enable comparability. This includes blood pressure, heart rate and temperature. [redacted]
PK samples (Section 5.5 and 5.2.5)	For PK sampling, see separate Flow chart and Section 5.6. • 10 minutes before the end of continuous infusion • 24 hours after stop of treatment (day 30)
Safety laboratory (Section 5.2.4)	Haematology, biochemistry, coagulation parameters and urinalysis (dipstick).
[redacted]	
Adverse events (Section 5.2.2)	Occurrence of AEs since last visit.
Concomitant therapies (Section 4.2)	Any new or any change in concomitant therapies since the last visit, will be recorded in the eCRF.
Body temperature, Blood pressure, heart rate (Section 5.2.6.2)	This examination includes blood pressure, heart rate and temperature.
Safety laboratory (Section 5.2.4)	Haematology, biochemistry, coagulation parameters and urinalysis (dipstick).
Adverse events (Section 5.2.2)	Occurrence of AEs since last visit.
Concomitant therapies (Section 4.2)	Any new or any change in concomitant therapies since the last visit, will be recorded in the eCRF.

6.2.4.2 Cycle 2 – 5 (or further cycles in case more than 5 cycles are administered)

Table 6.2.4.2: 1 Cycle 2 – 5 (or further cycles): Visit 1 (day 1)

Patient will be hospitalised for at least 24 hours.

Physical examination (Section 5.2.6.2)	A general physical examination will be performed, preferably by the same investigator through the study to enable comparability. This includes blood pressure, heart rate and temperature. Orienting neurological examination daily during hospitalisation.
[redacted]	
Weight (Section 5.2.6.2)	Weight is measured; preferably, the same weight scale should be used throughout the study to ensure consistency of data collected.
ECG/PK samples (Section 5.5 and 5.2.5)	For PK sampling, see separate Flow chart and Section 5.5. A 12-lead ECG will be done at the start of each cycle.
Safety laboratory (Section 5.2.4)	Haematology, biochemistry, coagulation parameters and urinalysis (dipstick).
[redacted]	
Adverse events (Section 5.2.2)	Occurrence of AEs since last visit.
Concomitant therapies (Section 4.2)	Any new or any change in concomitant therapies since the last visit, will be recorded in the eCRF.

Table 6.2.4.2: 1 (cont`d) Cycle 2 – 5 (or further cycles): Visit 1 (day 1)

Disease assessment: Clinical, MRI and blood and urine markers (Section 5.6.1)	Clinical: if patient has any new clinical symptoms of multiple myeloma, these should be recorded in the "disease assessment" page and as an AE when applicable (see Section 5.2.2.1). [redacted] MRI should be performed every other cycle: at or within 14 days before cycle 3, day 1, cycle 5, day1, cycle 7, day 1… and/or at time of progression or start of further anticancer therapy;
Administration of BI 836909 (Section 4.1)	4 weeks continuous intravenous infusion via infusion pump. Infusion bags must be exchanged approximately every 4 days
Call IWRS/ Administer BI 836909	The IWRS system needs to be accessed (see Section 4.1.4.2) before any BI 836909 is administered to the patient. Dispense medication for the first course of treatment (see Section 4.1.4), as directed by the IRT system.

Table 6.2.4.2: 2 Cycle 2 – 5 (or further cycles): Visit 2 - 4

Physical examination (Section 5.2.6.2)	A general physical examination will be performed, preferably by the same investigator through the study to enable comparability. This includes blood pressure, heart rate and temperature.
[redacted]	
Weight (Section 5.2.6.2)	Weight is measured; preferably, the same weight scale should be used throughout the study to ensure consistency of data collected.
ECG/PK samples (Section 5.5 and 5.2.5)	For PK sampling, see separate Flow chart and Section 5.5. A 12-lead ECG will be done at the start of each cycle.
Safety laboratory (Section 5.2.4)	Haematology, biochemistry, coagulation parameters and urinalysis (dipstick).
Adverse events (Section 5.2.2)	Occurrence of AEs since last visit.
Concomitant therapies (Section 4.2)	Any new or any change in concomitant therapies since the last visit, will be recorded in the eCRF.
Disease assessment: clinical and blood and urine markers (Section 5.6.1)	Clinical: if patient has any new clinical symptoms of multiple myeloma, these should be recorded in the "disease assessment" page and as an AE when applicable (see Section 5.2.2.1). [redacted]

Table 6.2.4.2: 2 (cont`d) Cycle 2 – 5 (or further cycles): Visit 2 - 4

Bone Marrow	Bone marrow aspirate will be done on day 29 of cycle 3: The following assessments will be performed: • MM cells in bone marrow; percentage (%) of plasma cells in bone marrow should be assessed locally according to institutional standards and documented in eCRF. • BCMA expression by myeloma cells in bone marrow • MRD (in case M protein/FLC becomes undetectable) Obtain bone marrow biopsy if aspirate could not be obtained (punctio sicca). One sample of bone marrow will be provided for DNA banking.
Administration of BI 836909 (Section 4.1)	4 weeks continuous intravenous infusion via infusion pump. Infusion bags must be exchanged approximately every 4 days.
Call IWRS/ Administer BI 836909	The IWRS system needs to be accessed (see Section 4.1.4.2) before any BI 836909 is administered to the patient. Dispense medication for the first course of treatment (see Section 4.1.4), as directed by the IWRS system.

Table 6.2.4.2: 3 Cycle 2 – 5 (or further cycles): Visit 6 (Day 36)

For all cycles except for last cycle

Body temperature, Blood pressure, heart rate (Section 5.2.6.2)	This examination includes blood pressure, heart rate and temperature.
Safety laboratory (Section 5.2.4)	Haematology, biochemistry, coagulation parameters and urinalysis (dipstick).
Adverse events (Section 5.2.2)	Occurrence of AEs since last visit.
Concomitant therapies (Section 4.2)	Any new or any change in concomitant therapies since the last visit, will be recorded in the eCRF.

6.2.5 Follow-Up Period

6.2.5.1 End of treatment visit (EOT)

The EOT visit will be performed after permanent discontinuation of trial medication for any reason as soon as possible but no later 1 week after permanent discontinuation of the trial medication or when the investigator decided with the patient to permanently discontinue the trial medication or became aware that the trial medication had been terminated.

Table 6.2.5.1: 1 Visit at the End of Treatment (EOT)

ECG (Section 5.2.5)	Resting 12-lead ECG (digital)
Physical examination (Section 5.2.6.2)	A general physical examination as well as an orientated neurological examination will be performed, preferably by the same investigator throughout the study to enable comparability. This includes blood pressure, heart rate and temperature
[redacted]	
Weight (Section 5.2.6.2)	Weight is measured; preferably, the same weight scale should be used throughout the study to ensure consistency of data collected.
Safety laboratory (Section 5.2.4)	Haematology, biochemistry, coagulation parameters, and urinalysis (dipstick).
Disease assessment: clinical and blood/MRI (Section 5.5.1)	Clinical: if patient has any new clinical symptoms of multiple myeloma, these should be recorded in the "disease assessment" page and as an AE when applicable (see Section 5.2.2.1).
[redacted]	
Bone Marrow aspirate (Section 5.6.1)	Total body MRA should be performed. The following assessments will be performed: • MM cells in bone marrow; percentage (%) of plasma cells in bone marrow should be assessed locally according to institutional standards and documented in eCRF. • BCMA expression by myeloma cells in bone marrow • MRD (in case M protein/FLC becomes undetectable) Obtain bone marrow biopsy if aspirate could not be obtained (punctio sicca). One sample of bone marrow will be provided for DNA banking.

Table 6.2.5.1: 1 (cont`d) Visit at the End of Treatment (EOT)

Adverse events (Section 5.2.2)	Occurrence of AEs since last visit.
Concomitant therapies (Section 4.2)	Any new or any change in concomitant therapies since the last visit, will be recorded in the eCRF.
IWRS	Contact IWRS to register EOT.
Termination of Trial Medication	Including reason for conclusion, date of last administration of the trial drug.

6.2.5.2 Residual effect period (REP)

The REP is defined in Section 5.2.3. The End of REP (EOR) visit should not be performed earlier than 30 days after permanent discontinuation of the trial medication. The information collected at this visit should include all new AEs that occurred after EOT and a follow-up of adverse events ongoing at EOT. Any subsequent anti-cancer therapy administered between EOT and REP visit must be documented to allow an assessment of newly reported AEs as well as patient`s status.

Table 6.2.5.3: 1 Residual effect period (REP)

Adverse events (Section 5.2.2)	All AEs, SAEs, AESIs regardless of related ness. This includes all deaths.
Patient status	Collect information for progression or relapse, death, lost to follow-up.
Other therapy for Multiple Myeloma	In case the patient receives other therapy for Multiple Myeloma

6.2.5.3 Extended follow up

In case of ongoing clinical benefit, patients can be followed up to collect data for duration of response. Follow-up visits for responders will be at 3, 6 and 12 months after EOT if a patient did not progress, started a new anti-cancer treatment, died, or withdrew informed consent and will assess related SAEs and AESIs.

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 STATISTICAL DESIGN – MODEL

The dose escalation procedure is described in Section 3.1.1. Cohorts of patients will be entered sequentially into escalating dosage tiers with the aim to identify the maximum tolerated dose of BI 836909.

This study is open-label, which allows the safety of each dosage of BI 836909 to be assessed before treating additional patients with higher doses. Patients will not be randomized; they will be assigned to the cohort that is being filled at the time the patient is ready to enter the trial.

7.2 NULL AND ALTERNATIVE HYPOTHESES

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

7.3 PLANNED ANALYSES

Only one analysis population (the treated set, see definition below) will be considered for efficacy and safety analyses. No Per protocol population will be used for analyses. However important protocol violations will be described.

Treated Set consists of all patients who received at least one application of BI 836909.

7.3.1 Primary endpoint analyses

In order to identify the MTD, the number of patients with DLTs during the first course at each dose level will be displayed descriptively by dose level.

In addition, the number of patients with all DLTs during any treatment course will be analysed. Analysis of other adverse events and laboratory parameters is described in Section 7.3.4.

7.3.2 Secondary endpoint analyses

Objective response rate (patients with sCR, CR, VGPR, or PR), and MRD response rate will be analysed descriptively. Progression free survival (PFS), duration of response (DOR) and duration of MRD response will be analysed using the Kaplan-Meier method. Details of censoring rules will be provided in the statistical analysis plan.

Refer to Section 7.3.5 for the planned analyses of secondary pharmacokinetic endpoints.

[redacted]

7.3.4 Safety analyses

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary. Standard BI summary tables and listings will be produced. Statistical analysis and reporting of adverse events will concentrate on treatment-emergent adverse events. To this end, all adverse events occurring between start of treatment and end of the residual effect period ("REP"; see definition in Section 5.2.3) will be considered 'treatment-emergent'. Adverse events that start before first drug intake and deteriorate under treatment will also be considered as 'treatment-emergent'.

Key measures of safety will include:

- The incidence and intensity (according to CTCAE criteria version 4.03) of adverse events;
- Time course and distribution of patients by maximum CTCAE grade according to version 4.03;
- Time course of laboratory changes

The severity and timing of adverse events will indicate the tolerability of the treatment regimen. Adverse events will be evaluated using the CTCAE grading scheme version 4.03. The overall incidence and intensity of adverse events, as well as relatedness of adverse events to treatment with BI 836909 will be reported for all dose cohorts. Serious adverse events will be tabulated. In addition, events leading to dose reduction or treatment discontinuation will be examined, but may not be reported as individual tables, depending upon the extent of overlap with the occurrence of DLT.

Laboratory data will be analysed both quantitatively as well as qualitatively. The latter will be done via comparison of laboratory data to their reference ranges. Values outside the reference range as well as values defined as clinically relevant will be highlighted in the listings.

7.3.5 Pharmacokinetic analyses

The secondary pharmacokinetic endpoint C_{ss} [redacted] will be descriptively explored, and if possible, dose proportionality will also be explored descriptively. Attainment of steady state will be determined by visual examination of the data.

Refer to Section 5.5.1 for pharmacokinetic parameters to be calculated. The derivation of the parameters will be according to sponsor's standard operating procedures.

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

Concentrations will be used for graphs and calculations in the format that is reported in the bioanalytical report. Only concentrations within the validated concentration range will be used for the calculation of pharmacokinetic parameters. Plasma concentrations will be plotted graphically versus time for all subjects as listed in the drug plasma concentration-time tables. For the presentation of the mean profiles, the geometric and arithmetic mean and the planned blood sampling times will be used. If the actual sampling time deviates significantly from the planned time, the corresponding plasma concentration will be excluded from the calculation of descriptive statistics.

Pharmacokinetic analyses of the plasma concentration-time data will be performed using a validated software program (e.g., Phoenix Winnonlin) and for this purpose the actual sampling time for pre-dose samples will be set to zero.

Pharmacokinetic parameters will be compared in a descriptive manner. The following descriptive statistics will be calculated for analyte concentrations as well as for all pharmacokinetic parameters: N, arithmetic mean, standard deviation, minimum, median, maximum, arithmetic coefficient of variation, geometric mean, and geometric coefficient of variation. The data format for descriptive statistics of concentrations will be identical with the data format of the respective concentrations. The descriptive statistics of pharmacokinetic parameters will be calculated using the individual values with the number of decimal places as provided by the evaluation program. Then the individual values as well as the descriptive statistics will be reported with three significant digits in the clinical trial report.

7.5 HANDLING OF MISSING DATA

No imputation will be performed on missing efficacy data. Missing baseline laboratory values will be imputed by the respective values from the screening visit. No other imputations will be performed on missing data although every effort will be made to obtain complete information on all adverse events, with particular emphasis on potential dose limiting toxicities.

7.5.1 Safety

With respect to safety evaluations, it is not planned to impute missing values although every effort will be made to obtain complete information on all adverse events, with particular emphasis on potential dose limiting toxicities.

7.5.2 Plasma concentration – time profiles

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

7.5.3 Pharmacokinetic assessment

In the noncompartmental analysis, concentration data identified with NOS, NOR, and NOA will not be considered. BLQ and NOP values in the lag phase will be set to zero. The lag phase is defined as the period between time zero and the first time point with a concentration above the quantification limit. All other BLQ/NOP values of the profile will be ignored. If the predose concentration is less than or equal to 5% of C_{ss} value in that subject, the subject’s data without any adjustments can be included in all pharmacokinetic measurements and calculations (i.e. the predose value will not be changed to zero). If the predose value is greater than 5% of C_{ss}, the subject should be dropped from all statistical evaluations. The individual pharmacokinetic parameters can be calculated and listed separately.

Every effort will be made to include all concentration data in an analysis. If not possible, a case to case decision is required whether the value should only be excluded from half-life estimation or the complete analysis. If a concentration is only excluded from half-life determination, it will be used for all other calculations (e.g. descriptive statistics) and for graphical presentation. If a concentration value is excluded from all calculations, it will not be presented graphically or used for the calculation of descriptive statistics and parameter determination. However the excluded concentration itself will be listed in the clinical trial report associated with an appropriate flag. If the actual sampling time will not be recorded or will be missing for a certain time point, the planned time will generally be used for this time point instead. Pharmacokinetic parameters which cannot be determined will be identified by "not calculated" (NC).

7.6 RANDOMISATION

No randomisation will be performed. Patients will be assigned into escalating dose groups by order of admission into the trial.

7.7 DETERMINATION OF SAMPLE SIZE

It is planned to include a total of up to 50 subjects in this trial. The planned sample size is not based on a power calculation.

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 investigator of the patient.

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

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

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

The certificate of insurance cover is made available to the investigator and the patients, and is stored 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 (IRB) / Independent Ethics Committee (IEC) and competent authority (CA) according to national and international regulations. The same applies for the implementation of changes introduced by amendments.

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

The Investigator must give a full explanation to trial patients including the items listed below in association with the use of the patient information form, which is prepared avoiding the use of technical terms and expressions. The patient is given sufficient time to consider participation in the trial. The Investigator obtains written consent of the patient's own free will with the informed consent form after confirming that the patient understands the contents. The Investigator must sign (or place a seal on) and date the informed consent form. If a trial collaborator has given a supplementary explanation, the trial collaborator also signs (or places a seal on) and dates the informed consent.

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

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

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 will be provided by the sponsor, either on paper or via remote data capture. For drug accountability, refer to Section 4.1.8.

8.3.1 Source documents

Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the investigator's site. Data reported on the eCRF must be consistent with the source data or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the trial; current medical records must also be available.

For the eCRF, the following data need to be derived from source documents:

- Patient identification (gender, date of birth)
- Patient participation in the trial (substance, trial number, patient number, date patient was informed)
- Dates of Patient's visits, including dispensing of trial medication
- Medical history (including trial indication and concomitant diseases, if applicable)
- Medication history
- Originals or copies of the imaging diagnostics
- ECG results (original or copies of the printouts)
- Adverse events and outcome events (onset date (mandatory), and end date (if applicable))
- Serious adverse events (onset date (mandatory), and end date (if available))
- Concomitant therapy (start date, changes)
- Originals or copies of laboratory results (in validated electronic format, if available)
- Completion of Patient's Participation in the trial
- Prior to allocation of a patient to a treatment into a clinical trial, there must be document evidence in the source data (e.g. medical records) that the trial participant meets all inclusion criteria and does not meet any exclusion criteria. The absence of records

(either medical records or testing conducted specific for a protocol) to support inclusion/exclusion criteria does not make the patient eligible for the clinical trial.

8.3.2 Direct access to source data and documents

The investigator / institution will permit trial-related monitoring, audits, IRB / IEC review and regulatory inspection, providing direct access to all related source data / documents. 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. For the BI 863909 this is the current version of the Investigator's Brochure (c02942358).

The current versions of these reference documents are provided in the ISF. No AE are classified as listed for trial 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 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 END OF TRIAL

The end of the trial is defined as the last follow up visit of the last patient.

The IEC / competent authority in each participating EU member state needs to be notified about the end of the trial or early termination of the trial.

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10. APPENDICES

10.1 INTERNATIONAL MYELOMA WORKING GROUP (IMWG) UNIFORM RESPONSE CRITERIA FOR MULTIPLE MYELOMA

Response	IMWG criteria[1]
sCR	CR as defined below plus normal FLC ratio and absence of clonal cells in bone marrow[2] by immunohistochemistry or immunofluorescence[3]
CR	Negative immunofixation on the serum and urine and disappearance of any soft tissue plasmacytomas and < 5% plasma cells in bone marrow[3]
VGPR	Serum and urine M-protein detectable by immunofixation but not on electrophoresis or > 90% reduction in serum M-protein plus urine M-protein level < 100 mg/24 h
PR	> 50% reduction of serum M-protein and reduction in 24 hours urinary M-protein by >90% or to < 200 mg/24 h If the serum and urine M-protein are unmeasurable,5 a > 50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria If serum and urine M-protein are not measurable, and serum free light assay is also not measureable, > 50% reduction in plasma cells is required in place of M-protein, provided baseline bone marrow plasma cell percentage was > 30% In addition to the above listed criteria, if present at baseline, a > 50% reduction in the size of soft tissue plasmacytomas is also required
SD	Not meeting criteria for CR, VGPR, PR, or progressive disease
Progressive disease[4]	Increase of > 25% from lowest response value in any one or more of the following: Serum M-component and/or (the absolute increase must be > 0.5 g/dL)[5] Urine M-component and/or (the absolute increase must be > 200 mg/24 h) Only in patients without measurable serum and urine M-protein levels; the difference between involved and uninvolved FLC levels. The absolute increase must be > 10 mg/dL Bone marrow plasma cell percentage; the absolute percentage must be > 10%[6] Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas Development of hypercalcaemia (corrected serum calcium > 11.5 mg/dL or 2.65 mmol/L) that can be attributed solely to the plasma cell proliferative disorder
Relapse	Clinical relapse requires one or more of: Direct indicators of increasing disease and/or end organ dysfunction (CRAB features) [5]. It is not used in calculation of time to progression or progression-free survival but is listed here as something that can be reported optionally or for use in clinical practice Development of new soft tissue plasmacytomas or bone lesions

	Definite increase in the size of existing plasmacytomas or bone lesions. A definite increase is defined as a 50% (and at least 1 cm) increase as measured serially by the sum of the products of the cross-diameters of the measurable lesion Hypercalcemia (> 11.5 mg/dL) [2.65 mmol/L] Decrease in haemoglobin of > 2 g/dL [1.25 mmol/L] Rise in serum creatinine by 2 mg/dL or more [177 mmol/L or more]
Relapse from CR5 (To be used only if the end point studied is DFS)[7]	Any one or more of the following: Reappearance of serum or urine M-protein by immunofixation or electrophoresis Development of > 5% plasma cells in the bone marrow[6] Appearance of any other sign of progression (i.e., new plasmacytoma, lytic bone lesion, or hypercalcaemia)

[1] Adapted from Durie BGM, et al. Leukemia 2006; 20: 1467-1473 (R14-4478); and Kyle RA, Rajkumar SV. Leukemia 2009; 23:3-9 (R15-0269).
Note: A clarification to IMWG criteria for coding CR and VGPR in patients in whom the only measurable disease is by serum FLC levels: CR in such patients is defined as a normal FLC ratio of 0.26–1.65 in addition to CR criteria listed above. VGPR in such patients is defined as a >90% decrease in the difference between involved and uninvolved free light chain (FLC) levels.

[2] Confirmation with repeat bone marrow biopsy not needed.

[3] Presence/absence of clonal cells is based upon the kappa/lambda ratio. An abnormal kappa/lambda ratio by immunohistochemistry and/or immunofluorescence requires a minimum of 100 plasma cells for analysis. An abnormal ratio reflecting presence of an abnormal clone is kappa/lambda of > 4:1 or < 1:2.

[4] All relapse categories require two consecutive assessments made at any time before classification as relapse or disease progression and/or the institution of any new therapy. In the IMWG criteria, CR patients must also meet the criteria for progressive disease shown here to be classified as progressive disease for the purposes of calculating time to progression and progression-free survival. The definitions of relapse, clinical relapse and relapse from CR are not to be used in calculation of time to progression or progression-free survival.

[5] For progressive disease, serum M-component increases of ≥1 gm/dL are sufficient to define relapse if starting M-component is ≥5 g/dL.

[6] Relapse from CR has the 5% cut-off versus 10% for other categories of relapse.

[7] For purposes of calculating time to progression and progression-free survival, CR patients should also be evaluated using criteria listed above for progressive disease.

10.2 FLOW CHART PHARMACOKINETIC ASSESSMENTS

BLOOD SAMPLING TIMES FOR PHARMACOKINETICS

Course	Week	Visit	Day	Time point after dose (h:min)	CRF time	Sample number	BI 836909 analysis in serum	ADA** analysis
1	1	1	1	Before start of infusion	0:00	S1-A	X	X
					1:00	S2-A	X	
					2:00	S3-A	X	
					4:00	S4-A	X	
					8:00	S5-A	X	
			2		24:00	S6-A	X	
			3		48:00	S7-A	X	
1	1	2	8	168h after start of infusion	168:00	S8-A	X	
1	2	3	15	336h after start of infusion	336:00	S9-A	X	X
1	3	4	22	504 h after start of infusion	504:00	S10-A	X	
1	4	5	29	Before end of infusion in cycle 1*	**671:50**	S11-A	X	
					673:00	S12-A	X	
					674:00	S13-A	X	
					676:00	S14-A	X	
					680:00	S15-A	X	
			30		**696:00**	S16-A	X	X
2	1	1	1	Before start of infusion	0:00	S17-A		X
2	2	3	15	14 days after start of infusion	336:00	S18-A	X	X

Course	Week	Visit	Day	Time point after dose (h:min)	CRF time	Sample number	BI 836909 analysis in serum	ADA** analysis
2	3	4	22	22 days after start of infusion	504:00	S19-A	X	
2	4	5	29	Before stop of infusion	**671:50***	S20-A	X	X
3	1	1	1	Before start of infusion	0:00	S21-A		X
3	2	3	15	14 days after start of infusion	336:00	S22-A	X	X
3	3	4	22	22 days after start of infusion	504	S23-A	X	
3	4	5	29	Before stop of infusion	672:00*	S24-A	X	X
4	1	1	1	Before start of infusion	0:00	S25-A		X
4	2	3	15	14 days after start of infusion	336:00	S26-A	X	X
4	3	4	22	22 days after start of infusion	504:00	S27-A	X	
4	4	5	29	Before stop of infusion	**671:50***	S28-A	X	X
5	1	1	1	Before start of infusion	0:00	S29-A		X
5	2	3	15	14 days after start of infusion	336:00	S30-A	X	X
5	3	4	22	22 days after start of infusion	504:00	S31-A	X	
5	4	5	29	Before stop of infusion	**671:50***	S32-A	X	X

*10 minutes before stop of infusion
** Anti Drug Antibodies

10.3 DEFINITIONS OF LABORATORY AND CLINICAL TUMOR LYSIS SYNDROM

Metabolic Abnormality	Criteria for Classification of Laboratory Tumor Lysis Syndrome	Criteria for Classification of Clinical Tumor Lysis Syndrome
Hyperuricemia	Uric acid >8.0 mg/dl (475.8 μmol/liter) in adults or above the upper limit of the normal range for age in children	
Hyperphosphatemia	Phosphorus >4.5 mg/dl (1.5 mmol/liter) in adults or >6.5 mg/dl (2.1 mmol/liter) in children	
Hyperkalemia	Potassium >6.0 mmol/liter	Cardiac dysrhythmia or sudden death probably or definitely caused by hyperkalemia
Hypocalcemia	Corrected calcium <7.0 mg/dl (1.75 mmol/liter) or ionized calcium <1.12 (0.3 mmol/liter) [†]	Cardiac dysrhythmia, sudden death, seizure, neuromuscular irritability (tetany, paresthesias, muscle twitching, carpopedal spasm, Trousseau's sign, Chvostek's sign, laryngospasm, or bronchospasm), hypotension, or heart failure probably or definitely caused by hypocalcemia
Acute kidney injury[†]	Not applicable	Increase in the serum creatinine level of 0.3 mg/dl (26.5 μmol/liter) (or a single value >1.5 times the upper limit of the age-appropriate normal range if no baseline creatinine measurement is available) or the presence of oliguria, defined as an average urine output of <0.5 ml/kg/hr for 6 hr

[*] In laboratory tumor lysis syndrome, two or more metabolic abnormalities must be present during the same 24-hour period within 3 days before the start of therapy or up to 7 days afterward. Clinical tumor lysis syndrome requires the presence of laboratory tumor lysis syndrome plus an increased creatinine level, seizures, cardiac dysrhythmia, or death.

[†] The corrected calcium level in milligrams per deciliter = measured calcium level in milligrams per deciliter + 0.8 × (4 − albumin in grams per deciliter).

[‡] Acute kidney injury is defined as an increase in the creatinine level of at least 0.3 mg per deciliter (26.5 μmol per liter) or a period of oliguria lasting 6 hours or more. By definition, if acute kidney injury is present, the patient has clinical tumor lysis syndrome.

10.4 CREATININE CLEARANCE ESTIMATED BY THE COCKCROFTGAULT (C-G) EQUATION

Estimated creatinine clearance rate (eCCR) using Cockcroft-Gault formula.

$$eCCR = \frac{(140 - age) \times weight \times FS}{Serum\ Creatinine \times 72}$$

Units: GFR [ml/min], age [years], weight [kg], estimated creatinine clearance rate [mg/dl],

FS is a correction Factor for Sex: in males FS = 1, in females FS = 0.85

Please refer to the ISF for local country formula in case you don't use the same units (kg, ml/min or mg/dl).

10.5 EASTERN COOPERATIVE ONCOLOGY GROUP (ECOG) PERFORMANCE SCORE

Grade	Description
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

Reference: R01-0787

10.6 CLINICAL EVALUATION OF LIVER INJURY

10.6.1 Introduction

Alterations of liver laboratory parameters, as described in Section 5.2.2.1 (Protocol-specified adverse event of special interest), are to be further evaluated using the following procedures:

10.6.2 Procedures

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

In addition,

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

and report these via the CRF.

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

Serology
Hepatitis A (Anti-IgM, Anti-IgG), Hepatitis B (HbsAg, Anti-HBs, DNA), Hepatitis C (Anti-HCV, RNA if Anti-HCV positive), Hepatitis D (Anti-IgM, Anti-IgG), Hepatitis E (Anti-HEV, Anti-HEV IgM, RNA if Anti-HEV IgM positive), Anti-Smooth Muscle antibody (titer), Anti-nuclear antibody (titer), Anti-LKM (liver-kidney microsomes) antibody, Anti-mitochondrial antibody
<project dependent:> Epstein Barr Virus (VCA IgG, VCA IgM), cytomegalovirus (IgG, IgM), herpes simplex virus (IgG, IgM), varicella (IgG, IgM), parvovirus (IgG, IgM), toxoplasmosis (IgG, IgM)>

Hormones, tumormarker
TSH

Haematology
Thrombocytes, eosinophils

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

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

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

Number of global amendment		1
Date of CTP revision		21 May 2015
EudraCT number		2014-004896-22
BI Trial number		1351.1
BI Investigational Product(s)		BI 863909
Title of protocol		An open label, phase I, dose escalation study to characterize the safety, tolerability, pharmacokinetics, and pharmacodynamics of intravenous and subcutaneous doses of BI 836909 in relapsed and/or refractory multiple myeloma patients
To be implemented only after approval of the IRB/IEC/Competent Authorities		X
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		☐
Can be implemented without IRB/IEC/ Competent Authority approval as changes involve logistical or administrative aspects only		☐
Sections to be changed		1. Synopsis Methodology and number of patients 2. Footnote 12 of Flow charts for part A and part B 3. Section 3.1 4. Section 3.2 5. Section 3.3.3 6. Section 4.1.4 7. Section 5.2.4.1 8. Section 5.2.4.2 9. Section 7.4
Description of change		**1.Synopsis Methodology and number of patients** **….** For the dose levels of **0.2 to 1.6 µg/day** single

Number of global amendment		1
		patient cohorts are entered. The following dose cohorts will be tested within the above-mentioned dose range: • **0.2, 0.4, 0.8 and 1.6 µg/day** • The DLT observation period for the single patient cohorts will be 2 weeks. If a patient has been on treatment in one of the above-mentioned dose cohorts for 2 weeks without DLT or other relevant safety findings the first patient of the next higher dose cohort will **be entered if agreed on by the safety committee. If a patient has reached DLT, then the safety committee recommends 3 + 3 cohorts. Patients may not proceed to the next higher dose level before completion of 6 patients.** **One intra-patient dose escalation is allowed within the single patient dose cohorts if the initial dose is tolerated and no DLT occurs during 1st cycle. In case of DLT additional patients will be entered into this cohort following a 3 + 3 design.** **For the dose levels ≥ 3.2 µg/day 3-6 patients will be treated per dose level and observed for 4 weeks during the first cycle before decision for dose escalation to the next dose cohort is made.** The following dose cohorts will be tested within the above-mentioned dose range: • **3.2, 6.5, 13, 25, 50 and 100 µg/day** and higher if MTD has not yet been established. Additional and intermediate dose cohorts will be entered if determined by the safety committee. Increments to the next higher dose **will not exceed 2-fold increases.** The DLT observation period will be extended to 4 weeks for all future cohorts before decision for dose escalation within the next dose cohort is made: • Per dose level 1 patient will be enrolled and treated for 1 week before all remaining patients for this cohort can be entered. **Additional patients should not start treatment before the previous patient has been treated for 48 hours in order to monitor initial transient toxicities**

Number of global amendment		1

due to cytokine release syndrome.

Number of patients:
….
Part A: Number of patients will depend on the number of dose levels to be tested before MTD determination or determination of the recommended dose. Based on preclinical data, it is expected that > 5 dose levels in addition to the **4 single-patient doses** will be tested. Around 20 to 40 patients will be treated during the dose escalation phase.
….

2.Footnote 12 for part A and part B

at screening and at each visit and at EOT; **during hospitalization in cycle 1 safety lab should be done before start of treatment on day 1 and repeated in the evening of day 1 as well as in the morning of days 2 and 3; in cycle 2 safety lab should be done before start of treatment on day 1 and in the morning of day 2.**
On day 29 of cycle 1 blood draw for safety lab should be done before the end of the infusion.

3.Section 3.1
Table 3.1.1

Dose level	Dose µg/d	Patients per cohort	Approximate increment to next dose
1	0.2	1	2x
2	**0.4**	**1**	**2x**
3	**0.8**	**1**	**2x**
4	**1.6**	**1**	**2x**
5	**3.2**	**3 (+3)**	**2x**
6	6.5	3 (+3)	2x
7	13	3 (+3)	2x
8	25	3 (+3)	2x
9	50	3 (+3)	2x
10	100…..	3 (+3)	2x

…..
For the dose levels 0.20 to 1.6 µg/day single patient cohorts are entered since no clinical

Number of global amendment		1
		activity is expected at these doses. If a patient has been on treatment in one of the above-mentioned dose cohorts for 2 weeks without DLT the first patient of the next higher dose cohort will be entered **if agreed on by the safety committee. If a patient has reached DLT, then the safety committee recommends the switch to a 3 + 3 cohort for the dose level at which the DLT occurred. Patients may not proceed to the next higher dose level before completion of 6 patients.** One intra-patient dose escalation is allowed within the single patient dose cohorts if the initial dose is tolerated well and no DLT occurs during 1st cycle. In case of DLT additional patients will be entered into this cohort following a 3+3 design. **For the dose levels ≥ 3.2 µg/day 3-6 patients will be treated per dose level and observed for 4 weeks during the first cycle before decision for dose escalation to the next dose cohort is made.** Per dose level 1 patient will be enrolled and treated for 1 week, than further patients will be enrolled. Patients should be entered sequentially. **Additional patients should not start treatment before the previous patient has been treated for 48 hours in order to monitor initial transient toxicities due to cytokine release syndrome.** **….** **4.Section 3.2** **…** Part A: **The following dose cohorts will be tested as single patient cohorts: 0.2, 0.4, 0.8 and 1.6 µg/day.** If a patient has been on treatment in one of the above-mentioned dose cohorts for 2 weeks without DLT the first patient of the next higher dose cohort will be entered. In case that a DLT has been observed in the single patient cohorts 5 additional patients will be entered on this actual dose level.

Number of global amendment		1
		Intra-patient dose escalation is allowed once to the next higher dose within the first 4 above-mentioned dose cohorts up to 1.6µg/d. In case that no DLTs have been observed during the first cycle within the single patient dose cohorts the patient can be treated at the next higher dose level in subsequent cycles. Only one intra-patient dose escalation step is allowed. This approach of intra-patient dose escalation reduces the number of patients treated at pharmacologically inactive doses to a minimum and increases the likelihood of treatment benefit for patients entered at low dose. Prior to treatment of a patient at the next higher cohort a safety committee quorum needs to be obtained to oversee the observation period of this dose level to make sure that no additional patients must be entered at that dose level and that a patient can be entered at the next higher dose level. If the safety committee recommends treatment of additional patients at the lower dose level 2 additional patients must be entered at the lower dose level first. The **3 + 3 design** will then be followed. For the dose levels **≥ 3.2 µg/day** 3-6 patients (3+3 design) will be treated per dose level and observed for 4 weeks before decision for dose escalation to the next dose cohort is made. **...** **5.Section 3.3.3** was changed to **…** **5. Last treatment with a therapeutic antibody less than 6 weeks prior to visit 1** **6. Prior allogeneic stem cell transplantation or solid organ transplantation** **7. Autologous stem cell transplantation < than 90 days at time of treatment start** **…..** was added **22. Patients with a known hypersensitivity to any component of the study drug** **23. Patients with other malignancies within 5 years at time of screening (except basal cell or squamous cell carcinoma of the skin or**

Number of global amendment		1

carcinoma in situ treated with curative therapy)

6.Section 4.1.4; table 4.1.4.1

Dose µg/day	Patients per cohort	Observation time of ongoing patients before enrolment/entry of next patient/cohort
0.2	1	2 weeks, then enrol next cohort
0.4	**1**	**As in previous cohort**
0.8	**1**	**As in previous cohort**
1.6	**1**	**As in previous cohort**
3.2	**3 (+3)**	**1 week for first patient, then enter next two patients; additional patients should not start treatment before the previous patient has been treated for 48 hours in order to monitor initial transient toxicities due to cytokine release syndrome. All 3 must have completed 4 weeks before enrolling next cohort**
6.5	3 (+3)	As in previous cohort
13	3 (+3)	As in previous cohort
25	3 (+3)	As in previous cohort
50	3 (+3)	As in previous cohort
100….	3 (+3)	As in previous cohort

7.Section 5.2.4.1

…..

Haematology Haemoglobin, red blood cell count (RBC), white blood cell count (WBC) with differential, platelets (PLT)

Biochemistry Glucose, sodium, potassium, total calcium, inorganic phosphate, creatinine, aspartate amino transferase (AST), alanine amino transferase (ALT), alkaline phosphatase (AP),

Number of global amendment		1
		lactate dehydrogenase (LDH), total bilirubin (if elevated provide direct bilirubin), urea, total protein, albumin, uric acid, **Ferritin (at baseline of cycle 1 only).** Serum immunoglobulin levels (IgG, IgM, IgA) at baseline, **day 15 and day 29 of each cycle only** Coagulation Activated partial thromboplastin time (aPTT), prothrombin time (PT)/international normalised ratio (INR),), **fibrinogen and D-Dimers in cycle 1 and 2; thereafter on day 1 of each of the following cycles only.** **…..** **8.Section 5.2.4.2** Tumour lysis syndrome (TLS) is characterized by metabolic derangements caused by the massive and abrupt release of cellular components into the blood after rapid lysis of malignant cells. The release of the intracellular metabolites can overwhelm normal homeostatic mechanisms, potentially leading to hyperuricemia, hyperkalemia, hyperphosphatemia, hypocalcemia, and uremia. This can result in impaired renal function, and in some cases, in acute renal failure and even death (R10-4517). To allow for early treatment in case TLS develops, vigilant monitoring is **recommended if clinically indicated. During the first 48 hours after the start of the first infusion/injection of BI 836909 in course 1, and during the first 24 hours after the start of the first infusion/injection in course 2, the below listed laboratory parameters need to be determined to screen for evidence of a tumour lysis syndrome monitored frequently, i.e. every 4-8 hours between the time points at which a complete safety laboratory has to be performed. The actual date and time of the blood samples should be recorded in the eCRF.** Haematology haemoglobin, haematocrit, red blood cell count (RBC), white blood cell count (WBC),+ differential, platelets (PLT)

Number of global amendment		1
		Biochemistry uric acid, potassium, calcium, inorganic phosphate, lactate dehydrogenase (LDH), creatinine, urea, ferritin. Coagulation Activated partial thromboplastin time (aPTT), prothrombin time (PT)/international normalised ratio (INR), **fibrinogen, D-dimer.** **9.Section 7.4** **…..** **1.** Preliminary analysis after the **four first cohorts from part A (for a minimum of 4 patients)** to check the PK/PD behaviour of BI 836909. In case BI 836909 shows undue difference from predicted exposure, if needed, the dosing escalation scheme of BI 836909 might be adapted. …..
Rationale for change		Changes 1 to 6 and 9 have been requested by the German Authority during the approval process Changes7 and 8 was done for clarification only.

Number of global amendment		2
Date of CTP revision		28 December 2016
EudraCT number		2014-004896-22
BI Trial number		1351.1
BI Investigational Product(s)		BI 863909
Title of protocol		An open label, phase I, dose escalation study to characterize the safety, tolerability, pharmacokinetics, and pharmacodynamics of intravenous doses of BI 836909 in relapsed and/or refractory multiple myeloma patients
To be implemented only after approval of the IRB/IEC/Competent Authorities		X
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		☐
Can be implemented without IRB/IEC/ Competent Authority approval as changes involve logistical or administrative aspects only		☐
Sections to be changed		1. PROTOCOL TITLE 2. CLINICAL TRIAL PROTOCOL SYNOPSIS 3. FLOW CHARTS and FOOTNOTES 4. 2.2 TRIAL OBJECTIVES 5. 3.1 OVERALL TRIAL DESIGN AND PLAN 6. 3.2 DISCUSSION OF TRIAL DESIGN, INCLUDING THE CHOICE OF CONTROL GROUP(S) 7. 3.3 SELECTION OF TRIAL POPULATION 8. 4. TREATMENTS 9. 5. VARIABLES AND THEIR ASSESSMENT 10. 6. INVESTIGATIONAL PLAN

Number of global amendment		2
		11. 7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE 12. 10.2 FLOW CHART PHARMACOKINETIC ASSESSMENTS
		All part B, expansion cohorts as well as follow up visits beyond the REP visit related items have been deleted in all corresponding parts of the protocol. Minor changes have been made for consistency between the different chapters of the protocol. Additional cohorts have been included because no DLTs occurred up to now and more cohorts to detect MTD may be needed. The corresponding parts of the protocol have been updated accordingly. Corresponding sections were changed to: **1.PROTOCOL TITLE** An open label, phase I, dose escalation study to characterize the safety, tolerability, pharmacokinetics, and pharmacodynamics of intravenous doses of BI 836909 in relapsed and/or refractory multiple myeloma patients **2. CLINICAL TRIAL PROTOCOL SYNOPSIS** **Objective(s):** **Primary objective:** To determine the maximum tolerated dose (MTD) as well as the dose limiting toxicities (DLT) of a 6-week regimen of BI 836909 given as continuous intravenous infusion in patients with relapsed and/or refractory multiple myeloma. Secondary objectives: Recommended dose for further development To provide preliminary findings on the safety profile and assess pharmacokinetic profile of BI 836909 To assess pharmacodynamic and anti-tumoral activity of BI 836909 To evaluate immunogenicity of BI 836909 **Methodology:** Phase I dose escalation trial of BI 836909 given as intravenous infusion. Starting dose: 0.20 µg/day A 6-week regimen will be tested (4 weeks of continuous intravenous administration of BI 836909 followed by a 2 weeks off-period). […]
Description of change		For the dose levels ≥ 3.2 µg/day 3-6 patients will be treated per dose level and observed for 4 weeks during the first cycle before decision for dose escalation to the next dose cohort is made. The following dose cohorts will be tested within the above-mentioned dose range:

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		• 3.2, 6.5, 13, 25, 50, 100, **200 and 400** µg/day and higher **doses** if MTD has not yet been established. Additional and intermediate dose cohorts will be entered if determined by the safety committee. • […] • Once the MTD of BI 836909 is determined **up to 6 additional patients** will be treated at the MTD or the recommended dose **for confirmation of safety.** **Number of patients total entered:** **Up to 50 patients depending on dose level reached** **Dose escalation:** Number of patients will depend on the number of dose levels to be tested before MTD determination or determination of the recommended dose. Based on preclinical data, it is expected that > 5 dose levels in addition to the 4 single-patient doses will be tested. **Up to 50 patients will be treated during the dose escalation phase. Up to 6 additional patients will be treated with MTD or recommended dose.** **Test product(s):** BI 836909 in vials for continuous intra-venous infusion. **Criteria for pharmacokinetics:** • Concentration at steady state after i.v. infusion ($Css_)$). **Statistical methods:** Patients with DLT, objective response rate, MRD will be explored and summarized by descriptive statistics. Kaplan-Meier methods will be used for time to event endpoints. The pharmacokinetic parameters Css, [redacted] **will be descriptively explored.** **3. FLOW CHARTS and FOOTNOTES** **FLOW CHART: BI 836909 CONTINUOUS ITRAVENOUS INFUSION** "Triplicate ECG for QTc assessment" as well as footnote 16 was deleted because expansion cohorts have been cancelled. Footnote 3:Follow up visit should be performed 30 days after the EOT (REP visit). Follow

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	up visit after EOT: report all AEs, SAEs, AESIs regardless of relatedness. This includes all deaths unless due to underlying disease (Section 6.2.5.2) Please note: Death should always be reported as SAE in this trial unless due to underlying disease. Footnote 8: within 14 days before day 1 cycle 1 or on day 1 cycle 1 before start of treatment, when M protein/ Free kappa/lambda light chain (FLC) becomes undetectable during treatment, on day 29 of cycle 3 and at EOT. Karyotyping: recent analysis will be accepted for screening before start of treatment if performed within 3 months prior to start of study medication and in case that no therapy has been given between assessment of karyotyping and study medication; otherwise, a baseline karyotype should be performed at screening; subsequent karyotyping could also be performed in subsequent marrow samples (tests to be done locally). Footnote 9: MRD (minimal residual disease assessment): when M protein/FLC becomes undetectable during treatment; day 29 of cycle 3 and EOT (tests to be done centrally). Footnote 10: Optional collection and bio-banking of a baseline bone marrow sample and a bone marrow sample on treatment when a complete response is reached. Footnote 13: Infusion bag will have to be exchanged during continuous infusion of BI 836909 approximately every 4 days; patients should either come to the clinic or bag change will be done by a home care service. Footnote 14: Clinical disease assessment must be performed: At screening, at start of each cycle as well as at EOT. […] Old footnote 16 was deleted Former Footnote 17 was changed to 16: Orienting neurological examination should be performed at screening as well as at EOT and daily during hospitalization required by the protocol. [redacted] **4. 2.2 TRIAL OBJECTIVES** The primary objective of this trial is to determine the maximum tolerated dose (MTD) of BI 836909 administered by continuous i.v. infusion in patients with relapsed and/or refractory multiple myeloma. If the MTD is not reached based on safety findings, a recommended dose for further development will be determined. This will depend on the safety data, pharmacokinetic/ pharmacodynamics data and potentially preliminary efficacy data. Secondary objectives are to document the safety and tolerability of BI 836909, to perform pharmacokinetic and pharmacodynamic analyses and to evaluate relevant biological effects in terms of

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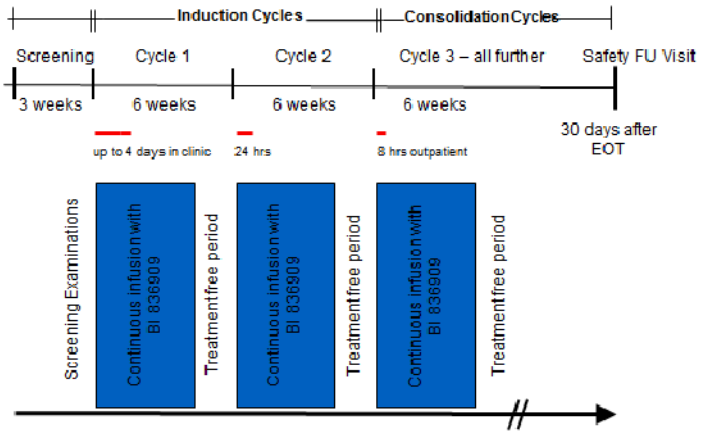
		parameters of efficacy. The starting dose is based on a Pharmacologically Active Dose (PAD) estimated from the EC50 of the most sensitive in vitro cytotoxicity assay and pharmacokinetic modelling. Assuming an average body surface area (BSA) of 1.7 m^2 the proposed starting dose of 0.12 µg/ m^2/day translates into a starting dose of 0.20 µg/d given by continuous intravenous injection. In the clinical trial the administered doses will not be BSA-adapted. The proposed starting dose is 4500 fold lower than the HNSTD (540 µg/m^2/day) and 1500 fold lower than the dose (180 µg/m^2/day) that did not result in cytokine release in the 4-week toxicology study in cynomolgus monkeys. **5. 3.1 OVERALL TRIAL DESIGN AND PLAN** The trial is an open-label, non-randomized phase I dose-escalation trial with modified 3+3 design to evaluate the tolerability and safety of BI 836909 given as continuous intravenous infusion as well as to determine the MTD or to establish the recommended dose for further development of BI 836909 administered as continuous intravenous infusion. MTD is defined as the highest dose of the dose level tested where ≤ 1 patient out of 6 develops dose limiting toxicity. If MTD cannot be determined based on safety findings, a recommended dose for further development will be determined based on pharmacokinetic and pharmacodynamics data. Overall study design:  ormed 30 Last patient out is defined as the REP visit completed by the last patient. This will be the end of the trial. **For patients who have entered the trial before the approval of the second revision last visit would be defined as the last follow up visit after the approval date.** The following dose levels will be tested:

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		Table 3.1.1 Dose escalation scheme

Dose level	Dose µg/d	Patients per cohort	Approximate increment to next dose
1	0.2	1	2x
2	**0.4**	**1**	**2x**
3	**0.8**	**1**	**2x**
4	**1.6**	**1**	**2x**
5	**3.2**	**3 (+3)**	**2x**
6	6.5	3 (+3)	2x
7	13	3 (+3)	2x
8	25	3 (+3)	2x
9	50	3 (+3)	2x
10	100	3 (+3)	2x
11	200	3 (+3)	2x
12	400*	3 (+3)	2x

*further doses will be tested in case that MTD could not be confirmed at a dose level of 400 µg/day. Intermediate dose cohorts will be entered if determined by the safety committee, for example, in case that the dose cohort 400 µg/day exceeds MTD (> 1 patient out of 6 with DLT) and no DLT is observed on 200 µg/day consider 300 µg/day.

[…]

In the dose escalation part the trial safety committee (for details see Section 3.1.1) can determine to enter additional and intermediate dose cohorts at any time e.g. **if DLTs or other safety events, pharmacodynamics activity or antitumor efficacy occur.** The safety committee will also determine to switch from single patient cohorts to a 3+3 design at doses below 3.2µg/d if DLTs, pharmacodynamic activity or antitumor efficacy occur.
PK/PD data might be taken into account for dose escalation decisions if available.
Patients should be entered sequentially. Treatment initiation of more than 1 new patient per day will not be permitted during the dose escalation phase.

Once the MTD or the recommended dose for better characterization of safety and early evaluation of anti-tumour activity is determined up to **6 additional** patients will be treated with MTD or the recommended dose. […]

3.1.1 Administrative structure of the trial
[…]

Number of global amendment		2
		A safety committee (SC) of the investigators in cooperation with the responsible trial monitor and the medical project leader of the sponsor **as well as medical representatives from Amgen** will be implemented to analyse ongoing safety information and decide on further steps in dose finding. Prior to escalating the dose to the next higher dose cohort there will be a safety teleconference or meeting between trial investigators and the medical project leader of the sponsor to discuss any findings in the ongoing and already recruited cohorts, this means that all available clinical and safety data including repeated cycles of prior dose cohorts will be taken into consideration for assessments and decision making. Participation of the coordinating investigator or [redacted] deputy is a mandatory requirement for this committee to establish a quorum. After the defined observation period of each cohort this safety committee will discuss the need to enter additional patients or dose cohorts or release the next dose cohort and dose increment as per protocol. The same is true for the decision to switch from single patient cohorts to the 3+3 design**. Step dosing may be implemented based on cytokine release syndrome qualifying for DLT following the following guidance:** **- Restart with previous dose level for 4 days (one bag) and then escalate to current dose level until the end of the cycle.** The composition of the SC will be documented in BIRDS. The tasks and responsibilities will be agreed in contracts between the SC members and the Sponsor. SC will decide on the switch from single patient cohorts to the 3+3 design independently from defined dose cohorts based on clinical activity (antitumor response) and/or clinically relevant safety or pharmacodynamics findings. […] Clinical disease status will be assessed at screening and at the start of each new cycle (e.g, before cycle 2, 3, 4 and 5 etc.) as well as at EOT with physical examination and clinical assessment of the multiple myeloma. MRI scans in this trial will be performed prior to treatment, at screening and every other cycle at day 1, cycle 3, day 1, cycle 5, day1, cycle 7, day 1 and/or at time of progression or start of further anticancer therapy. Results from routine assessments (MRI) for multiple myeloma are accepted for screening if performed no later than 28 days before start of treatment. Bone marrow examination, MRI scan and additional CT scans will be performed at time points outlined in the Flow chart. Results of MRI scans, additional CT scans, optional PET scan or bone marrow

Number of global amendment		2
		examination performed during the conduct of the trial should be reported in the eCRF. After the EOT visit which must occur immediately at time of permanent discontinuation of study medication but no later than 7 days after last drug administration, the patient will have a follow up visit within 30 days after EOT (REP visit) for assessment of AEs /SAEs, **patient status and further anti-cancer treatment.** **6. 3.2 DISCUSSION OF TRIAL DESIGN, INCLUDING THE CHOICE OF CONTROL GROUP(S)** The primary objective of this trial is to determine the MTD. The most important secondary objective is to assess the safety of BI 836909 given as continuous intravenous infusion. For the first 4 doses up to and including 1.6µg/d dose cohorts single patient cohorts have been chosen since no clinical benefit is expected at these low doses. For the remaining dose cohorts a standard 3+3 design has been chosen as this is an established standard approach in phase I studies in oncology: The following dose cohorts will be tested as single patient cohorts: 0.2, 0.4, 0.8 and 1.6 µg/day. […] **7. 3.3 SELECTION OF TRIAL POPULATION** A total number of approximately **50 patients** is expected to be entered into the trial. The number of patients depends on the number of dose escalation steps. A total of 5 sites will participate; this means that a total number of approximately 6 to 10 patients should be entered per site. […] **8. 4. TREATMENTS** 4.1.1.1 Description of portable pump for continuous intravenous infusion of BI 836909 BodyGuardTM 323 Multi-Therapy Ambulatory Infusion Pump (Ceasarea Medical Electronics GmbH; 72805 Lichtenstein; Germany) will be used in this trial for the 4 –week continuous rate controlled intravenous infusion. Site personnel will be trained on the use of the pump by the vendor. Detailed instructions will be available in the ISF. […] **4.1.4 Drug assignment and administration of doses for each patient** […]

<table>
<tr><td>Number of global amendment</td><td></td><td>2</td></tr>
<tr><td></td><td></td><td>Table 4.1.4.1: Dose escalation scheme
<table>
<tr><th>Dose µg/day</th><th>Patients per cohort</th><th>Observation time of ongoing patients before enrolment/entry of next patient/cohort</th></tr>
<tr><td>0.2</td><td>1</td><td>2 weeks, then enrol next cohort</td></tr>
<tr><td>0.4</td><td>1</td><td>As in previous cohort</td></tr>
<tr><td>0.8</td><td>1</td><td>As in previous cohort</td></tr>
<tr><td>1.6</td><td>1</td><td>As in previous cohort</td></tr>
<tr><td>3.2</td><td>3 (+3)</td><td>1 week for first patient, then enter next two patients; additional patients should not start treatment before the previous patient has been treated for 48 hours in order to monitor initial transient toxicities due to cytokine release syndrome. All 3 must have completed 4 weeks before enrolling next cohort</td></tr>
<tr><td>6.5</td><td>3 (+3)</td><td>As in previous cohort</td></tr>
<tr><td>13</td><td>3 (+3)</td><td>As in previous cohort</td></tr>
<tr><td>25</td><td>3 (+3)</td><td>As in previous cohort</td></tr>
<tr><td>50</td><td>3 (+3)</td><td>As in previous cohort</td></tr>
<tr><td>100</td><td>3 (+3)</td><td>As in previous cohort</td></tr>
<tr><td>200</td><td>3 (+3)</td><td>As in previous cohort</td></tr>
<tr><td>400….*</td><td>3 (+3)</td><td>As in previous cohort</td></tr>
</table>
*further and intermediate dose cohorts may be added […]

4.1.4.1.2 Monitoring for infusion-related reactions and cytokine release syndromes
Close monitoring of the patient during and after the infusion of BI 836909 is required for evaluation of infusion-related risks. The measures of monitoring include:
• Hospitalization of patients with access to intensive care days 1–4 of cycle 1 and in case of intra-patient dose escalation within the first cycle of dose escalation.
• Hospitalization of patients with access to intensive care on day 1 of cycle 2 (for a total of 24 hours) and in case of intra-patient dose escalation within the first cycle of dose escalation.
• Frequent measurements and documentation of blood pressure and heart rate (see Section 5.2.6.1).
• In courses 2 and higher the patients are required to be hospitalized under close surveillance with access to intensive care days 1-3 again in case of infusion related events in earlier treatment courses. If no infusion related events occurred in earlier treatment courses an observation</td></tr>
</table>

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		period of 4 - 8 hours in continuous infusion of […] the hospital will suffice at start of each BI 836909 in courses 3 and higher. 4.1.4.3 Dose reductions and dose delays Related SAEs/AEs of ≥ grade 2 or non-drug related SAEs/AEs of ≥ grade 2 deemed intolerable by the patient or the treating physician and not responding to appropriate medical management will result in a pause until resolution to baseline or grade 1. A pause of a maximum duration of 14 days and a dose reduction to the next lower dose level is allowed if clinically indicated. Only one dose de-escalation step is allowed. DLT events in any cycle, cases meeting the pre-defined hepatic injury criteria (ref. 5.2.2.1) and infusion related reactions or cytokine release syndromes ≥ grade 3 will lead to permanent discontinuation in the dose escalation phases. After recovery to baseline or grade 1 continuation of the cycle at the next lower dose tier is allowed. Only one dose de-escalation step is allowed. CNS events ≥ grade 2 irrespective of relatedness that have not resolved to baseline or grade 1 within one week despite treatment interruption will lead to permanent discontinuation in the dose escalation phase. CNS events that have resolved to baseline or grade 1 within one week can be continued at the next lower dose level. Only one dose de-escalation step is allowed. In case of dose reductions all future courses will also be at the reduced dose level. […] 4.2.2.2 Restrictions on diet and life style No restrictions apply with regards to diet or life style unless based on restrictions due to the portable pump used within the study. **4.3 TREATMENT COMPLIANCE** BI 836909 will be administered as a continuous intravenous infusion (c.i.v.) via infusion pump over a period of 4 weeks. Infusion bags will have to be exchanged **approximately** every 4 days either at site or by a trained care provider. Persons involved in exchange of the bag will document compliance. Compliance may also be verified by pharmacokinetic assessments. Any discrepancies will be explained in the CRF by the investigator or his/her deputy. **9. 5. VARIABLES AND THEIR ASSESSMENT** […] **5.1.1 Endpoint(s) of efficacy**

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		The efficacy endpoints will be assessed at the time points specified in the flowcharts. Efficacy endpoints will be secondary or further endpoints in the trial and will be evaluated according to the response criteria of the International Myeloma Working Group (IMWG, 2006; Appendix 10.1). Secondary endpoints of efficacy are: • Objective response rate (percentage of patients with stringent complete response (sCR), complete response (CR), partial response (PR) and very good partial response (VGPR)) • Duration of response (DOR) • Minimal residual disease (MRD) response rate • Duration of MRD response. • Progression-free survival (PFS) [redacted] **5.1.2 Assessment of Efficacy** 5.1.2.1 Laboratory parameters The following laboratory parameters must be evaluated to assess response of treatment: • Multiple myeloma (MM) cells in bone marrow Analysis of myeloma cells in bone marrow will be conducted using a diagnostic FACS panel including markers for CD45, CD38, CD19, CD138, CD56 and kappa/lambda chains. Scheduled sampling time points will be as follows (see flow charts): within 14 days before day 1 cycle 1 or in cycle 1, day 1 before start of treatment, when M protein/FLC becomes undetectable during treatment, on day 29 of cycle 3 and at EOT. **The analysis will be performed centrally. […]** **5.1.2.8 Overall survival (OS) was deleted** **5.1.2.9 Supportive care requirement: was deleted** [redacted] **5.2.1 Endpoint(s) of safety**

Number of global amendment		2
		The primary objective is to assess the safety of the drug in humans and to determine the MTD of BI 836909. Primary Endpoints are the following: • Maximum tolerated dose (MTD) of BI 836909 MTD is defined as the highest dose level tested where ≤ 1 patient out of 6 develop dose limiting toxicity. If MTD cannot be determined based on safety findings, a recommended dose for further development will be determined based on pharmacokinetic and pharmacodynamic data. **The MTD will be defined on the basis of DLT observed during cycle 1**. However, for those patients who receive more than one cycle of BI 836909, all adverse events corresponding to the definition of DLT (Section 5.2.1.1) will be considered for the purpose of confirming the MTD and for the selection of the recommended dose for further development. In regular intervals, all available safety data including adverse events qualifying for DLT will be reviewed by the safety committee. • Number of patients with dose limiting toxicities The safety of BI 836909 will be assessed by a descriptive analysis of incidence and intensity of adverse events graded according to CTCAE (version 4.03), the incidence dose limiting toxicity (DLT), laboratory data and results of physical examination. Further endpoint of safety: • Immunogenicity of BI 836909 (frequency of patients developing anti-drug antibodies) The safety data will be reviewed in regular intervals as well as ad hoc if needed. The safety endpoints will be assessed in a descriptive way without confirmatory analyses. 5.2.3. Adverse event collection and reporting […] Examples of exempted events of PD are: • Progression of underlying malignancy (Progressive disease PD): if PD is clearly consistent with the suspected progression of the underlying malignancy as defined by the respective response criteria. • Hospitalization/Procedures due solely to the progression of underlying malignancy (PD)

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	• Clinical symptoms and/or signs of progression (with or without confirmation by objective criteria e.g. imaging, clinical measurement): if the symptom can exclusively be determined to be due to the progression of the underlying malignancy and does meet the expected pattern of progression for the disease under study. Please note, when there is evidence suggesting a causal relationship between the drug and the progression of the underlying disease, the event must be reported as (S)AE. Exempted events are monitored at appropriate intervals by an independent committee such as the Safety Monitoring Committee. […] 5.2.5 Electrocardiogram A 12-lead resting electrocardiogram (ECG) will be performed in all patients at the screening visit and at the beginning of each cycle (except for cycle 1) and at the EOT visit. The ECG will be assessed for pathological results (to be recorded as either baseline condition, concomitant disease or AE) by the investigator. Additional examinations should be done whenever the investigator deems necessary. For safety monitoring 12-lead ECGs (I, II, III, aVR, aVL, aVF, V1 - V6) will be recorded using an electrocardiograph. All ECGs will be recorded for a 10 second duration after the subjects have rested for at least 5 min in a supine position. […] 5.5.1 Pharmacokinetic endpoint(s) If data allow, the following pharmacokinetic parameters will be evaluated using non-compartmental analysis methods according to the internal BI Standard Operating Procedure (SOP). Secondary pharmacokinetic endpoint is: • Serum concentration at steady state (Css) for c.i.v. [redacted]

Number of global amendment	2
	[redacted]
	5.6.1.4 Immunophenotyping Diagnostic multiple myeloma flow cytometry including MRD Analysis of myeloma cells in bone marrow will be conducted using a diagnostic flow cytometry panel including markers for CD45, CD38, CD19, CD138, CD56 and kappa/lambda chains. The analysis will be performed centrally. In order to assess minimal residual disease the flow cytometric panel may include 6-color-analysis such as cytIgλ /cytIgkappa/CD19/CD56/CD38/CD45 and cytIgλ/CD19/cytIg kappa/CD138/CD38/CD45 (R14-4637). Modifications according to updated guidance are possible.
	[redacted]

Number of global amendment		2
		[redacted] **10 6 INVESTIGATIONAL PLAN** […] **6.2.2 Disease and Response Assessments for Multiple Myeloma** Clinical disease status for multiple myeloma will be assessed at screening, at the start of each cycle as well as at EOT. At screening and subsequently the evaluation of multiple myeloma will be done according to IMWG (2006). If a patient has clinical symptoms of multiple myeloma at screening, they should be recorded as baseline conditions. Biomarkers in blood and urine will be done according to specific Flow chart for biomarkers. Total body MRI should be performed within 14 days before day 1, cycle 1; results from routine assessments (MRI) for multiple myeloma are accepted if performed no later than 28 days before start of treatment. Total body MRI should be performed at or within 14 days before day 1, cycle 3; day 1, cycle 5; day 1, cycle 7 as well as every other cycle thereafter and at time of EOT or at time of progression or start of further anticancer therapy. Bone marrow aspirates will be done within 14 days before day 1 cycle 1 or at cycle 1, day 1 before start of treatment, when M protein/FLC becomes undetectable during treatment, at day 29 of cycle 3 and at EOT. For karyotyping the recent analysis will be accepted if performed within 3 months prior to start of study medication in case that no therapy has been given between assessment of karyotyping and study medication; otherwise, a baseline karyotype should be performed at screening; subsequent karyotyping could be performed in subsequent marrow samples. The biomarker assessments will be performed as specified in the Flow charts. A bone marrow biopsy should be performed if aspirate could not be obtained (punctio sicca). One sample of bone marrow will be provided for DNA banking in case that the patient has given consent for pharmacogenetic testing (baseline bone marrow, a bone marrow sample on treatment when a complete response is reached as well as during follow up). […] 6.2.4.1 Cycle 1 Patients will be hospitalized for the first 3 – 4 days. Table 6.2.4.1: 1 Visit 1 (Day 1-3 or 4)

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Physical examination (Section 5.2.6.2)	A general physical examination will be performed, preferably by the same investigator through the study to enable comparability. This includes blood pressure, heart rate and temperature. Additional time points for blood pressure, heart rate and body temperature at the day of start of administration of BI 836909 are: prior to the start of premedication and infusion, then every 30 (±10) minutes after start of the infusion of BI 836909 for the first 4 hours and additionally 3 times during hospitalisation (in the evening of day 1 as well as in the morning of day 2 and 3). Orienting neurological examination daily during hospitalisation.
[redacted]	
Weight (Section 5.2.6.2)	Weight is measured; preferably, the same weight scale should be used throughout the study to ensure consistency of data collected.
PK samples (Section 5.5 and Section 5.2.5)	For PK sampling, see separate Flow chart and Section 5.5
Safety laboratory (Section 5.2.4)	Haematology, biochemistry, coagulation parameters and urinalysis (dipstick).
Adverse events (section 5.2.2)	Occurance of AEs since last visit.
[…]	

Table 6.2.4.1: 3 Visit 5 (Day 29 and day 30)

Physical examination and [redacted]	A general physical examination will be performed, preferably by the same investigator through the study to enable comparability. This includes blood pressure, heart rate and temperature.
[redacted]	

Number of global amendment	2

PK samples (Section 5.5 and Section 5.2.5)	For PK sampling, see separate Flow chart and Section 5.6. • 10 minutes before the end of continuous infusion or • 24 hours after stop of treatment (day 30)
Safety laboratory (Section 5.2.4)	Haematology, biochemistry, coagulation parameters and urinalysis (dipstick).
[redacted]	
Adverse events (Section 5.2.2)	Occurrence of AEs since last visit.
Concomitant therapies (Section 4.2)	Any new or any change in concomitant therapies since the last visit, will be recorded in the eCRF.

[…]

6.2.4.2 Cycle 2 – 5 (or further cycles in case more than 5 cycles are administered)

Table 6.2.4.2: 1 Cycle 2 – 5 (or further cycles): Visit 1 (day 1) Patient will be hospitalized for at least 24 hours.

Physical examination (Section 5.2.6.2)	A general physical examination will be performed, preferably by the same investigator through the study to enable comparability. This includes blood pressure, heart rate and temperature. Orienting neurological examination daily during hospitalisation.

Number of global amendment	2

[redacted]

Weight (Section 5.2.6.2)	Weight is measured; preferably, the same weight scale should be used throughout the study to ensure consistency of data collected.
ECG/PK samples (Section 5.5 and Section 5.2.5)	For PK sampling, see separate Flow chart and Section 5.5. A 12-lead ECG will be done at the start of each cycle.
Safety laboratory (Section 5.2.4)	Haematology, biochemistry, coagulation parameters and urinalysis (dipstick).

[redacted]

Adverse events (Section 5.2.2)	Occurrence of AEs since last visit.
Concomitant therapies (Section 4.2)	Any new or any change in concomitant therapies since the last visit, will be recorded in the eCRF.

Number of global amendment		2
		Disease assessment: Clinical, MRI and blood and urine markers (Section 5.6.1) — Clinical: if patient has any new clinical symptoms of multiple myeloma, these should be recorded in the "disease assessment" page and as an AE when applicable (see Section 5.2.2.1). [redacted] MRI should be performed every other cycle: at or within 14 days before cycle 3, day 1, cycle 5, day1, cycle 7, day 1… and/or at time of progression or start of further anticancer therapy;
		Administration of BI 836909 (Section 4.1) — 4 weeks continuous intravenous infusion via infusion pump. Infusion bags must be exchanged approximately every 4 days
		Call IWRS/ Administer BI 836909 — The IWRS system needs to be accessed (see Section 4.1.4.2) before any BI 836909 is administered to the patient. Dispense medication for the first course of treatment (see Section 4.1.4), as directed by the IRT system.
		[…]
		6.2.5.2 Residual effect period (REP) The REP is defined in Section 5.2.3. The End of REP (EOR) visit should not be performed earlier than 30 days after permanent discontinuation of the trial medication. The information collected at this visit should include all new AEs that occurred after EOT and a follow-up of adverse events ongoing at EOT. Any subsequent anti-cancer therapy administered between EOT and REP visit must be documented to allow an assessment of newly reported AEs as well as **patient`s status. .**

Number of global amendment		2
		Table 6.2.5.3: 1 Residual effect period (REP) Adverse events (Section 5.2.2) — All AEs, SAEs, AESIs regardless of relatedness. This includes all deaths. Patient status — Collect information for progression or relapse, death, lost to follow-up. Other therapy for Multiple Myeloma — In case the patient receives other therapy for Multiple Myeloma 11 7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE […] **7.3 PLANNED ANALYSES** Only one analysis population (the treated set, **see definition below**) will be considered for efficacy and safety analyses. No Per protocol population will be used for analyses. However **important** protocol violations will be described. Treated Set consists of all patients who received at least one application of BI 836909. **7.3.1 Primary endpoint analyses** In order to identify the MTD, the number of patients with DLTs during the first course at each dose level will be displayed descriptively by dose level. In addition, the number of patients with all DLTs during any treatment course will be analysed. Analysis of other adverse events and laboratory parameters is described in Section 7.3.4. […] [redacted] **7.3.5 Pharmacokinetic analyses** The secondary pharmacokinetic endpoint Css [redacted] will be descriptively explored, and if possible, dose proportionality will also be explored descriptively. Attainment of steady state will be determined by visual examination of the data. […]

Number of global amendment		2
		7.4 INTERIM ANALYSES An interim analysis will be performed as soon as the MTD is determined. To be specific, the date of Last Patient Out is defined by the date when the subject number 6 treated at MTD has completed cycle 1 including 2 weeks off-period before 6 additional subjects enter. This analysis will be restricted to the following aspects: • Safety evaluations including summary of patients with DLT (See Sections 7.3.4 and 7.3.1). • Pharmacokinetic evaluations (See Section 7.3.5). • Preliminary efficacy evaluations on objective response rate (See Section 7.3.2). The analyses will be in descriptive nature. No inferential statistical analyses will be performed Results of this evaluation will be documented within an interim report and archived. The analysis will be defined in more detail in the Trial Statistical Analysis Plan. The sponsor will continuously monitor the safety. The sponsor and the investigators will perform safety evaluations regularly, and if considered necessary at additional ad hoc meetings. The evaluations will be unblinded to dose. **7.5.3 Pharmacokinetic assessment** In the noncompartmental analysis, concentration data identified with NOS, NOR, and NOA will not be considered. BLQ and NOP values in the lag phase will be set to zero. The lag phase is defined as the period between time zero and the first time point with a concentration above the quantification limit. All other BLQ/NOP values of the profile will be ignored. If the predose concentration is less than or equal to 5% of Css value in that subject, the subject's data without any adjustments can be included in all pharmacokinetic measurements and calculations (i.e. the predose value will not be changed to zero). If the predose value is greater than 5% of Css, the subject should be dropped from all statistical evaluations. The individual pharmacokinetic parameters can be calculated and listed separately. **7.7 DETERMINATION OF SAMPLE SIZE** It is planned to include a total of up to **50** subjects in this trial. The planned sample size is not based on a power calculation.

Number of global amendment		2
		10.2 FLOW CHART PHARMACOKINETIK ASSESSMENTS BLOOD SAMPLING TIMES FOR PHARMACOKINETICS Triple ECG for QTc assessment for previous expansion was deleted.
Rationale for change		BI 836909 has been out-licenced to AMGEN. Development of the solution for subcutaneous injection of BI 836909 will not be pursued by Amgen and therefore Arm B has been cancelled and therefore all part B related parts of the protocol have been deleted. The same is true for the expansion cohort for the continuous infusion with . BI 836909. Efficacy as well as safety of BI 836909 will be tested within a newly designed study and therefore the previous expansion cohort was cancelled and all the expansion cohort related parts of the protocol have been deleted, but additional 6 patients will be treated at MTD or recommended dose for the confirmation of MTD and safety. Also follow up visits beyond the REP visit have been cancelled and the respective parts of the protocol have been deleted because efficacy will be tested within a phase II study. Additional cohorts have been included because no DLTs occurred up to now and more cohorts to detect MTD may be needed. The corresponding parts of the protocol have been updated accordingly. For safety reason 5.1.1 Endpoints efficacy The analysis of supportive care requirements (percentage […]) was cancelled due to small size of the amended study.

Number of global amendment		3
Date of CTP revision		07 Jun 2017
EudraCT number		2014-004896-22
BI Trial number		1351.1
BI Investigational Product(s)		BI 863909
Title of protocol		An open label, phase I, dose escalation study to characterize the safety, tolerability, pharmacokinetics, and pharmacodynamics of intravenous doses of BI 836909 in relapsed and/or refractory multiple myeloma patients
To be implemented only after approval of the IRB/IEC/Competent Authorities		X
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		☐
Can be implemented without IRB/IEC/ Competent Authority approval as changes involve logistical or administrative aspects only		☐
Sections to be changed		1. Synopsis, Titel page and Methodology 2. Footnote 8 of Flow chart: BI 836909 CONTINUOUS INTRAVENOUS INFUSION [redacted] 4. Section 3.1; Table 3.1:1 and foot notes 5. Section 4.1.4; Table 4.1.4:1 and footnotes 6. Section 5.1.2.1 7. Section 5.6.1.1 8. Section 6.2.3; Table 6.2.3:1 9. Section 6.2.4; Table 6.2.4:2 10. Section 6.2.5.1; Table 6.2.5.1:1

Number of global amendment		3
Description of change		1. The following on the Titel page: Trial Clinical Monitor: [redacted] Was changed to Trial Clinical Monitor: [redacted] The following for Methodology within synopsis **……** The following dose cohorts will be tested within the above-mentioned dose range: • 3.2, 6.5, 13, 25, 50, 100, 200 and 400 µg/day and higher doses if MTD has not yet been established. Additional and intermediate dose cohorts will be entered if determined by the safety committee. **Was changed to:** **…..** The following dose cohorts will be tested within the above-mentioned dose range: 3.2, 6.5, 13, 25, 50, 100, 200, 400 **and 800 µg/day. Intermediate dose cohorts with 50% increments of previous dose will be entered if determined by the safety committee**. 2. Flow Chart: CONTINUOUS INTRAVENOUS INFUSION The following was added to foot note 8 Percentage (%) of plasma cells in bone marrow should be assessed locally according to institutional standards and documented in eCRF. [redacted]

Number of global amendment		3

[redacted]

4. Section 3.1; Table 3.1:1and foot notes the following:

Dose level	Dose µg/d	Patients per cohort	Approximate increment to next dose
1	0.2	1	2x
2	0.4	1	2x
3	0.8	1	2x
4	1.6	1	2x
5	3.2	3 (+3)	2x
6	6.5	3 (+3)	2x
7	13	3 (+3)	2x
8	25	3 (+3)	2x
9	50	3 (+3)	2x
10	100	3 (+3)	2x
11	200	3 (+3)	2x
12	400*	3 (+3)	2x

*further doses will be tested in case that MTD could not be confirmed at a dose level of 400 µg/day. Intermediate dose cohorts will be entered if determined by the safety committee, for example, in case that the dose cohort 400 µg/day exceeds MTD (> 1 patient out of 6 with DLT) and no DLT is observed on 200 µg/day consider 300 µg/day,

was changed to:

Dose level	Dose µg/d	Patients per cohort	Approximate increment to next dose
1	0.2	1	2x
2	**0.4**	**1**	**2x**
3	**0.8**	**1**	**2x**
4	**1.6**	**1**	**2x**
5	**3.2**	**3 (+3)**	**2x**
6	6.5	3 (+3)	2x
7	13	3 (+3)	2x
8	25	3 (+3)	2x
9	50	3 (+3)	2x
10	100*	3 (+3)	2x

Number of global amendment		3

11	200*	3 (+3)	2x
12	400*	3 (+3)	2x
13	800*	3 (+3)	2x

*Intermediate dose cohorts with up to 50% increment versus the previous cohort will be entered if determined by the safety committee,in case that the dose of a cohort exceeds MTD (> 1 patient out of 6 with DLT) and the previous cohort is well tolerated.
For example:
- 75µg/day in case a dose of 100µg/day exceeds MTD
150µg/day in case a dose of 200µg/day exceeds MTD
- 300µg/day in case a dose of 400µg/day exceeds MTD
- 600µg/day in case a dose of 800µg/day exceeds MTD
The above-mentioned intermediate dose cohorts will follow the 3 (+3) design.

5. Section 4.1.4; Table 4.1.4:1 and footnotes
The following:
……

Table 4.1.4: 1 Dose escalation scheme

Dose µg/day	Patients per cohort	Observation time of ongoing patients before enrolment/entry of next patient/cohort
0.2	1	2 weeks, then enrol next cohort
0.4	1	As in previous cohort
0.8	1	As in previous cohort
1.6	1	As in previous cohort
3.2	3 (+3)	1 week for first patient, then enter next two patients; additional patients should not start treatment before the previous patient has been treated for 48 hours in order to monitor initial transient toxicities due to cytokine release syndrome. All 3 must have completed 4 weeks before enrolling next cohort
6.5	3 (+3)	As in previous cohort
13	3 (+3)	As in previous cohort
25	3 (+3)	As in previous cohort
50	3 (+3)	As in previous cohort

Number of global amendment		3

100	3 (+3)	As in previous cohort
200	3 (+3)	As in previous cohort
400….*	3 (+3)	As in previous cohort

*further and intermediate dose cohorts may be added

was changed to:

Table 4.1.4: 1 Dose escalation scheme

Dose µg/day	Patients per cohort	Observation time of ongoing patients before enrolment/entry of next patient/cohort
0.2	1	2 weeks, then enrol next cohort
0.4	1	As in previous cohort
0.8	1	As in previous cohort
1.6	1	As in previous cohort
3.2	3 (+3)	1 week for first patient, then enter next two patients; additional patients should not start treatment before the previous patient has been treated for 48 hours in order to monitor initial transient toxicities due to cytokine release syndrome. All 3 must have completed 4 weeks before enrolling next cohort
6.5	3 (+3)	As in previous cohort
13	3 (+3)	As in previous cohort
25	3 (+3)	As in previous cohort
50	3 (+3)	As in previous cohort
100	3 (+3)	As in previous cohort
200	3 (+3)	As in previous cohort
400	3 (+3)	As in previous cohort
800	3 (+3)	As in previous cohort

*Intermediate dose cohorts may be added based on decision of the safety committee (see table 3.1:1) and will follow the above-mentioned rules.

6. Section 5.1.2.1
The following

Number of global amendment		3
		…….. The following laboratory parameters must be evaluated to assess response of treatment: •Multiple myeloma (MM) cells in bone marrow Analysis of myeloma cells in bone marrow will be conducted using a diagnostic FACS panel including markers for CD45, CD38, CD19, CD138, CD56 and kappa/lambda chains. Scheduled sampling time points will be as follows (see flow charts): within 14 days before day 1 cycle 1or in cycle 1, day 1 before start of treatment, when M protein/FLC becomes undetectable during treatment, on day 29 of cycle 3 and at EOT. The analysis will be performed centrally. …… Was changed to: …. The following laboratory parameters must be evaluated to assess response of treatment: •Multiple myeloma (MM) cells in bone marrow Analysis of myeloma cells in bone marrow will be conducted using a diagnostic FACS panel including markers for CD45, CD38, CD19, CD138, CD56 and kappa/lambda chains. Scheduled sampling time points will be as follows (see flow charts): within 14 days before day 1 cycle 1or in cycle 1, day 1 before start of treatment, when M protein/FLC becomes undetectable during treatment, on day 29 of cycle 3 and at EOT. The analysis will be performed centrally. **Percentage (%) of plasma cells in bone marrow should be assessed locally according to institutional standards and documented in eCRF at each timepoint**. …. 7. Section 5.6.1.1 The following: ……. [redacted] Was changed to:

Number of global amendment		3
		[redacted] 8. Section 6.2.3 The following: …… **Bone marrow aspirate for disease assessment and DNA banking of bone marrow (Section 5.6.1)** Karyotyping: recent analysis will be accepted if performed within 3 months prior to start of study medication in case that no therapy has been given between assessment of karyotyping and study medication; otherwise, a baseline karyotype should be performed at screening; subsequent karyotyping could be performed in subsequent marrow samples. The following assessments will be performed (see Flow charts): • MM cells in bone marrow • BCMA expression by myeloma cells in bone marrow Obtain bone marrow biopsy if aspirate could not be obtained (*punctio sicca*). One sample of bone marrow will be provided for DNA banking.

Number of global amendment		3
		<table><tr><td>Disease assessment: Clinical/MRI and blood/urine (Section 5.6.1)</td><td>Evaluation of multiple myeloma according to IMWG (2006) Clinical: if patient has clinical symptoms of Multiple Myeloma, they should be recorded as baseline conditions. Total body MRI should be performed; results from routine assessments (MRI) for multiple myeloma are accepted if performed no later than 28 days before start of treatment. Biomarkers in blood and urine according to specific Flow chart for biomarkers:</td></tr><tr><td>Adverse events (Section 5.2.2)</td><td>Occurrence of AEs since signing the Informed Consent Form will be documented. For patients who become screen failures, if an AE occurs during this period, the patient should be followed until the PI determines the patient is a screen failure.</td></tr><tr><td>Concomitant therapies (Section 4.2)</td><td>All concomitant therapies (including transfusions and anti- infectives) at trial entry and/or during screening will be recorded in the eCRF.</td></tr></table> Was changed to:

Number of global amendment		3	
		Bone marrow aspirate for disease assessment and DNA banking of bone marrow (Section 5.6.1)	Karyotyping: recent analysis will be accepted if performed within 3 months prior to start of study medication in case that no therapy has been given between assessment of karyotyping and study medication; otherwise, a baseline karyotype should be performed at screening; subsequent karyotyping could be performed in subsequent marrow samples. The following assessments will be performed (see Flow charts): • **MM cells in bone marrow; percentage (%) of plasma cells in bone marrow should be assessed locally according to institutional standards and documented in eCRF.** • BCMA expression by myeloma cells in bone marrow Obtain bone marrow biopsy if aspirate could not be obtained (*punctio sicca*). One sample of bone marrow will be provided for DNA banking.

Number of global amendment		3
		Disease assessment: Clinical/MRI and blood/urine (Section 5.6.1) — Evaluation of multiple myeloma according to IMWG (2006) Clinical: if patient has clinical symptoms of Multiple Myeloma, they should be recorded as baseline conditions. Total body MRI should be performed; results from routine assessments (MRI) for multiple myeloma are accepted if performed no later than 28 days before start of treatment. [redacted]
		Adverse events (Section 5.2.2) — Occurrence of AEs since signing the Informed Consent Form will be documented. For patients who become screen failures, if an AE occurs during this period, the patient should be followed until the PI determines the patient is a screen failure.
		Concomitant therapies (Section 4.2) — All concomitant therapies (including transfusions and anti- infectives) at trial entry and/or during screening will be recorded in the eCRF.

Number of global amendment		3
		9. Section 6.2.4, table 6.2.4.2:2 …… Table 6.2.4.2: 2 Cycle 2 – 5 (or further cycles): Visit 2 - 4

Physical examination (Section 5.2.6.2)	A general physical examination will be performed, preferably by the same investigator through the study to enable comparability. This includes blood pressure, heart rate and temperature.
[redacted]	
Weight (Section 5.2.6.2)	Weight is measured; preferably, the same weight scale should be used throughout the study to ensure consistency of data collected.
ECG/PK samples (Section 5.5 and 5.2.5)	For PK sampling, see separate Flow chart and Section 5.5. A 12-lead ECG will be done at the start of each cycle.
Safety laboratory (Section 5.2.4)	Haematology, biochemistry, coagulation parameters and urinalysis (dipstick).
Adverse events (Section 5.2.2)	Occurrence of AEs since last visit.
Concomitant therapies (Section 4.2)	Any new or any change in concomitant therapies since the last visit, will be recorded in the eCRF.

Number of global amendment		3
		Disease assessment: clinical and blood and urine markers (Section 5.6.1) — Clinical: if patient has any new clinical symptoms of multiple myeloma, these should be recorded in the "disease assessment" page and as an AE when applicable (see Section 5.2.2.1). [redacted]
		Bone Marrow — Bone marrow aspirate will be done on day 29 of cycle 3: The following assessments will be performed: • MM cells in bone marrow • BCMA expression by myeloma cells in bone marrow • MRD (in case M protein/FLC becomes undetectable) Obtain bone marrow biopsy if aspirate could not be obtained (punctio sicca). One sample of bone marrow will be provided for DNA banking.
		…..
		Was changed to:
		…..

Number of global amendment	3	
	Physical examination (Section 5.2.6.2)	A general physical examination will be performed, preferably by the same investigator through the study to enable comparability. This includes blood pressure, heart rate and temperature.
	[redacted]	
	Weight (Section 5.2.6.2)	Weight is measured; preferably, the same weight scale should be used throughout the study to ensure consistency of data collected.
	ECG/PK samples (Section 5.5 and 5.2.5)	For PK sampling, see separate Flow chart and Section 5.5. A 12-lead ECG will be done at the start of each cycle.
	Safety laboratory (Section 5.2.4)	Haematology, biochemistry, coagulation parameters and urinalysis (dipstick).
	Adverse events (Section 5.2.2)	Occurrence of AEs since last visit.
	Concomitant therapies (Section 4.2)	Any new or any change in concomitant therapies since the last visit, will be recorded in the eCRF.

Number of global amendment		3
		Disease assessment: clinical and blood and urine markers (Section 5.6.1) — Clinical: if patient has any new clinical symptoms of multiple myeloma, these should be recorded in the "disease assessment" page and as an AE when applicable (see Section 5.2.2.1). [redacted]
		Bone Marrow — Bone marrow aspirate will be done on day 29 of cycle 3: The following assessments will be performed: • MM cells in bone marrow; percentage (%) of plasma cells in bone marrow should be assessed locally according to institutional standards and documented in eCRF. • BCMA expression by myeloma cells in bone marrow • MRD (in case M protein/FLC becomes undetectable) Obtain bone marrow biopsy if aspirate could not be obtained (punctio sicca). One sample of bone marrow will be provided for DNA banking.

Number of global amendment		3
		10. Section 6.2.5.1 The following: Table 6.2.5.1:1 Visit at the end of Treatment (EOT) ECG (Section 5.2.5) — Resting 12-lead ECG (digital) Physical examination (Section 5.2.6.2) — A general physical examination as well as an orientated neurological examination will be performed, preferably by the same investigator throughout the study to enable comparability. This includes [redacted] Weight (Section 5.2.6.2) — Weight is measured; preferably, the same weight scale should be used throughout the study to ensure consistency of data Safety laboratory (Section 5.2.4) — Haematology, biochemistry, coagulation parameters, and urinalysis (dipstick). Disease assessment: clinical and blood/MRI (Section 5.5.1) — Clinical: if patient has any new clinical symptoms of multiple myeloma, these should be recorded in the "disease assessment" page and as an AE when applicable (see Section 5.2.2.1). [redacted] Total body MRA should be performed.

Number of global amendment	3

Bone Marrow aspirate (Section 5.6.1)	The following assessments will be performed: • MM cells in bone marrow; percentage (%) of plasma cells in bone marrow should be assessed locally according to institutional standards and documented in eCRF. • BCMA expression by myeloma cells in bone marrow • MRD (in case M protein/FLC becomes undetectable) Obtain bone marrow biopsy if aspirate could not be obtained (punctio sicca). One sample of bone marrow will be provided for DNA banking.

…

Was changed to:

ECG (Section 5.2.5)	Resting 12-lead ECG (digital)
Physical examination (Section 5.2.6.2)	A general physical examination as well as an orientated neurological examination will be performed, preferably by the same investigator throughout the study to enable comparability. This includes [redacted]
Weight (Section 5.2.6.2)	Weight is measured; preferably, the same weight scale should be used throughout the study to ensure consistency of data
Safety laboratory (Section 5.2.4)	Haematology, biochemistry, coagulation parameters, and urinalysis (dipstick).

Number of global amendment		3
		Disease assessment: clinical and blood/MRI (Section 5.5.1) — Clinical: if patient has any new clinical symptoms of multiple myeloma, these should be recorded in the "disease assessment" page and as an AE when applicable (see Section 5.2.2.1). [redacted] Total body MRA should be performed.
		Bone Marrow aspirate (Section 5.6.1) — The following assessments will be performed: • MM cells in bone marrow; percentage (%) of plasma cells in bone marrow should be assessed locally according to institutional standards and documented in eCRF. • BCMA expression by myeloma cells in bone marrow • MRD (in case M protein/FLC becomes undetectable) Obtain bone marrow biopsy if aspirate could not be obtained (punctio sicca). One sample of bone marrow will be provided for DNA banking.
Rationale for change		1. Change in responsibility 2. Request of the Germany authority PEI to define the highest dose as well as the intermediate doses 3. Correlation between soluable BCMA and free drug; it is important to know the sBCMA levels before start of treatment; therefore one additional sampling of sBCMA has been implemented 4. Necessity of documentation of % of plasma cells in bone marrow for response assessment.

Number of global amendment		4
Date of CTP revision		26 Nov 2018
EudraCT number		2014-004896-22
BI Trial number		1351.1
BI Investigational Product(s)		BI 863909
Title of protocol		An open label, phase I, dose escalation study to characterize the safety, tolerability, pharmacokinetics, and pharmacodynamics of intravenous doses of BI 836909 in relapsed and/or refractory multiple myeloma patients
To be implemented only after approval of the IRB/IEC/Competent Authorities		X
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		☐
Can be implemented without IRB/IEC/ Competent Authority approval as changes involve logistical or administrative aspects only		☐
Sections to be changed		1. Titel page 2. Flow Chart, Section 3.1, Section 6.2.5.3 3. Section 2.3 4. Section 4.1.4.1.4 5. Section 4.2.1.2.3 6. Appendix 10.1

Number of global amendment		4
Description of change		1. The following on the Titel page: Trial Clinical Monitor Was changed to **Clinical Trial Leader** 2. FlowChart, Section 3.1 Overall trial design and plan, Section 6.2.5.3 Extended follow up Wording was introduced to allow for extended follow up for responders: In case of ongoing clinical benefit, patients can be followed up to collect data for duration of response. Follow-up visits for responders will be at 3, 6 and 12 months after EOT if a patient did not progress, started a new anti-cancer treatment, died, or withdrew informed consent and will assess related SAEs and AESIs. 3. 2.3 Benefit-Risk Assessment The following was added: Cytokine release can be associated with clinical symptoms such as fever, chills, nausea, vomiting, hypotension, dyspnoea, tachypnea, headache, tachycardia, rash, and/or hypoxia. 4. 4.1.4.1.4 Handling of infusion-related reactions or cytokine release syndromes Recommendations for CRS management were modified and Table 4.1.4.1.4: 1 Grading and management of cytokine release syndrome was added. 5. 4.2.1.2.3 Infections The following was added: Prophylactic antibiotics, antifungal and antivirals are allowed and should be given according to institutional standards. Pneumocystis prophylaxis should also be given according to institutional standards. For patients who are considered to have an increased risk for herpes infections, the prophylaxis is mandatory unless medically contraindicated. Subjects who may experience neutropenia for 7 days or longer are at a high risk for infectious complications. As appropriate, these subjects will be administered prophylactic antibacterial, antifungal, and antiviral medications. These subjects will be monitored for early signs of breakthrough infections after the initiation of antibacterial therapy to prompt additional evaluation and

Number of global amendment		4
		possible therapy modification. ~~Infections should be treated according to local guidelines/standards.~~ Patients who develop fever >38.3°C or a sustained temperature of >38°C ≥1 h will be hospitalised, undergo the following diagnostic work-up and started on empirical treatment with broad spectrum i.v. antibiotics according to institutional standards: - Blood cultures from central line and peripheral veins - Urine culture - CT-Thorax low dose - Respiratory virus by pharyngeal wash (Parainfluenza 1-4, Influenza A + B, Adenovirus, Metapneumovirus, Echovirus, Rhinovirus, Bocavirus, Coronavirus, Entrovirus und RSV by multiplex PCR) Subjects with active systemic infections requiring IV antibiotics, antivirals, or antifungals should not be dosed with BI 836909 until infection has resolved and if being treated with an anti-infectious therapy, the course of such therapy should have been completed. Patients requiring interruption of treatment for >14 days due to active infection will be permanently discontinued. 6. 10.1 International Myeloma Working Group (IMWG) uniform resonse criteria for multiple myeloma The following was added: SD – Not meeting criteria for CR, VGPR, PR, or progressive disease
Rationale for change		1. Change in nomenclature 2. Collection of data for long-term responders 3. Request of the French authority ANSM to add additional clinical signs and symptoms as described in CTCAE v5 in order to enhance investigators' awareness for occurrence of CRS clinical events. However, the grading of CRS will continue to be based on CTCAE v4 until completion of the trial. 4. Request of the French authority ANSM to add risk minimization measures and detailed procedures in case of suspicion of CRS. 5. Correction/completion of IMWG criteria.

APPROVAL / SIGNATURE PAGE

Document Number: c02587386 **Technical Version Number:5.0**

Document Name: clinical-trial-protocol-revision-04

Title: An open label, phase I, dose escalation study to characterize the safety, tolerability, pharmacokinetics, and pharmacodynamics of intravenous doses of BI 836909 in relapsed and/or refractory multiple myeloma patients

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Author-Clinical Trial Leader	[redacted]	26 Nov 2018 10:38 CET
Approval-Therapeutic Area [redacted]		26 Nov 2018 10:47 CET
Approval-Translational Medicine Expert		26 Nov 2018 10:52 CET
Approval-Translational Medicine Expert		26 Nov 2018 11:00 CET
Approval-Biostatistics		26 Nov 2018 14:46 CET
Author-Trial Clinical Pharmacokineticist		26 Nov 2018 21:49 CET
Approval-Team Member Medicine		27 Nov 2018 10:42 CET
Verification-Paper Signature Completion		29 Nov 2018 07:17 CET

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed