Clinical Trial Protocol

Doc. No.: c02158149-09

EudraCT No.:	2010-024456-29
BI Trial No.:	1270.2
BI Investigational Product(s):	BI 836826
Title:	A Phase I, Open-Label, Dose-Escalation Trial with BI 836826 in Patients with Relapsed or Refractory non-Hodgkin Lymphoma of B cell Origin
Clinical Phase:	Phase I
Trial Clinical Monitor:	On behalf of Phone: Fax:
Co-ordinating Investigator:	 Phone: Fax:
Status:	Final Protocol (Revised Protocol (based on global amendment(s))
Version and Date:	**Version: 6** **Date: 13 Apr 2016**

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001-MCS-40-106_RD-03 (10.0) / Saved on: 20 Oct 2011

CLINICAL TRIAL PROTOCOL SYNOPSIS

Name of company: Boehringer Ingelheim		**Tabulated Trial Protocol**	
Name of finished product: Not Applicable			
Name of active ingredient: BI 836826			
Protocol date: 25 Feb 2011	**Trial number:** 1270.2		**Revision date:** 13 Apr 2016

Title of trial:	A Phase I, Open-Label, Dose-Escalation Trial with BI 836826 in Patients with Relapsed or Refractory non-Hodgkin Lymphoma of B cell Origin
Co-ordinating Investigator:	
Trial sites:	Multi-centre trial
Clinical phase:	Phase I
Objectives:	To investigate the maximum tolerated dose (MTD), safety and tolerability, and efficacy of BI 836826 monotherapy in patients with relapsed or refractory non-Hodgkin lymphoma
Methodology:	Open-label dose-escalation
No. of patients:	Approximately 66
total entered:	Approximately 53
each treatment:	1 to 6 patients at each dose level, up to 4 patients treated at the 100 mg dose in expansion cohort, additional cohort (up to 12) of Korean patients:3-6 patients at 50 mg, and 3-6 patients at 75 mg
Diagnosis :	Non-Hodgkin lymphoma of B cell origin
Main criteria for inclusion:	Relapsed or refractory non-Hodgkin lymphoma of B cell origin not eligible for intensive anti-lymphoma treatment
Test product:	BI 836826
dose:	Starting dose will be 1 mg

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Name of company: Boehringer Ingelheim		**Tabulated Trial Protocol**	
Name of finished product: Not Applicable			
Name of active ingredient: BI 836826			
Protocol date: 25 Feb 2011	**Trial number:** 1270.2		**Revision date:** 13 Apr 2016
mode of admin. :	BI 836826 administered intravenously as single agent treatment		
Comparator products: **dose:** **mode of admin. :**	Not applicable		
Duration of treatment:	Patients are eligible for up to 3 courses with a total of 12 administrations of BI 836826. Each course comprises of 4 administrations in weekly intervals followed by treatment free observation/rest. The duration of two first courses is each 7 weeks and the duration of the third course is 12 weeks. The maximum duration of treatment and observation period/rest is 26 weeks before follow-up.		
Criteria for efficacy and pharmacodynamics:	Reduction in tumour size, best overall response, progression free survival, failure free survival, plasma concentration time profiles		
Criteria for safety:	Maximum tolerated dose, incidence and intensity of adverse events graded according to the common terminology criteria for adverse events (CTCAE, version 4.0), incidence of dose limiting toxicity, laboratory parameters.		
Statistical methods:	Descriptive statistics		

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FLOWCHARTS

Flowchart for Course 1

Trial Periods	**Screen**	**Treatment and observation/rest**												**EOT**	**FU**
Course *		**1**													
Week		**1**			**2**			**3**		**4**	**5**	**6**	**7**	If no signs of progression and agreement on further treatment for the patient, please continue to **Visit 1 on Flowchart for Course 2** If the patient has disease progression or withdraws, please continue to **EOT visit on Flowchart for Course 3**	
Visit **	**Screen**	**1**		**2**	**3**		**4**	**5**	**6**	**7**	**8**	**9**	**10**		
Days	**-14 to -1**	**1**	**2**	**3 + 2**	**8**	**9**	**10 +2**	**15**	**17 +2**	**22**	**29 ±2**	**36 ± 2**	**43 ±2**		
Informed consent	x														
Demographics	x														
Medical history	x														
Review of in-/exclusion criteria	x	x [1]													
Eligibility for trial	x														
12-lead ECG	x														
Height	x														
Weight	x	x	x		x	x		x		x			x		
Physical examination, incl. tumour size (lymph nodes, spleen, liver),	x	x								x			x		
Vital signs [2]	x	x	x	x	x	x	x	x	x	x	x	x	x		
Dose assignment	x [3]														
Concomitant therapy	x	x	x	x	x	x	x	x	x	x	x	x	x		
General safety laboratory parameters [4]	x	x	x	x	x	x	x	x	x	x	x	x	x		
Administration of BI 836826		x			x			x		x					
Screening for Tumour Lysis Syndrome [5]		x	x		x	x									
Adverse events		x	x	x	x	x	x	x	x	x	x	x	x		
Disease/response assessm. (clinical/imaging)	x	x [6]								x [6]			x [6]		
Serum pregnancy test [7]	x	x								x					
CMV monitoring [8]	x	x						x		x	x	x	x		
Lymphocyte typing (B/T/NK cells)		x		x	x		x	x	x	x	x	x	x		
Virology screening [10] (HBV, HCV, HIV, CMV)	x														
	x														
CT scan of neck, thorax, abdomen and pelvis	x [11]														

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EOT: End of treatment visit, to be performed at withdrawal from further treatment (<12 administrations) or at the latest 8 weeks after the last administration of BI 836826 (12 administrations)
FU: Follow-up visits (starts after EOT) at least every 6 weeks until 6 months after EOT visit, details see section 6.2.3.2
CMV: Cytomegalovirus
HBV: Hepatitis B virus
HCV: Hepatitis C virus
HIV: Human immunodeficiency virus

* the planned duration of course 1 is 7 weeks (49 days)
** the visit number follows the course number, i.e. visit 2 course 1 will read C1_V2 and visit 2 course 2 will read C2_V2 …

1 Review of eligibility
2 For details during and after infusion of BI 836826, refer to section 5.2.5.1
3 After informed consent, and review of in- and exclusion criteria, and before the first administration of the trial drug
4 For details refer to section 5.2.3.1
5 Screening for tumour lysis syndrome in between safety laboratory assessments (section 5.2.3.2)
6 Disease / response assessment will be based on clinical judgement when recent CT is not available
7 For women of childbearing potential only (please refer to sections 3.3.3 (exclusion criterion 20) and 5.2.3.1)
8 Quantitative CMV DNA PCR (section 5.2.3.3.2)

10 Please refer to section 5.2.3.3.1
11 CT scan may be performed up to 4 weeks prior to first infusion according to the standard of care in this patient population

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Flowchart for Course 2

Trial Periods	**Treatment and observation/rest**											**EOT**	**FU**
Course *	**2**												
Week	**8**			**9**		**10**		**11**	**12**	**13**	**14**		
Visit **	**1**		**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**		
Days	**1**	**2**	**3 +2**	**8**	**9 +4**	**15**	**17 +2**	**22**	**29 ±2**	**36 ±5**	**43 ±2**		
Eligibility for course 2	x[1]												
Vital signs [2]	x	x	x	x	x	x	x	x	x	x	x		
Weight	x	x		x		x		x			x		
Physical examination, incl tumour size (lymph nodes, spleen, liver)	x							x			x		
Disease / response assessment (clinical/imaging)	x[3]							x[3]			x[4]		
Serum pregnancy test [5]	x							x					
Concomitant therapy	x	x	x	x	x	x	x	x	x	x	x		
General safety laboratory parameters [6]	x	x	x	x	x	x	x	x	x	x	x		
Administration of BI 836826	x			x		x		x					
Screening for Tumour Lysis Syndrome [7]	x	x		x									
Adverse events	x	x	x	x	x	x	x	x	x	x	x		
CMV monitoring [8]	x			x		x		x	x	x	x		
Lymphocyte typing (B/T/NK cells)	x		x	x	x	x	x	x	x	x	x		
CT scan of neck, thorax, abdomen and pelvis										x			

If clinical benefit and agreement on further treatment for the patient, please continue to **Visit 1 Flowchart for Course 3**

If the patient has disease progression or withdraws, please continue to **EOT visit on Flowchart for Course 3**

EOT: End of treatment visit, to be performed at withdrawal from further treatment (<12 administrations) or at the latest 8 weeks after the last administration of BI 836826 (12 administrations)
FU: Follow-up visits (starts after EOT) at least every 6 weeks until 6 months after EOT visit, details see section 6.2.3.2
CMV: Cytomegalovirus

* the planned duration of course 2 is 7 weeks (49 days)
** the visit number follows the course number, i.e. visit 2 course 1 will read C1_V2 and visit 2 course 2 will read C2_V2

1 Can be performed within 7±2 days prior to this visit
2 For details during and after infusion of BI 836826, refer to section 5.2.5.1
3 Disease / response assessment will be based on clinical judgement when recent CT is not available. Radiological assessments will be performed following the local standard of care.
4 Assessment can be performed prior to visit 10, if CT scan from visit 9 is available.
5 For women of childbearing potential only (please refer to sections 3.3.3 (exclusion criterion 20) and 5.2.3.1)
6 For details refer to section 5.2.3.1
7 Screening for tumour lysis syndrome in between safety laboratory assessments (section 5.2.3.2)
8 Quantitative CMV DNA PCR (section 5.2.3.3.2)

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Flowchart for Course 3, End of Treatment visit and Follow-up

Trial Periods	**Treatment and observation/rest**									**EOT**	**FU**
Course *	**3**										
Week	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**23**	**25**	**see[12]**	
Visit **	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**		
Days	**1**	**8**	**15**	**22**	**29 (+2)**	**36 (+5)**	**43 (+5)**	**57 (±5)**	**71 (±5)**		
Eligibility for course 3	x[1]										
Vital signs [2]	x	x	x	x	x	x	x	x	x	x	x
Weight	x	x	x	x	x	x	x	x	x	x	x
Physical examination, incl. tumour size (lymph nodes, spleen, liver),	x			x			x			x	x
Disease / response assessment (clinical/imaging)	x			x[3]						x	x[3]
Serum pregnancy test [4]	x			x						x	
Concomitant therapy	x	x	x	x	x	x	x	x	x	x	x[5]
General safety laboratory parameters [6]	x	x	x	x	x	x	x	x	x	x	x
Administration of BI 836826	x	x	x	x							
Screening for Tumour Lysis Syndrome [7]	x	x									
Adverse events	x	x	x	x	x	x	x	x	x	x	x[8]
CMV monitoring [9]	x	x	x	x	x	x	x	x	x	x	x
Lymphocyte typing (B/T/NK cells)	x	x	x	x	x	x	x	x		x	x
CT scan of neck, thorax, abdomen and pelvis									x	x[11]	
12-lead ECG										x	
Completion of active trial treatment										x	
Status (remission, progression, death)										x	x
Other therapy for lymphoma										x	x

EOT: End of treatment visit, to be performed at withdrawal from further treatment (<12 administrations) or at the latest 8 weeks after the last administration of BI 836826 (12 administrations)
FU: Follow-up visits (starts after EOT) at least every 6 weeks until 6 months after EOT visit, details see section 6.2.3.2
CMV: Cytomegalovirus

* the planned duration of course 3 is 12 weeks (84 days)
** the visit number follows the course number, i.e. visit 2 course 1 will read C1_V2 and visit 2 course 2 will read C2_V2 …

1 Can be performed within 7±2 days prior to this visit
2 For details during and after infusion of BI 836826, refer to section 5.2.5.1
3 Disease / response assessment will be based on clinical judgement when recent CT is not available
4 For women of childbearing potential only (please refer to sections 3.3.3 (exclusion criterion 20) and 5.2.3.1)
5 Concomitant therapy during FU only in case indicated for treatment of an AE (section 4.2.1)
6 For details refer to section 5.2.3.1
7 Screening for tumour lysis syndrome in between safety laboratory assessments (section 5.2.3.2)
8 For AE assessment during FU refer to sections 5.2.1 and 6.2.3.2

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9 Quantitative CMV DNA PCR (section 5.2.3.3.2)

11 In case end of treatment occurs before week 26, a CT scan can be performed at the EOT visit if clinically indicated for response assessment (*e.g.* progression)
12 If 12 infusions has been administered the EOT should be performed at the latest in week 26 (day 77±5 of course 3)

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ABBREVIATIONS

ADCC	Antibody dependent cellular cytotoxicity
AE	Adverse event
ALT	Alanine amino transferase
anti-HBs	Hepatitis B surface antibody
anti-HBc	Hepatitis B core antibody
anti-HCV	Hepatitis C antibody
AP	Alkaline phosphatase
aPTT	Activated partial thromboplastin time
AST	Aspartate amino transferase
B-NHL	B cell Non-Hodgkin lymphoma
CD	Cluster of Differentiation
CDC	Complement dependent cytotoxicity
CHOP	cyclophosphamide, hydroxydaunorubicin, oncovin , and prednisolone
CI	Confidence Interval

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CLL	Chronic lymphocytic leukaemia
CMV	Cytomegalovirus
CNS	Central nervous system
COPD	Chronic Obstructive Pulmonary Disease
CR	Complete remission
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Clinical Research Organisation
CRu	Complete remission unconfirmed
CT	Computer tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTMF	Clinical Trial Master File
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
DILI	Drug-Induced Liver Injury
DLBCL	Diffuse large B-cell lymphoma
DLT	Dose limiting toxicity
DNA	Deoxyribonucleic acid
DSMB	Data Safety Monitoring Board
eCRF	Electronic Case Report Form
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group

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EOT	End of treatment
EudraCT	European Clinical Trials Database
FAS	Full Analysis Set
FDA	Food and Drug Administration
FFS	Failure free survival
FL	Follicular lymphoma
FU	Follow-up
GCP	Good Clinical Practice
G-CSF	Granulocyte colony stimulating factor
GFR	Glomerular filtration rate
GvHD	Graft versus host disease
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIV	Human immunodeficiency virus
IB	Investigator's Brochure
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
INR	International normalised ratio
IPI	International prognostic index
IRB	Institutional Review Board

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ISF	Investigator Site File
IUD	Intrauterine device
i.v.	Intravenous
LDH	Lactate dehydrogenase
MCL	Mantle cell lymphoma
MTD	Maximum tolerated dose
MedDRA	Medical Dictionary for Drug Regulatory Activities
MRT	Mean residence time
NHL	Non-Hodgkin lymphoma
NK cells	Natural killer cells
OBD	Optimal biological dose
OPU	Operative unit
ORR	Overall response rate
PCR	Polymerase chain reaction
PD	Progressive disease
PET	Positron emission tomography
PFS	Progression free survival
PLT	Platelets

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p.o.	per os (oral)
PR	Partial remission
PT	Prothrombin time
RBC	Red blood cell count
RR	Response rate
SAE	Serious adverse event
SD	Stable disease
SDV	Source data verification
SMIP	Small modular immuno pharmaceutical
SOP	Standard operating procedure
SPD	Sum of product of diameter
SUSAR	Suspected unexpected serious adverse reaction
$t_{1/2}$	Terminal half-life
TDMAP	Trial data management and analysis plan
TLS	Tumour lysis syndrome
WBC	White blood cell count
WHO	World Health Organisation

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1. INTRODUCTION

1.1 MEDICAL BACKGROUND

Non-Hodgkin lymphoma (NHL) encompasses several subgroups of lymphomas with variable clinical courses. In the US 65.500 new cases of NHL are estimated for 2010 (website cancer.org). Approximately 90% of NHL is of B cell origin (B-NHL) (R10-4834) and they belong to mature B cell malignancies according to the World Health Organization (WHO) classification (R10-6296). The incidence of B-NHL is 15-20 per 100.000 (seer.cancer.gov). Historically, the lymphomas are divided into aggressive lymphomas, *i.e.* rapidly growing tumours and indolent lymphomas, *i.e.* slower growing tumours. The aggressive subtypes account for approximately half of the incidence of lymphomas. Among the aggressive subgroups, the diffuse large B-cell lymphoma (DLBCL) is the most common one and represents 30-40% of all B-NHL in adults (R10-6296). The most frequent indolent subtype is follicular lymphoma (FL) accounting for a quarter of the B-NHL (R10-6296). B cell lymphoma is occurring in the entire world with an increasing incidence over the last decades. The median age at diagnosis is around 65 years. There is a slight male predominance in the incidence.

The diagnosis of lymphoma is based on histology of a biopsy, preferably a whole lymph node. The classification of lymphomas has developed over the years with the improvement of diagnostic tools. Today, WHO classification from 2008 is widely accepted and is based on morphology often combined with immunophenotyping and genetics (R10-6296). The majority of the B-NHL expresses B-cell markers like CD19, CD20, CD22 and CD79a. A homogenous CD37 expression is also observed in the majority of B-NHL, as well as in chronic lymphocytic leukaemia (CLL) (R08-2979, R08-2943, R08-2981, R08-2942, R08-2945).

The Ann Arbor staging system is used to describe disease involvement in NHL (R10-6400 and appendix 10.4). The disease stage is determined by computerized tomography (CT) scanning and bone marrow biopsy/aspirate. Extra-nodal disease as well as B symptoms (*i.e.* unexplained fever, night sweats or weight loss) further describes the disease status at diagnosis. The addition of ^{18}F-deoxyglucose-positron emission tomography (PET) scanning for staging and early response evaluation can identify patients with DLBCL who are likely to achieve a durable response (R10-6359). Combination of [^{18}F]Flourodeoxyglucose-positron emission tomography (PET) with computer tomography (CT) scanning has been reported to be superior to PET alone (R10-6358). The role of PET/CT performed during the treatment of DLBCL to guide eventual therapy modifications to improve outcome is less clear due to non lymphoma specific PET positivity (R10-6313). The role of PET scanning for the indolent lymphomas and for refractory setting is more uncertain (R10-1462).

Risk assessment at diagnosis with the international prognostic index (IPI) has been clinically useful for the patients with DLBCL (R10-6349). The index encompasses of 5 parameters: age >60 years, stage III or IV, ≥2 extranodal sites, performance status ≥2 and lactate dehydrogenase (LDH) above upper limit of normal as prognostic factors. Recently, an

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analysis of the prognostic relevance of IPI for patients who received rituximab as part of their first line therapy confirms the significance of IPI for progression free survival (PFS) and overall survival (R10-6639). Similarly, a prognostic index for FL (FLIPI) has been assessed. Initially, retrospectively for PFS identifying age >60 years, stage III-IV, haemoglobin <7.5 mmol/l, serum lactate dehydrogenase (LDH) >upper limit of normal and >4 nodal sites as adverse prognostic factors (R10-6350). Recently, a prospectively validated prognostic index (FLIPI 2) taking the use of rituximab into account has been established. Age >60 years, haemoglobin <7.5 mmol/l, $beta_2$microglobulin >upper limit of normal, largest node longest diameter >6 cm and bone marrow involvement were identified as adverse factors (R10-6348). The higher the number of risk factors is the poorer the prognosis is. These prognostic markers are commonly used in clinical practice.

Over many decades therapy for aggressive B-NHL has been chemotherapy, often as combination chemotherapy with the gold standard being cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) (P10-13325). Over the last 15 years, the addition of rituximab (anti-CD20 antibody) to chemotherapy (immunochemotherapy) has improved the response rates, progression-free survival (PFS) and overall survival significantly for both DLBCL and follicular lymphoma (R10-4775, P10-13258, P10-13259, R10-6361). Mantle cell lymphoma (MCL) often has an aggressive clinical course remains an essentially incurable disease despite improved therapies (P10-13257). Approximately half of the patients with aggressive B-NHL will not be cured and will eventually die of their disease (R10-4775, R10-4774).

For FL combination chemotherapy, alkylating agents, purine analogs and anthracyclins, together with rituximab is the most frequently used first line therapy. Recently, one trial showed improved progression free survival (PFS) with bendamustine and rituximab compared to R-CHOP in indolent lymphomas (R10-6362). Despite a median overall survival of >10 years (R10-6303) the only curable therapy for FL is allogeneic stem cell transplantation, which constitutes an experimental therapy option for only a minority of the patients (R10-6310).

For patients with aggressive lymphoma, *e.g.* DLBCL, who have relapsed after high-dose therapy and stem cell support or who are ineligible for transplantation, no proven best regimen exists (P10-13007), and treatment options are considered palliative. Primarily refractory patients may respond to alternative chemotherapy, but generally they have a poor prognosis (R10-6351). Treatment with rituximab given as a single agent was reported to yield a response rate of 37% in previously untreated DLBCL elderly patients and patients with relapsed/refractory DLBCL who had not previously been treated with rituximab (R10-6352). A CD22 monoclonal antibody (mAb) (epratuzumab) tested in a dose-escalation trial led to an objective response in 5 out of 33 patients (15%) with relapsed or refractory aggressive NHL (R10-6285). In a similar patient population the CD40 mAb (dacetuzumab) led to an overall response rate (ORR) of 12% (R10-6360). For relapsed FL response rate (RR) decreases and PFS shortens with each additional treatment regimen compared to RR and PFS for first line treatment. For patients with relapse, who are not eligible for high-dose therapy with stem cell support or who relapse after this therapy, there is no gold standard of care (R10-6310). For

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patients who have rituximab refractory disease which may also be chemotherapy refractory, RR is only 11 to 25% with the novel CD20 antibodies, ofatumumab and afutuzumab (R10-6363, R10-6316) and with bendamustine the RR was 77% with a median PFS of 8.3 months (P10-13065).

1.2 DRUG PROFILE

BI 836826 is a mouse-chimeric antibody of the IgG_1 isotype, directed against human CD37.

CD37, a member of the tetraspanin superfamily, is a glycosylated cell surface protein which is predominantly expressed on B cells, with highest expression levels on mature peripheral blood B cells. The CD37 antigen is expressed on the majority of malignant cells in patients with B-NHL and CLL (R08-2979, R08-2943, R08-2981, R08-2945, R08-2942).

The physiological function of CD37 in humans remains unknown (R08-2979, R08-2946). Mice deficient for CD37 display no changes in development and cellular composition of lymphoid organs but have reduced levels of IgG1 and attenuated T-cell mediated immune reactions (R09-5412). Studies with CD37-/- T cells suggest a role for CD37 in T cell proliferation and regulation of IgA response (R09-4740, R09-5414).

BI 836826 has been investigated preclinically; This phase 1 trial is the first trial in humans with B-NHL malignancies, and few others are in the planning phase. There are also additional trials currently ongoing with BI 836826 in patients with chronic lymphocytic leukemia (CLL).

In vitro assays demonstrated that BI 836826 specifically recognizes human CD37 and binds with high affinity to this antigen. The number of BI 836826 binding sites was 53000 for B cells and 1900 for T cells on average, *i.e.* a 28-fold higher expression is seen on B cells. BI 836826 was able to deplete endogenous, normal B cells and Ramos Burkitt lymphoma cells in a human whole blood assay without affecting endogenous T-cells and monocytes. Data from the analysis of primary CLL patient derived blood samples indicates that BI 836826 efficiently depletes malignant CLL cells (R10-6346). BI 836826 is a potent inducer of apoptosis and antibody dependent cellular cytotoxicity (ADCC) and does not show CDC activity (R10-6345). The pro-apoptotic activity of BI 836826 does not depend on IgG cross-linking.

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2. RATIONALE, OBJECTIVES, AND BENEFIT – RISK ASSESSMENT

2.1 RATIONALE FOR PERFORMING THE TRIAL

CD37 is predominantly expressed on B cells, with highest expression levels on mature peripheral blood B cells, reduced levels on plasma cells and low levels on monocytes, T cells, macrophages, and granulocytes (R08-2979, R09-4740, R09-4739). The physiological function of CD37 in humans remains unknown (R08-2979, R08-2946). However, mice deficient for CD37 display no changes in development and cellular composition of lymphoid organs but have reduced levels of IgG_1 and attenuated T cell mediated immune reactions (R09-5412). The majority of malignant cells in patients with B-NHL express the CD37 antigen (R08-2979, R08-2943, R08-2981, R08-2945, R08-2942). Therefore, targeting CD37 in malignancies of B cell origin may offer a new treatment option.

Clinical data of advanced B-NHL patients who were treated with the fully murine CD37 antibody MB-1 are published (R10-2734, R10-2735). In these trials, administration of a radio-immunoconjugate of MB-1 was safe, led to fast and specific B cell reduction, a low degree of T cell reduction and induced tumour shrinkage in advanced B-NHL patients already with tracer doses of the attached isotope.

The anti-CD37 small modular immuno-pharmaceutical (SMIP) TRU-016 was well tolerated in an ongoing phase I trial at doses up to 20 mg/kg in patients with CLL, with predominantly haematological dose limiting toxicities. No formal maximum tolerated dose has been defined (R10-6640).

The clinical experience with MB-1 and TRU-016 supports the assumption that targeting CD37 in the human leads to lymphocyte reduction and consecutive lymph node shrinkage with an acceptable side effect profile.

2.2 TRIAL OBJECTIVES

The primary objective of this trial is to determine the maximum tolerated dose (MTD) of BI 836826 in patients with NHL of B cell origin. BI 836826 is a new biological entity and the maximum planned single dose was1400 mg. However, the MTD has been reached at 100 mg in monotherapy. This dose was declared based on safety demonstrated during the dose escalation which was performed in Caucasian patients. During the expansion phase additional sites were added in South Korea. A total of 4 patients have been enrolled into expansion cohort at 100mg, and all of them were from S. Korea. Three out of 4 Korean patients have developed significant toxicities (infections) which lead to the need of exploring a lower dose levels (50 and 75mg) in a designated escalation cohort of Korean patients to further characterize safety and efficacy of BI 836826 (c02337389-01). Secondary objectives are to document the safety and tolerability of BI 836826, to perform pharmacodynamic analyses and to evaluate relevant biological effects in terms of parameters of efficacy.

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2.3 BENEFIT - RISK ASSESSMENT

Progress in understanding the biologic behaviour of the different subtypes of NHL has been achieved and effective treatment regimens have been developed. However, most patients with indolent NHL and approximately half of the patients with aggressive NHL still die of their disease. In particular, patients with resistant disease, patients who are not considered eligible for high-dose immunochemotherapy, patients with relapse after high-dose immunochemotherapy with stem cell support and patients with rituximab refractory disease have a need for new therapeutic options.

Patients with relapse of aggressive B-NHL, either after high-dose immune-chemotherapy with stem cell support or patients who are not candidates for high-dose therapy (*e.g.* due to comorbidity) are offered immunotherapy, chemotherapy, radiotherapy and/or prednisone. However, these therapies are considered palliative. For patients who are not candidates for allogeneic transplantation and have progression of indolent B-NHL after at least two prior therapies no standard therapy exists. Available treatment options are not curative and response may be limited with short lasting effect. In the clinical setting, the depletion of B cells with BI 836826 may potentially result in an anti-tumour activity as a monotherapy. Further development in combination with other monoclonal antibodies or cytotoxic drugs may be possible in patients with NHL of B cell origin. Targeting CD37 may potentially offer a benefit to the patients, because cross-resistance with prior therapies is not expected.

BI 836826 is a monoclonal antibody which specifically targets CD37. *In vitro*, BI 836826 was able to induce apoptosis and antibody dependent cell mediated cytotoxicity of the target cells. *In vivo* studies in mice and cynomolgus monkeys show depletion of B cells from blood and lymphatic organs.

<u>Human experience with BI 836826</u>
Preliminary data from two ongoing Phase 1 monotherapy trials are available, one in relapsed CLL and the other in relapsed NHL.

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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 836826, and to determine the MTD or to establish the recommended dose for further development.

Single patient cohorts will be treated until a drug-related adverse event of CTCAE grade 2 or higher occurs during the first two weeks of the first treatment course, *i.e.* from first infusion to 7 days after the second infusion. When this occurs the single patient cohort and all subsequent cohorts will be expanded to three patients, following a fixed dose-escalation design with dose de-escalation steps (R04-0569), *i.e.* the single patient cohort will be expanded with 2 additional patients to 3 patients in total. When one patient of the cohort of three patients experiences a dose limiting toxicity (DLT) (for definition see 5.2.1.1), three additional patients will be treated at the same dose level according to a standard 3+3 design. If none of the three additional patients experiences a DLT, then the dose-escalation will be continued by treating the next cohort of three patients at the next higher dose level. If at least two out of up to six patients at a dose level experience a DLT, the MTD has been exceeded and the dose will be de-escalated until a dose level is reached in which at most one DLT out of six patients is observed (R01-0028). At the MTD, no more than one patient out of six patients may experience DLT, *i.e.* the MTD is defined as the highest dose studied for which the incidence of dose-limiting toxicity is no more than 17% during the first 2 weeks of the first course.

During the dose-escalation phase, each patient will receive 1 infusion given once weekly 4 times (days 1, 8, 15 and 22) followed by observation for at least 27 days after the last infusion. Unless the first administration will be split (refer section 4.1). Patients, who are without clinical signs of progression after the first 4 infusions and tolerate the drug well, can receive an additional course with 4 infusions (once weekly) at the same dose in agreement between investigator and clinical monitor of Boehringer Ingelheim. Course 1 and 2 will have duration of 7 weeks each (Figure 3.1: 1). Patients with response or stable disease with clinical benefit (*e.g.* tumour reduction, improvement in disease related symptoms) after the second course can receive a third course of 4 infusions (once weekly) if there is good tolerability of the drug. The third course can only be started after agreement between investigator and clinical monitor of Boehringer Ingelheim. The duration of the third course will be 12 weeks, 4 infusions once weekly followed by 55 days of observation after last infusion. In general, a maximum of 12 infusions is allowed per patient. After the end of treatment (EOT) visit the patients will be followed at least every 6 weeks for up to 6 months after EOT.

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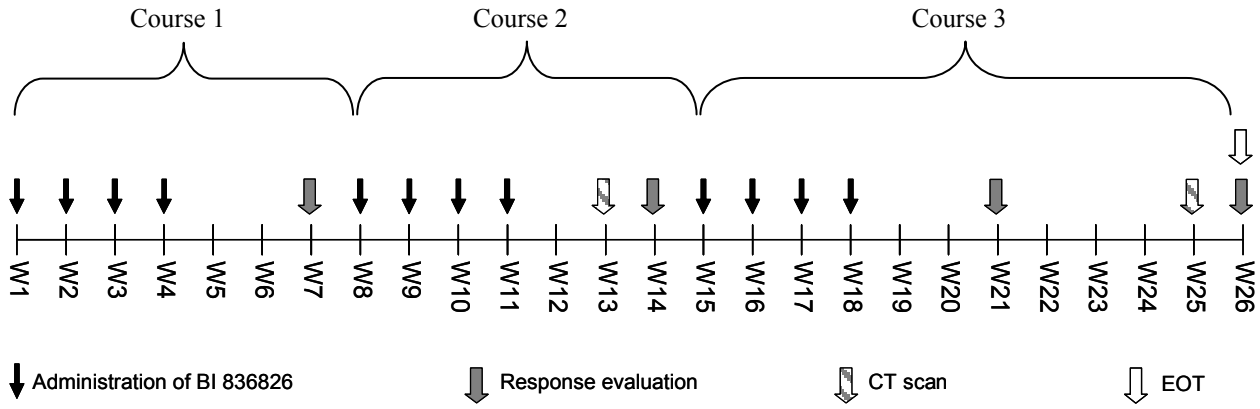

Figure 3.1: 1: Treatment schedule for 1270.2

Enrollment will be sequential during dose-escalation. For early evaluation of adverse events, there will be at least 7 days between each patient within a dose cohort and at least 14 days between the first infusion of the last patient at a dose level and the first infusion to the first patient at the next higher dose level.

Depending on the observed adverse events, dose cohorts on escalating dose levels will be enrolled until the MTD has been defined by the occurrence of DLT (see section 5.2.1.1). Before each dose-escalation, the available data of all previous dose cohorts will be reviewed. The data will also be independently assessed by a data safety monitoring board (DSMB) who will give recommendation for the dose for the next cohort (see section 4.1.3). Once the MTD is defined, a dose for treatment of the expansion cohort will be determined, which will not exceed the MTD. In case an MTD will not be reached at the highest predefined dose of 1400 mg, an OBD may be defined instead. An OBD will be determined by the sponsor of the trial using all available data from safety and pharmacodynamic analyses (*e.g.* depletion of B cells) and efficacy (*e.g.* reduction in tumour size). The dose recommendation for the expansion cohort (either MTD or OBD) will be independently reviewed by the DSMB in the same way as outlined previously for the dose-escalation phase of the trial. The competent authority will receive a summary of all safety findings observed by that time and the recommended dose for the expansion cohort.

After the MTD, it was planned to enroll up to 40 patients into an expansion cohort to better characterize the safety of BI 836826 and to enable a potential adaptation of the recommendation for a phase II dose prior to starting the next trials. Approximately half of the patient population in the expansion cohort was planned to have aggressive NHL and approximately half would have indolent NHL. Preliminary evaluation of efficacy in the expansion cohort was also planned. Due to safety signals in the initial three out of four Korean patients enrolled into expansion cohort at the defined MTD of 100mg, this cohort will be closed for enrollment. Instead, lower dose escalation cohorts of 50mg and 75 mg will be open to test the safety, tolerability in additional Korean patients (3-6 patients per dose level) following the 3+3 design. An initial safety analysis will be performed after the first 3 patients have been enrolled at 50mg. If the number of observed DLTs is 0, the

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dose will be escalated to 75 mg in three additional Korean patients. If there is one DLT observed at 50 mg dose, the 50 mg cohort will be expanded to 6 patients. If none of the three additional patients experiences a DLT, the dose will be escalated to 75 mg. Patients enrolled in the additional cohort of Korean patients will receive the same dosing schedule as described above provided that treatment is considered safe based on the emerging data on safety from patients treated during the dose-escalation phase. No more than one patient can initiate dosing on any given day.

3.1.1 Administrative structure of the trial

Boehringer Ingelheim is the sponsor of this trial. The participating investigators will be physicians experienced and specialized in the treatment of NHL and in the conduct of phase I trials.

A Data Safety Monitoring Board (DSMB) will perform regular safety assessments, provide recommendations for dose-escalation and for continuation, modification or termination the trial. Frequency of meetings, functions and responsibilities of the DSMB will be described in the DSMB Charter.

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

The primary objective of this trial is to determine the MTD. The most important secondary objective is to assess the safety of BI 836826. This can be achieved by an open-label, single arm trial design without a control group.

The investigational drug BI 836826 will be administered as monotherapy. At the lowest dose cohorts, single patients are to be enrolled to limit the number of patients who are receiving doses of the drug which may not exert a relevant pharmacodynamic effect in humans. Stipulated by drug related adverse events CTCAE grade 2 or higher, cohorts of single patients will be expanded to cohorts of at least 3 patients as described in section 3.1, and the trial design will follow a standard 3+3 design with dose-escalation and de-escalation. According to the interim safety analysis of the trial results, the MTD was defined for Caucasian patients to be 100 mg. Once the MTD has been defined for Asian patients the enrollment will be stopped. Given the recent safety signals at 100 mg, the current expansion cohort at MTD of 100 mg will be closed for enrollment after having enrolled 4 patients from S Korea, and a new, small cohort will be open to test the 50 mg and 75 mg dose in Korean patients.

At screening, blood samples are drawn, a physical examination and a routine CT scan are performed, and the patient is evaluated for eligibility in the trial. Bone marrow aspirate/biopsy may be performed at the discretion of the investigator. In case a bone marrow aspirate/biopsy has been performed after the latest therapy before this trial, it should be recorded.

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Clinical disease status will be assessed at screening, at the administration of the first and the last of the 4 infusions and 3 weeks after the last infusion of a respective course with physical examination, clinical assessment of the B-NHL, and blood samples. CT scans in this trial will be performed in accordance with published guidelines for response evaluation in lymphoma (R04-1585) and correspond to the use in clinical practice (section 5.1.2.2). A CT scan will be done prior to treatment (may be performed up to 8 weeks (preferably 4 weeks) prior to first infusion), after 2 courses of treatment, (*i.e.* at week 13 +/- window), and just before the end of treatment (EOT) visit (*i.e.* week 25 +/- window). If the CT scans are not possible or available, magnetic resonance imaging can be used instead. However the same imaging methods should be used consistently throughout the trial. Bone marrow examination, PET scan and additional CT scans will be performed at the discretion of the investigator. Results of CT scan, 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 may occur at the latest at week 26, the patient will enter the follow-up phase. During the follow-up phase, disease status evaluations (physical examination, clinical assessment of lymphoma, and blood samples) should be performed at least every 6 weeks until 6 months after the EOT visit, administration of new anti-lymphoma therapy or death, whatever occurs first. More frequent visits may be indicated, *e.g.* for follow-up of laboratory parameters or adverse events which have not been resolved at the EOT visit.

3.3 SELECTION OF TRIAL POPULATION

3.3.1 Main diagnosis for study entry

The eligible patients for the trial are patients with non-Hodgkin lymphoma of B cell origin, who have progression of disease either after having received high-dose therapy with stem cell support or who are not eligible for high-dose therapy. There is no standard of care for these patients and only minorities of the patients obtain durable responses and/or long progression free intervals with the current available therapies.

3.3.2 Inclusion criteria

1. Patients with relapsed or refractory non-Hodgkin lymphoma of B cell origin (mature B cell lymphoma according to WHO) not considered candidates for intensive anti-lymphoma therapy
2. Patients must have either aggressive NHL and received at least one prior anti-CD20 containing immunochemotherapy or indolent NHL and received anti-CD20 therapy and at least two prior therapies (see appendix 10.2)
   a. Patients with aggressive NHL who have received at least one prior anti-CD20 containing immunochemotherapy and have
      i. relapse/progression and is not considered a candidate for high-dose immunochemotherapy with autologous stem cell support or allogeneic transplantation
      ii. relapse/progression after high-dose immunochemotherapy with autologous stem cell support
      iii. relapse/progression after allogeneic stem cell transplantation if without

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immunosuppression for at least 8 weeks and no evidence of active GvHD (this criterion applies only for the expansion cohort)

b. Patients with indolent NHL who have received anti-CD20 therapy and at least two prior therapies and have
   i. relapse/progression and is not considered a candidate for high-dose immunochemotherapy with autologous stem cell support or allogeneic transplantation
   ii. relapse/progression after high-dose immunochemotherapy with autologous stem cell support
   iii. relapse after allogeneic stem cell transplantation if without immunosuppression for at least 8 weeks and no evidence of active GvHD (this criterion applies only for the expansion cohort)

3. Measurable disease on CT scan with involvement of at least one clearly demarcated lesion ≥2 cm or two or more clearly demarcated lesions of >1.5 cm at longest diameter (this criterion applies only for the expansion cohort)
4. Relapse or progression of disease with an indication for therapy as per investigator's judgement
5. Life expectancy of ≥3 months as per investigator's judgement
6. ECOG Performance Status 0 or1 (see appendix 10.3)
7. Age ≥18 years
8. Written informed consent which is consistent with ICH-GCP guidelines and local legislation

3.3.3 Exclusion criteria

1. Primary central nervous system (CNS) lymphoma or known CNS involvement
2. Prior history of malignancy other than a mature B cell neoplasm according to WHO classification (R10-6296) (except basal cell or squamous cell carcinoma of the skin, or carcinoma *in situ* of the uterine cervix or breast treated with curative therapy) unless the subject has been free of disease and without treatment for at least 5 years
3. Last chemotherapy < 4weeks prior to visit 1
4. Last anti-CD20 therapy (non-radiolabelled) <4 weeks prior to visit 1
5. Last corticosteroid <2 weeks prior to visit 1 unless the dose is ≤10 mg/day prednisolone or equivalent
6. High-dose therapy with stem cell support <6 months prior to visit 1
7. Radio-immunotherapy <3 months prior to visit 1
8. Prior allogeneic stem cell transplant (this criterion applies only for the dose-escalation cohorts)
9. AST or ALT >2.5 x upper limit of normal (CTCAE grade 2 or higher)
10. Total bilirubin >1.5 x upper limit of normal (CTCAE grade 2 or higher)
11. Absolute neutrophil count <1.0 x 10^9/L (without growth factor support)
12. Platelets <25 x 10^9/L (without growth factor support or transfusions)
13. Calculated GFR < 45 mL/min (see appendix 10.5)
14. Proteinuria CTCAE grade 2 or higher

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15. Significant concurrent medical disease or condition which according to the investigator's judgement 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 with the exception of extra systoles or minor conduction abnormalities
16. Chronic or ongoing infection requiring treatment at the time of enrolment or within the previous two weeks
17. Active hepatitis B or hepatitis C, or laboratory evidence for a chronic infection with hepatitis B or C (see 5.2.3.3.1)
18. HIV infection
19. CMV viraemia
20. 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, some 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 sterilised by hysterectomy or bilateral tubal ligation/salpingectomy, or postmenopausal for at least two years
21. Pregnancy or breast feeding
22. Known or suspected active alcohol or drug abuse as per investigator's judgment
23. Treatment with another investigational drug within the past four weeks before start of therapy or concomitantly with this trial
24. Prior treatment with BI 836826
25. Patients unable to comply with the protocol as per investigator's judgement

3.3.4 Removal of patients from therapy or assessments

3.3.4.1 Removal of individual patients

A patient has to discontinue trial drug administration in case

- A DLT occurs which does not recover to a degree that allows treatment continuation (see 4.1.4.3)
- Progressive disease or any other concomitant diagnosis/symptom develops resulting in an indication to start any other therapy for lymphoma, including deterioration of general condition

An individual patient is to be withdrawn from trial in case

- The patient withdraws consent. Patients are free to discontinue their participation in this trial at any time without the need to justify the decision
- The patient needs concomitant drugs that may interfere with the investigational product (please refer to section 4.2.2)

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- The patient is no longer able to participate for other reasons (*e.g.* adverse events unrelated to therapy or disease progression, concomitant diagnoses, pregnancy, surgery or administrative reasons). The investigator may also stop a patient's participation if the patient is unable to attend trial visits

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

All withdrawals will be documented and the reason for withdrawal recorded and discussed, as necessary, in the final report of the trial. As soon as a patient is withdrawn from the trial, the EOT has to be performed if feasible (see Flowchart for Course 3). Every effort should be made to follow-up patients in case an AE is still ongoing at the time of withdrawal.

Patients who have not completed at least two administrations will be replaced at the same dose level.

Patients who terminate trial treatment due to DLT will not be replaced.

3.3.4.2 Discontinuation of the trial by the sponsor

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

1. Violation of GCP, the clinical trial protocol (CTP), or the contract by a trial site or investigator, disturbing the appropriate conduct of the trial
2. Emergence of any efficacy/safety information that could significantly affect continuation of the trial
3. Failure to meet expected enrolment goals overall or at a particular trial site

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

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4. TREATMENTS

4.1 TREATMENTS TO BE ADMINISTERED

BI 836826 will be administered as an intravenous infusion. The first course of treatment has a duration of 7 weeks which starts with one infusion weekly 4 times followed by 27 days of observation after the 4th infusion (Figure 3.1:1), unless the split first dose administration described below will be implemented. A second course similar to course 1 can be administered, if the drug is well tolerated and the patient has no clinical signs of progression, judged by the treating physician. An additional third course of 4 weekly administrations can be given to the patients with response (*i.e.* complete or partial remission) and patients with stable disease, who tolerate the drug well and have clinical benefit. Clinical benefit can be improvement of clinical symptoms, and/or reduction in tumour size not meeting the criteria for a partial remission at the response assessment at the end of the second course.

The first infusion in each course should be started at a rate of 10 mL/h. The infusion rate can be increased every 30 (+/-10) minutes by 10 mL/h to a maximum of 80 mL/h as long as tolerated by the patient. If considered safe by the investigator, the subsequent infusions may be given with shorter interval for increasing the rate, but the maximum rate should not exceed 120 mL/h.

If adverse events which are considered related to the infusion schedule, *e.g.* infusion-related reaction, are not well controlled by the above schedule an alternative administration will be used. The first administration in course 1 will be split into two infusions, a low dose on day 1 followed by the full dose on the day 2. The first part of the administration will be 10% of the full dose, but not exceeding 10 mg given on day 1. The day after the second part of the administration will be the full planned dose for the patient (please refer the flowchart in section 10.7). The same infusion schedule should be employed as described above, starting with a rate of 10 mL/h. Premedication is mandatory before both infusions as they will be considered as the first administration (section 4.1.4.1.1.). The potential change of the first infusion into two infusions will be assessed and may be modified by the DSMB. In subsequent administrations, the full dose of BI 836826 will be administered as a rate-controlled intravenous infusion on day 1.

If symptoms of an infusion related reaction occur, the infusion should be temporarily stopped. Upon recovery, it should be resumed at 50% of the rate at which the reaction occurred for at least 30 minutes. Lower rates may be selected if clinically indicated. Depending on the time of occurrence and the severity of the reaction, the investigator may consider administering additional supportive medication, e.g. corticosteroids. A stepwise re-increase of the infusion rate to a maximum of 80 mL/h is possible.

For medical reason, the duration of the infusion may be expanded until the use-by date and use-by time indicated on the label is reached. The actual duration of the infusion needs to be documented in the eCRF including actual start and end time, actual time points for interruption and restart of the infusion and the actual infusion rates.

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

4.1.1 Identity of BI investigational product and comparator product

Substance (INN):	BI 836826
Pharmaceutical form:	Solution for infusion after dilution
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Unit strength:	10 mg/mL (vials with 10 mL)
Daily dose:	See section 4.1.3
Duration of use:	Single dose or split dose (2 doses) only applicable for course 1 once weekly for 4 times followed by 27 days of observation after last administration, *i.e* 7 weeks = course 1. A similar additional course 2 can be given, if drug is well tolerated and no signs of progression. For patients with remission or stable disease with clinical benefit additional weekly infusion for 4 times followed by 55 days of observation can be administered (course 3). Maximum 12 infusions = 3 courses. Further infusions only after agreement between sponsor and investigator on a case by case
Route of administration:	Intravenous
Posology:	Rate controlled infusion See Section 4.1.6

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 sections 4.1.3 and 4.1.4.

4.1.3 Selection of doses in the trial

BI 836826 will be administered as a rate-controlled, intravenous infusion..

A fixed dose of 1 mg BI 836826 per patient is expected to be the safe first in human starting dose for patients with an advanced haematological malignancy. The calculation of the safe starting dose of 1 mg in humans was based on data from studies in cynomolgus monkeys and from *ex vivo* experiments with primary B cells obtained from fresh blood samples of CLL patients. This dose is anticipated to represent a low pharmacologically active dose which may be capable to result in a detectable B cell reduction in the peripheral blood. For details please refer to the Investigator's Brochure, section 5.3.6 (c01715907-08).

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The dose was planned to be escalated in cohorts at predefined dose levels based on a multiplication factor of approximately 3 in the low dose range (1-25 mg), a factor of 2 at doses of 25-800 mg and from the dose of 800 mg and onwards additional 200 mg per dose. The dose levels were initially planned to be: 1 mg, 3 mg, 9 mg, 25 mg, 50 mg, 100 mg, 200 mg, 400 mg, 800 mg, 1000 mg, 1200 mg and 1400 mg, however the MTD was established at 100mg based on safety data from Caucasian patients. An additional cohort of Korean patients will be tested at 50 and 75mg.Every time a dose-escalation is to be performed, all patients at the last cohort must have had 2 infusions of BI 836826 and at least 7 days observation after the second infusion. The available data of all previous dose cohorts will be reviewed. The data will be provided to the DSMB who will be asked to provide an independent assessment including the dose recommendation for the next cohort. As a result, lower dose increments than the predefined levels will be possible.

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. In the dose-escalation phase there will be at least 7 days between first dose for patients in the same dose cohort and at least 14 days between first dose for last patient and first dose for first patient in different dose cohorts. 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 836826 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. Enrollment will only be possible after the sponsor has notified the site by written confirmation of the dose and earliest possible date of first administration.

BI 836826 will be administered as an intravenous infusion under the supervision of the investigator or designated personnel.

BI 836826 may be administered at any time during the day. However, to facilitate blood sampling for and pharmacodynamic analyses, it is recommended to start the infusion during the morning hours.

4.1.4.1 Prophylactic measures

4.1.4.1.1 Premedication

Premedication is mandatory 30-120 minutes prior to the administration of BI 836826 to prevent/reduce severity of infusion-related reactions, unless a contraindication for premedication exists. The premedication for the first and the second administration of the first course should include

- Acetaminophen/paracetamol 1000 mg p.o. or a clinically comparable dose, or equivalent
- Antihistamine *p.o.* or *i.v.*, equivalent to diphenhydramine 50 mg *i.v.*
- Glucocorticoid *i.v.*, equivalent to prednisolone 100 mg

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If BI 836826 has been well tolerated without signs of infusion-related reactions during the second administration, glucocorticoid premedication may be reduced to 50% of the administered dose starting with the third administration, *i.e.* glucocorticoid i.v., equivalent to prednisolone 50 mg at third administration and glucocorticoid i.v., equivalent to prednisolone 25 mg at fourth administration.

If a second and third course of 4 administrations is initiated, the premedication dose has to be repeated with glucocorticoid i.v., equivalent to prednisolone 100 mg at the first and second administration of BI 836826. If the infusion is well tolerated, glucocorticoid i.v. can be reduced as described above.

4.1.4.1.2 Monitoring for infusion-related reactions

Close monitoring of the patient during and after the infusion of BI 836826 is required for evaluation of infusion-related risks. The measures of monitoring include:

- Hospitalization of patients with access to intensive care
- Frequent measurements and documentation of blood pressure and heart rate (see section 5.2.5.1)

During the treatment the patients are required to be hospitalized under close surveillance with access to intensive care for at least 48 hours during the first infusion of BI 836826 and at least 24 hours during the second infusion (both in course 1). Hospitalization is also required for at least 24 hours during the first infusion in course 2. If there is no relevant infusion-related adverse events, the decision to hospitalize the patient is left to the discretion of the investigator.

If the split first dose administration is employed patients are required to be hospitalized under close surveillance with access to intensive care for at least 72 hours for the 1st visit in course 1 and at least 24 hours during the second infusion in course 2. Hospitalization is required for at least 24 hours during the first infusion in course 2. In case of no relevant infusion-related adverse events, the decision to hospitalize the patient is left to the discretion of the investigator.

4.1.4.1.3 Tumour lysis syndrome

All patients have to be monitored for clinical or laboratory evidence of tumour lysis syndrome (see section 5.2.3.2). To prevent tumour lysis syndrome, all patients should receive appropriate hydration and allopurinol 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 5.2.3.2.CTCAE 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 (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).

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4.1.4.2 Handling of infusion-related reactions

In case of an infusion-related reaction, 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. The time between start and end of infusion may not exceed 24 hours. In case management of an infusion-related reaction would require more than 24 hours between start and end of the infusion of BI 836826, the infusion has to be stopped at 24 hours and the residual solution has to be discarded. The actual dose which has been administered prior to reaching this time limit has to be documented.

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

Infusion-related reactions CTCAE grade 3 and 4 are defined to be significant adverse events 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 may be considered by the investigator as guidance:

- In the case of an infusion-related reaction CTCAE grade 1, the infusion rate of BI 836826 should be reduced, *e.g.* to 50% of the target rate, or the infusion should be temporarily interrupted and resumed as soon as considered clinically manageable by the investigator.
- In the case of an infusion-related reaction CTCAE grade 2 or 3, the infusion with BI 836826 should be stopped immediately. Only in case all symptoms have resolved, administration of BI 836826 may be resumed. The investigator may consider to re-start at a slower infusion rate, *e.g.* of 50% of the target rate, and increase the infusion rate as tolerated to the target rate.
- In the case of an infusion-related reaction CTCAE grade 4, the infusion has to be stopped immediately. These patients should not be re-exposed to BI 836826 after the event.

4.1.4.3 Management of infections:

During treatment with BI 836826 patients need to be carefully monitored for infections at each clinic visit. Frequent blood counts monitoring will help to identify patients with prolonged neutropenia who might be at risk for severe infections. It is highly recommended that the treatment of infection starts immediately upon very first clinical symptoms. Depending on investigators' assessment the use of growth factors, antibiotics, antifungals, and antivirals should be considered, and implemented with no delay. The next administration of BI 836826 needs to be delayed until the patient has cleared an infection and has recovered from neutropenia as outlined in sec: 4.1.4.4

4.1.4.4 Continuation of Treatment during a Course, or beginning a new course

Adverse events and laboratory values will be evaluated continuously by the sponsor. Prior to each administration of BI 836826, adverse events and safety laboratory will be assessed. To

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continue treatment with a further infusion of BI 836826, all of the following criteria must be met:

(1) No active infection

(2) Neutrophils ≥1000 /µL (1.0 x 10^9/L) and platelets ≥25.000 /µL (25 x 10^9/L), with or without growth factor support or transfusions.

(3) no evidence of progressive disease

(4) 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 grade 1 or pre-treatment value.)

In case criterion 1 and/or 4 is not fulfilled, blood counts and/or the adverse event should be re-evaluated for up to three weeks. A delay during a course should be communicated to the clinical monitor at Boehringer Ingelheim. As soon as all criteria 1-4 are met, the investigator in agreement with the clinical monitor at Boehringer Ingelheim may continue the treatment (unless other criteria for discontinuation or withdrawal apply, see section 3.3.4.1). If a visit with administration of BI 836826 is delayed, all subsequent visits with treatment administration will be recalculated based on the actual date of delayed visit. If a visit is delayed less than 5 days, the delay may be caught up by shortening the observation period of the course after agreement between investigator and clinical monitor of the trial, provided that patient fulfills all the requirement for the next treatment (see section 6.1).

In case an adverse event is continuing at a CTCAE grade 2 or higher without recovery to grade 1 within 5 weeks after the last BI 836826 infusion and this is above the pre-treatment level, the investigator in agreement with the clinical monitor at Boehringer Ingelheim may continue BI 836826 only in the case that the event is considered not drug-related by investigator and sponsor.

Administration of the trial drug has to be stopped temporarily in case of a DLT (see section 5.2.1.1). Patients may continue therapy only after recovery from the DLT to at least CTCAE grade 1 or pre-treatment value. The future dose of BI 836826 must be finally agreed on between the sponsor and the investigator. A reduction of the dose will be allowed only once for an individual patient during the whole trial. Treatment has to be discontinued in case the DLT is not reversible.

Intra-patient dose-escalation of BI 836826 will not be allowed in this trial.

During the dose-escalation phase, the first course (4 administrations as weekly infusions) should be given to all patients. In absence of clinical progression judged by the investigator, treatment with BI 836826 can be continued for the second course, (*i.e.* another 4 administrations) in agreement with the investigator and the clinical monitor of the sponsor. Patients with a complete or partial remission by CT scan after 8 administrations or stable disease with improvement in clinical symptoms may receive additional 4 administrations weekly as consolidation therapy after discussion between the investigator and the clinical

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monitor of the sponsor. Continuation of BI 836826 beyond 12 administrations will only be possible on a case by case basis after discussion between the investigator-and the clinical monitor of the sponsor.

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.

4.1.5 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 refractory NHL of B cell origin. 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 836826 will be supplied in 10 mL vials containing 100 mg BI 836826. For details of packaging and the description of the label, refer to the ISF. Medication will be delivered to the investigator's pharmacy where the total dose per patient will be prepared upon request from the investigator.

For preparation of the BI 836826 infusion solution, the content of the vial of BI 836826 will be diluted in 0.9% sodium chloride. The content of several vials may be needed for administration of the requested dose. For further details, please refer to instructions included in the ISF.

4.1.7 Storage conditions

BI 836826 has to be stored in a limited access area at the temperature indicated on the trial drug label. 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 836826, please refer to the IB (c01715907-08) and the ISF.

4.1.8 Drug accountability

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

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

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

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

4.2 CONCOMITANT THERAPY, RESTRICTIONS, AND RESCUE TREATMENT

4.2.1 Rescue medication, emergency procedures, and additional treatment

4.2.1.1 Rescue medication

Rescue medication in term of an antidote to reverse the action of BI 836826 is not available. Potential side effects of BI 836826 have to be treated symptomatically.

4.2.1.2 Supportive care

Patients should receive supportive care according to local guidelines regarding treatment of infusion-related reactions (section 4.1.4.2 and section 5.2.5.1), infections, blood product support, analgesics, skin and mouth care, etc.
In the case of a tumour lysis syndrome, supportive therapy including rasburicase may be used as clinically indicated at the investigator's discretion (section 5.2.3.2).

4.2.1.2.1 Antibiotics and Antivirals

Prophylactic antibiotics and antivirals are allowed. For patients who are considered to have an increased risk for herpes and/or pneumocystis jiroveci infections, the prophylaxis is mandatory, unless medically contraindicated (see below). For patients who are considered to have an increased risk for other infections, prophylactic therapy is recommended, unless medically contraindicated.

Prophylactic antiviral therapy is mandatory for patients with a history of recurrent herpes virus infections, herpes infection during previous anti-lymphoma therapy, neutropenia and/or low CD4+ cell counts (<200 cells/µl), *e.g.* acyclovir 400 mg three times a day orally.

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Prophylactic antiviral therapy (*e.g.* nucleoside reverse transcriptase inhibitor) and/or monitoring of hepatitis B DNA in the blood is recommended for patients with a history of hepatitis B infection.

Prophylaxis against pneumocystis jiroveci, *e.g.* oral trimethoprim/sulfamethoxazole 800 mg/160 mg every other day is mandatory to patients who are considered at increased risk, *e.g.* patients with low CD4+ cell counts (<350 cells/µl).

Infections should be treated early, i.e. at the first clinical signs, with a broadband antibiotics, and other agents (antivirals, antifungals, growth factors), as deemed appropriate by the investigator. The investigators are expected to apply treatment according to local guidelines/standard.

4.2.1.2.2 Growth factors

The use of growth factors such 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 weeks for better assessment of safety parameters.

Prophylactic antibiotics and antiviral drugs are allowed during therapy.

4.2.1.3 Concomitant medication

All concomitant therapies to provide adequate care may be given as clinically necessary, unless given as anti-lymphoma therapy. All concomitant treatments should be recorded in the eCRF except for vitamins or nutrient supplements. Trade name, indication and dates of administration of concomitant therapies will be documented. For parenteral nutrition during the trial, the components need not to be specified in detail. It should just be indicated as 'parenteral nutrition'. If a patient needs 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 the EOT visit, only concomitant therapy indicated for treatment of an adverse event has to be reported or if given as new anti-lymphoma therapy.

CMV reactivation during treatment should be treated according to local standards or available guidelines (R10-4431).

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

Prior therapies for lymphoma must have been discontinued at least of two weeks before the first administration of the trial drug (see exclusion criteria section 3.3.3 for details) and the patient must have recovered from all clinically relevant reversible toxicities. A time interval

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of at least four weeks must have elapsed from the last administration of any other investigational treatment for NHL to the first administration of BI 836826.

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 (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.

Immunoglobulins may not be used within four weeks prior to the first trial infusion and two weeks after the last infusion of BI 836826.

4.2.2.2 Restrictions on diet and life style

No restrictions apply with regard to diet or life style.

4.3 TREATMENT COMPLIANCE

BI 836826 will be administered as a single intravenous infusion under supervision of the investigator or dedicated clinic personnel.

Any discrepancies will be explained in the CRF by the investigator or his/her deputy.

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5. VARIABLES AND THEIR ASSESSMENT

5.1 EFFICACY

5.1.1 Endpoints 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 this trial.

Secondary endpoints of efficacy are:

- Tumour size reduction (lymph nodes, spleen and liver nodules) defined as best % change from baseline in SPD (all lymph nodes, only spleen nodules, only liver nodules) from CT scan data
- Best overall response according to Standardized or Revised Response Criteria for Malignant Lymphoma (R04-1585) (see section 5.1.2.2)
- Progression free survival
- Failure free survival

5.1.2 Assessment of efficacy

5.1.2.1 Tumour size

Tumour size of lymph nodes, spleen and liver, nodules will be measured throughout the trial. Nodal, spleen, liver and other locations amenable to clinical examination should be assessed at indicated time point as well as by CT scans (see flowcharts). The tumour size of the lymph nodes will be measured as sum of products of diameter (SPD) of two perpendicular dimensions for up to 6 indicator lesions identified at baseline CT scan. Spleen and liver will be described, if considered enlarged at baseline by physical examination or CT scan. If nodules are present in spleen and/or liver, the diameter of these will be measured in two perpendicular dimensions. The change in SPD, spleen and liver nodules will be compared to baseline and will be listed by time point.

CT scan description will rely on the description by the local radiologist at the investigational site.

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5.1.2.2 Assessment and definition of overall best response

CT scan will be required for response assessment. CT scan will be performed at screening, at week 13 and week 25. A CT scan may be performed at end of treatment if therapy terminates earlier, *e.g.* to document progression. Bone marrow biopsy/aspirate may be performed as indicated by the investigator, but it will not be mandatory. The best response at any of CT scans done will be overall best response. Response will be assessed according to the standardized response criteria from 1999 (R04-1585).

5.1.2.2.1 Complete remission

Complete remission (CR) requires complete disappearance of all evidence of disease.

1. Complete disappearance of all detectable clinical and radiographic evidence of disease and disappearance of all disease-related symptoms if present before therapy and normalization of those biochemical abnormalities definitely assignable to NHL
2. Absence of significant lymphadenopathy, *i.e.* lymph nodes ≤1.5 cm at the greatest transverse diameter for nodes >1.5 cm before therapy. Nodes between 1.1 and 1.5 cm at the long axis and >1 cm at the short axis before therapy must have decreased to ≤1.0 cm in their short axis
3. Spleen, if enlarged by CT scan before therapy, must have regressed in size and must not be palpable on physical examination
4. Other organs considered enlarged before therapy due to lymphoma must have regressed in size
5. Bone marrow aspirate and biopsy demonstrate absence of residual disease (if performed)

5.1.2.2.2 Complete remission unconfirmed

To have CRu the patients have to fulfil criteria 1 and 3 and 4 under 5.1.2.2.1 and at least one of the following features.

1. A residual lymph node mass greater than 1.5 cm in greatest transverse diameter that has regressed by more than 75% in their SPD. Individual nodes that were previously confluent must have regressed by more than 75% in their SPD compared to the size of original mass
2. Indeterminate bone marrow (increased number or size of aggregates without cytologic or architectural atypia)

5.1.2.2.3 Partial remission

Partial remission (PR) requires all of the following.

1. Decrease of at least 50% in SPD of up to six of the largest dominant nodes or nodal masses
2. No increase in size of other nodes or liver or spleen

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3. Hepatic and splenic nodules must have regressed by ≥50% in SPD or in the greatest transverse diameter for single nodules
4. Disease in other organs are considered assessable and not measurable disease
5. No new sites of disease should be observed

5.1.2.2.4 Stable disease

Stable disease (SD) is defined as failure to attain the criteria for a CR, CRu or a PR and does not fulfil those for progressive disease.

5.1.2.2.5 Relapsed disease (after CR, CRu)/ Progressive disease (after PR, SD)

At least one of the following criteria is required:

- Any new lesion >1.5 cm in any axis
- Increase of ≥50% from nadir in SPD of any previously involved nodes or single nodes or the size of hepatic or splenic nodules. A lymph node with a diameter of the short axis of <1 cm must increase by ≥50% and to a size of 1.5 x 1.5 cm or more than 1.5 cm in the long axis
- ≥50% increase in the longest diameter of any single previously identified node >1 cm in its short axis

5.1.2.3 Progression free survival

PFS is defined as the time from first treatment with BI 836826 until disease progression or death.

5.1.2.4 Failure free survival

Some patients will receive a next line of therapy, although no formal PD may have been diagnosed at the time when the next treatment is indicated according to investigator assessment. In addition to PFS, the failure free survival (FFS) will be calculated to assess this group of patients. FFS is defined as the time from first treatment with BI 836826 until objective disease progression or death or start of next lymphoma therapy.

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5.2 SAFETY

5.2.1 Endpoints of safety

The primary objective is to assess the safety of the drug in humans and to determine the MTD of BI 836826. If an MTD is not reached, an OBD may be defined. For details on determination of MTD/OBD, please refer to sections 3.1, 5.2.1.1 and 7.3.1.

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The safety of BI 836826 will be assessed by a descriptive analysis of incidence and intensity of adverse events graded according to CTCAE (version 4.0), the incidence dose limiting toxicity (DLT), laboratory data and results of physical examination.

An independent DSMB will review the safety data 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 grade 3 or higher, except infusion-related reactions associated with the administration of BI 836826.

Complications resulting from haematological adverse events, e.g. bleeding due to thrombocytopenia or infection due to neutropenia are classified as non-haematological adverse events and are covered by the above definition of DLT. Nevertheless, haematological adverse events, e.g. neutropenia, thrombocytopenia and anemia will be considered for definition of the dose for further development.

The MTD will be defined on the basis of DLT observed during the first 2 weeks of the first treatment course. In case of a delay of the second administration, evaluation of DLT should be prolonged to 7 days after the second administration. However, for those patients who receive more than two doses of BI 836826, all adverse events corresponding to the above definition of DLT will be considered for the purpose of confirming the MTD and for the selection of the recommended dose for treatment of the expansion cohort and for further development. In regular intervals, all available safety data including adverse events qualifying for DLT will be submitted to the DSMB. The DSMB will independently assess this information and provide recommendations for trial conduct and dose-escalation.

5.2.2 Assessment of adverse events

5.2.2.1 Definitions of adverse events

Adverse event

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

Protocol-specified significant adverse events

A protocol-specified significant adverse event is defined as an adverse event which is of particular concern for safety monitoring within this trial. These adverse events need to be handled by the investigator according to the rules defined for SAE reporting. “Significant” in this context is a regulatory term that is not related to a clinical assessment. Based on

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preclinical data and experience with other monoclonal antibodies significant adverse events defined for this trial are:

- Infusion-related reactions (CTCAE grade 3 or higher)
- Tumour lysis syndrome
- Any event that qualifies for DLT (refer to 5.2.1.1)
- DILI
  Although rare, drug-induced liver injury (DILI) is under constant surveillance by sponsors and regulators and is considered a protocol-specified significant adverse event. Timely detection, evaluation, and follow-up of laboratory alterations of selected liver laboratory parameters to distinguish an effect of the underlying malignancy on liver function from other causes such as DILI are important for patient safety. The following are considered as Protocol-specified significant events: Hepatic injury defined by the following alterations of liver parameters:

  - For patients with normal liver function (ALT, AST and bilirubin within normal limits) at baseline an elevation of AST and/or ALT ≥3 fold ULN combined with an elevation of bilirubin ≥2 fold ULN measured in the same blood draw sample. Patients showing these lab abnormalities need to be followed up according to Appendix 10.6 of this clinical trial protocol and the "DILI checklist" provided in the ISF.

  - For patients with impaired liver function at baseline an elevation of AST and/or ALT >5 fold ULN combined with an elevation of total bilirubin >2 fold ULN measured in the same blood draw sample. Patients showing these lab abnormalities need to be followed up according to Appenddix 10.6 of this clinical trial protocol and the “DILI checklist” provided in ISF.

Protocol-specified significant adverse events are to be reported in an expedited manner similar to Serious Adverse Events, even if they do not meet any of the seriousness criteria - for details see section 5.2.2.2. If the investigator determines any protocol-specific significant adverse event is related to study drug, the administration of the study drug must be managed according to section 4.1.4 of the protocol.

Serious adverse event

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

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Intensity of adverse event

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

Causal relationship of adverse event

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

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.

Worsening of the underlying disease or other pre-existing conditions

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

If progressive disease occurs and is associated with symptoms or meets one of the seriousness criteria, the verbatim "Progressive Disease" should not be reported, instead the signs and symptoms of progressive disease will be reported as an adverse event or a serious AE (if applicable). The only exception to the above is in the event of death when attributed to progressive disease but where signs and symptoms are not available. In this situation it is acceptable to report the progression as the serious AE with the term Neoplasm Progression.

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

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

5.2.2.2 Adverse event and serious adverse event reporting

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

All adverse events, serious, protocol-specified and non-serious, occurring during the course of the clinical trial (*i.e.*, from signing the informed consent onwards through the observational phase (up to 8 weeks after last drug administration), table 5.2.2.2:1) will be collected, documented and reported to the sponsor by the investigator on the appropriate eCRFs / SAE reporting forms. Reporting will be done according to the specific definitions and instructions detailed in the 'Adverse Event Reporting' section of the Investigator Site File.

For each adverse event, the investigator will provide the onset date, end date, intensity/ CTCAE grading (according to CTCAE, version 4.0, (R10-4848) treatment required, outcome,

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seriousness, and action taken with the investigational drug. The investigator will determine the relationship of the investigational drug to all AEs as defined in section 5.2.2.1.

All AEs, including those persisting at the End of Treatment (EOT) visit must be followed until recovery or in case of persistence, sufficient characterization has been achieved and the clinical monitor and the investigator agree to not pursue them further.

SAEs and any trial drug related AE grade 3 still ongoing after the end of trial have to be followed until recovery or assessed to be chronic or stable by the investigator.

Table 5.2.2.2:1 AE/SAE reporting requirements

Time Period	Reporting requirements
From signature of informed consent until 8 weeks after last administration of study drug	Report all AEs, SAEs regardless of relatedness. This includes all deaths.
Post treatment (>8 weeks after last administration of study drug) until end of follow-up (6 months after the end of treatment visit)	Report AEs and SAEs which are considered related to study drug or study design / procedures. Please note: All events leading to death should always be reported as SAE in this trial.
After the individual patient's end of the trial	The Investigator does not need to actively monitor the patient for AEs but should only report relevant SAEs and relevant AESIs of which the Investigator may become aware of.

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 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 or the next business day whichever is shorter) 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 significant events. 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.
- Protocol defined significant AEs, *i.e.* infusion-related reactions CTCAE grade 3 or higher, tumour lysis syndrome and events qualifying for a DLT (see sections 5.2.1.1 and 5.2.2.1)

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

Pregnancy

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

5.2.3 Assessment of safety laboratory parameters

5.2.3.1 General safety laboratory parameters

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

Haematology	Haemoglobin, red blood cell count (RBC), white blood cell count (WBC) with differential, platelets (PLT) Reticulocytes have to be measured only at visit of the first and last administration of each treatment course, at the EOT visit and during follow-up.
Biochemistry	Glucose, sodium, potassium, 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 Serum immunoglobulin levels (IgG, IgM, IgA), direct antiglobulin test have to be measured only at visit of first and last administration of each treatment course, at the EOT visit and during follow-up.
Coagulation	Activated partial thromboplastin time (aPTT), prothrombin time (PT)/international normalised ratio (INR)

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Urine	pH, glucose, erythrocytes, leukocytes, protein, nitrite will be analysed by dipstick and reported as semiquantitative measurements. In case of pathological findings, further evaluation should be performed and results documented.
Pregnancy test	A serum pregnancy test needs to be obtained at the time points indicated in the 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.

5.2.3.2 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. During the first 48 hours after the start of the first infusion of BI 836826 in course 1, and during the first 24 hours after the start of the second infusion in course 1 and of the first infusion 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. Monitoring for TLS of the second infusion of course 2 and the first and second infusion of course 3 are be performed while the patient is in hospital. In case of the split first dose administration the same parameters need to be determined during the first 72 hours after the start of the low dose of BI 836826 in course 1, and for other infusions the monitoring should be as above described. 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

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5.2.3.3 Virology

5.2.3.3.1 Screening for hepatitis B, hepatitis C, cytomegalovirus 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.

Cytomegalovirus serology (CMV IgG and IgM) should be included in this assessment to allow for differentiation between a primary CMV infection and reactivation of CMV during the trial.

5.2.3.3.2 CMV monitoring

Monitoring of CMV has to be performed at the time points indicated in the flowchart according to local standards. Quantitative PCR assays to detect CMV DNA are considered acceptable for the purpose of this trial. The same method should be used for all treated patients in the same investigational site. Results have to be reported in the eCRF.

5.2.3.4 Lymphocyte typing

At the time points indicated in the flowchart, lymphocyte sub-populations (B cells**,** CD4+ T cells, CD8+ T cells, NK cells) will be quantitatively analysed by standard flow cytometry protocols in a specialized laboratory either at the investigational site or at a centralized laboratory. Detailed instructions are included in the laboratory manual in the ISF. Results have to be reported in the eCRF.

5.2.4 Electrocardiogram

A 12-lead resting ECG will be performed in all patients at the screening visit and at the EOT visit. The ECG will be assessed for pathological results (to be recorded as either concomitant disease or AE) by the investigator. Additional examinations should be done whenever the investigator deems necessary.

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5.2.5 Assessment of other safety parameters

5.2.5.1 Vital signs

Blood pressure, pulse rate and temperature have to be recorded at each visit. At visits with infusion of BI 836826 measures have to be recorded prior to the start of premedication and infusion of BI 836826. Additional time points at which blood pressure and pulse rate have to be documented are every 30 (±10) minutes after start of the infusion of BI 836826, and 60 (±10) minutes after the end of the infusion, thereafter every 4-8 hours: For the first infusion in course 1 monitoring has to be until at least 48 hours after the start of the infusion. For the second infusion in course 1 and the first infusion in course 2 monitoring has to be until at least 24 hours after the start of the infusion. In case of the split first dose administration monitoring has to be at least 72 hours after the start of the low dose.

Patients have to be monitored by means of an automated monitoring device for continuous ECG-monitoring and non-invasive intermittent blood pressure monitoring with alarming function during the infusion. Since infusion-related reactions are expected to occur mainly during the first and second administration (as documented for other monoclonal antibodies used for treatment), intensive surveillance with the automated monitoring device should be continued for 24 hours after the start of the first and second infusions in the first course. Depending on the tolerability of the infusion, the investigator should decide whether to prolong and/or intensify monitoring. Monitoring has to be adequately documented in source documents.

For patients who did not experience infusion-related reactions CTCAE grade 2 or higher during previous infusions, the automated monitoring and vital sign documentation can be shorten in duration beyond 60 (±10) minutes after the start of infusion as clinically appropriate jugded by the investigator. However, this only applies to the 2nd to 4th infusion of the 2nd and 3rd treatment course.

5.2.5.2 Physical examination

A physical examination including weight
will be performed at screening and at the time points specified in the flowchart. During the physical examination, the patient should be assessed for possible adverse events.

5.3 OTHER

5.3.1 Other endpoints

Exploratory evaluation of the parameters outlined in section 5.3.2 will be performed in this trial, without being defined as formal endpoints.

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5.3.2 Other assessments

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 NHL (month and year may be sufficient) will be recorded in the eCRF. The Ann Arbor stage at diagnosis and at screening should be recorded (see appendix 10.4). 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 (complete remission, partial remission, stable disease, progressive disease, unknown) and the date of progression after each prior therapy (year and month may be sufficient). If the patient has received chemotherapy with autologous or allogeneic 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). Previous surgeries within the past five years should be recorded. In addition, any previous surgery, which may affect tumour assessment in this trial according to the investigator, *e.g.* splenectomy or removal of lymph nodes, 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.

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5.4 APPROPRIATENESS OF MEASUREMENTS

Determination of MTD (or an OBD/recommended dose for further development) is based on toxicities graded according to CTCAE (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 are well established (R04-1585).

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6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

During the treatment phase, patients are required to be hospitalized under close surveillance with access to intensive care for at least 48 hours after the first dose of BI 836826 to allow close monitoring for infusion-related reactions, tumour lysis syndrome or other adverse events. In case of the split first dose administration patients are required to be hospitalized for at least 72 hours after the start of the low dose of BI 836826. If the first administration of BI 836826 was well tolerated by a patient the investigator may evaluate the risk for an infusion-related reaction and other adverse events in view of relevant comorbidities or disease-related symptoms, and as a result, shorten the duration of surveillance up to 24 hours for the second administration in course 1. If the first 2 infusions of the first treatment course are well tolerated, the 3rd and 4th infusion may be administered on an outpatient basis. For the first treatment of the second course patients need to be hospitalized with surveillance for 24 hours after start of the infusion. If the first infusion of the second treatment course has been well tolerated with limited and easily manageable infusion reactions, the second and subsequent infusions of the second and third treatment course can be administered as an out-patient visit at discretion of the investigator.

In case a visit with administration of BI 836826 is delayed please inform the clinical monitor or the CRA. All subsequent visits with treatment administration will be recalculated based on the actual date of delayed visit. The treatment schedule of weekly infusion should be adhered to, but the visit may be delayed 1-2 days for administrative reasons. To allow for recovery from adverse events or to fulfil the criteria for treatment continuation, delays of more than 2 days are possible as outlined in section 4.1.4.3. If a visit is delayed less than 5 days, the delay may be caught up by shortening the observation period of the course after agreement between investigator and clinical monitor of the trial. Postponement of an infusion for up to 3 weeks can be allowed, but further treatment has to be confirmed by the sponsor. This will be a maximum length of course 1 and 2 to 10 weeks.

In case a patient misses a visit, where there is no planned treatment, the delayed visit should be scheduled as soon as possible and documented with the actual date and the reason for the delayed visit. The next visit, should still take place at the time it was originally scheduled in this treatment course.

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

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

6.2.1 Screening and run-in period(s)

The screening period, *i.e.* the phase after informed consent and before the first administration of the trial drug, may be as long as 14 days. However, a pre trial CT scan, performed as part of routine clinical practice, can be used as the baseline CT scan given that the CT scan is

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valid and encompass neck, thorax, abdomen and pelvis, and it should been performed preferably within 4 weeks before visit 1. If the patient has not receive any anti lymphoma treatments and regarded a clinical stable by the investigator, the pre trial CT scan within 8 weeks before visit 1 can be employed. Parameters and investigations according to flowchart for course 1 have to be obtained and / or performed, please refer to flowchart for Course 1.

6.2.2 Treatment periods

The treatment is given in courses with 4 administrations of a weekly infusion followed by observation/rest. Patients can receive up to three courses, *i.e.* 12 administrations. The duration of the first two courses is 7 weeks and for the third course 12 weeks, hence a 3-week or an 8-week observation/rest after the infusions of BI 836826.

6.2.2.1 Course 1

In the first course there are 4 visits with treatment and 6 visits for safety assessment. The first two administrations are given as an in-hospital stay for safety, tumour lysis assessment

Between the visits with infusion of BI 836826 safety visits will be performed. After last infusion the safety visits will be weekly. Clinical disease assessment will be performed at the first infusion visit (visit 1) and the last infusion visit (visit 7) as well as the last visit in the course (visit 10).

For details see flowchart for Course 1.

In case of the split first dose administration patients are required to be hospitalized under close surveillance with access to intensive care for at least 72 hours after the start of the low dose of BI 836826 to allow close monitoring for infusion-related reactions. Please refer the flowchart in section 10.7 for clinical disease, safety

6.2.2.2 Course 2

In the second course there are 4 visits with treatment and 6 visits for safety and response assessment. The first administration is given as an in-hospital stay for safety, tumour lysis assessment Between the visits with infusion of BI 836826 safety visits will be performed. After last infusion the safety visits will be weekly. Clinical disease assessment will be performed at the first infusion visit (visit 1) and the last infusion visit (visit 7). A CT scan of neck, thorax, abdomen and pelvis must be performed at visit 9 to be available for the disease assessment and response evaluation that are planned to be done at the last visit in the course 2 (visit 10).

For details see flowchart for Course 2.

6.2.2.3 Course 3

In the third course there are 4 visits with treatment and 5 visits for safety and response assessment. All infusions can be given as out-patient, if recent previous infusions have been well tolerated. Clinical disease assessment will be performed at the first (visit 1) and at the last infusion (visit 4).

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CT scan of neck, thorax, abdomen and pelvis will be performed at visit 9 (week 25) unless the EOT visit is performed prior to week 26. Disease assessment, response evaluation with CT scan (see appendix 10.1) will be done at the EOT visit (see below section 6.2.3.1). For details see flowchart for Course 3.

6.2.3 End of treatment and follow-up period

6.2.3.1 End of treatment

The end of treatment (EOT) visit should be performed if patient and investigator refrain from further therapy at any time during the treatment period. For patients who receive course 3 (12 administrations) at the latest 8 weeks after the last administration of BI 836826. If the patient concludes the trial within a treatment course, the information required to be collected at the EOT visit should be obtained as early as possible, preferably immediately. This includes a CT scan, which may be performed if it is considered clinically indicated, *e.g.* to document disease progression. At the EOT visit assessment of all safety and efficacy parameters should be performed according to flowchart for course 3. The status of the patient at EOT has to be documented, *e.g.* in case the patient has progressive disease the date of first documentation of PD has to be recorded. The reason for the completion of active trial treatment or premature discontinuation of trial, if applicable, has to be stated together with date of last administration of the trial drug. If the patient receives other therapy for lymphoma, the therapy has to be stated by name and date of first treatment. For detail see flowchart for Course 3.

6.2.3.2 Follow-up

Follow-up visits will be performed after the EOT visit in case a patient has completed treatment according to protocol or is not eligible for further treatment courses prior to administration of the maximum number of courses. Follow-up will end in case the patient is

- lost to follow-up
- receives new anti-lymphoma therapy
- withdraws consent
- in case the investigator and sponsor agree not to pursue further follow-up visits
- death

Follow-up visits should be performed at 6 weeks intervals or more frequent if appropriate. Follow-up visits should be done at the investigational site, but may be performed by telephone interview in case the patient is unable to visit the investigator. Follow-up visits should be performed up to 6 months after the end of treatment visit. At the last follow-up visit, an end of trial assessment will be performed and documented in the eCRF. For follow-up of patients with adverse events which have not recovered at the last planned follow-up visit please refer to section 5.2.2.2.

The following will be obtained and / or performed (see flowchart for Course 3):

- Vital signs (see section 5.2.5.1), weight, physical examination

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- Disease assessment: clinical assessment of tumour size (lymph nodes, spleen, liver), imaging if applicable
- Changes in concomitant therapies
- Safety laboratory parameters as specified in section 5.2.3.1
- Adverse events
- CMV monitoring (see section 5.2.3.3.2)
- Lymphocyte typing (see section 5.2.3.4)
- Status of the patient: date of progression (in case, the patient experienced PD) date death (if applicable)
- Treatment with any other anti-lymphoma drug (report start date of treatment and therapy)

6.2.3.3 End of the whole trial

The clinical trial will be analyzed and reported after the last patient has completed his / her last visit, *i.e.* the latest 6 months after the EOT of the last patient. In case the trial is ended by the sponsor when patients are still being treated with BI 836826 when the final report of the trial is being prepared, the patients will either be included in a follow-up trial or alternatively kept on treatment in this trial. Those patients will then be reported in a revised report and it will be noted in the original report that such a revised report will be written.

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7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 STATISTICAL DESIGN - MODEL

This trial will be performed as an open-label study. The primary objective of the trial is to determine the MTD of BI 836826. To determine the MTD, patients are entered sequentially into escalating dose tiers, initially in single patient cohorts and later on using the 3+3 design (see section 4.1.4.). If MTD is not reached in the trial, an optimal biologic dose (OBD) can be selected using all available data from safety and pharmacodynamic analyses, B cell depletion and reduction of tumour size. After the MTD/OBD has been determined, an expansion cohort of up to 20 patients with an aggressive NHL and up to 20 patient with indolent NHL was planned at a dose level supposed to be recommended for later studies. Due to safety signals in the initial three out of four Korean patients enrolled into the expansion cohort at the defined MTD of 100 mg the cohort was closed for all patients. Lower dose cohorts will be tested in Korean patients to explore safety at lower doses of 50 and 75 mg in Korean patients.

7.2 NULL AND ALTERNATIVE HYPOTHESES

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

7.3 PLANNED ANALYSES

7.3.1 Primary analyses

The primary objective for this study is the tolerability and safety of BI 836826 as reflected by the MTD (for a definition of MTD, please refer to section 3.1 and section 5.2.1.1). In order to identify the MTD, the number of DLTs during the first two weeks of the first course at each dose level must be presented. For the analysis of tolerability and safety, please refer to section 7.3.3. If an MTD is not reached, an OBD can be determined from available data on safety and pharmacodynamic analyses, B cell depletion and reduction in tumour size (see sections 2.2 and 3.1).

7.3.2 Secondary analyses

7.3.2.1 Tumour size

The tumour size of the lymph nodes will be measured as sum of products of diameter (SPD) of two perpendicular dimensions for of up to 6 indicator lesions identified at baseline CT scan. Spleen and liver will be described, if considered enlarged at baseline by physical examination or CT scan. If nodules are present in spleen and/or liver, the diameter of these will be measured in two perpendicular dimensions. The change in SPD, spleen and liver nodules will be compared to baseline and will be listed by time point.

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7.3.2.3 Best overall response

Best overall response is the best response (CR, CRu, PR, SD or PD in this order) with respect to all time points. Remission rate is the rate of patients that either have CR, CRu or PR as best overall response. Best overall response and remission rate will be analysed descriptively. Frequency distributions and other descriptive statistical measures will be used to examine these variables.

7.3.2.4 Progression free survival, failure free survival,

These time-to-event variables will be analysed descriptively or with the Kaplan-Meier method, if applicable. Details of censoring rules will be provided in the statistical analysis plan.

7.3.3 Safety analyses

All patients who have received any amount of trial drug will be included in the safety analysis. The occurrence of dose limiting toxicity (DLT) as well as the incidence and intensity of adverse events, graded according to CTCAE, laboratory parameters and vital signs will be evaluated.

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. The overall incidence and intensity of adverse events, as well as relatedness of adverse events to treatment with BI 836826 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

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examined, but may not be reported as individual tables, depending upon the extent of overlap with the occurrence of DLT.

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

Events that start from first administration of BI 836826 until 8 weeks after the last administration of BI 836826 will be considered as having occurred during treatment. In general, later events will be attributed to the post study period and will be presented separately. However, post study events will be examined to determine whether they need to be combined with on treatment events in an additional table.

7.3.4 Interim analyses

The sponsor will continuously monitor the safety. The sponsor and the DSMB will perform safety evaluations regularly, and if considered necessary at additional ad hoc meetings. The evaluations will be unblinded to dose.

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

After the MTD was determined in Caucasian patients an evaluation of the safety aspects was performed. Results of this evaluation were be documented and archived. The analysis was defined in more detail in the Statistical Analysis Plan.

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7.4 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 RANDOMISATION

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

7.6 DETERMINATION OF SAMPLE SIZE

Assuming 3 cohorts of 1 patient only, 3 cohorts of 3 patients (*i.e.* no patients with DLT at given level) and 3 cohorts of 6 patients (*i.e.* 1 DLT witnessed in first 3 patients so further 3 patients exposed with no DLTs), 30 patients will be necessary for the dose-escalation part of this trial.

The purpose of this amendment is to introduce additional doses to be tested in Korean population. The testing will occur accordingly to 3+3 rule, therefore 3-6 patients are needed per each dose level (50mg and 75mg) to assess safety.

With 41 patients enrolled so far, and additional up to 12 patients to be enrolled, the expected number of patients on this trial will be approximately 53.

Note that in general, the final sample size depends on the observations made in the trial.

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8. INFORMED CONSENT, DATA PROTECTION; TRIAL RECORDS

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

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

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 according to national and international regulations. The same applies for the implementation of changes introduced by amendments.

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

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

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

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8.2 DATA QUALITY ASSURANCE

The trial will be conducted in compliance with the protocol, the principles laid down in the Declaration of Helsinki (please, refer to section 8), local law and according to the principles of GCP and the company standard operating procedures (SOPs). To inform all investigators about the trial drugs and the procedures of the trial, either an investigator meeting will be performed prior to start of the trial, or each investigator will be visited individually by the Clinical Monitor and the Clinical Research Associate (CRA). Each investigator will receive an ISF with all information relevant for the performance of the trial. Investigators will be visited at regular intervals for on-site monitoring by a Boehringer Ingelheim employee or a CRA authorised by BI. At these occasions, source data verification (SDV) will be performed and a check will be done whether the eCRFs are kept current. The information in the eCRF and information in source documents will be cross-checked as described in section 8.3.1.

8.3 RECORDS

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

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

8.3.1 Source documents

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

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

For eCRFs all data must be derived from source documents.

The data management procedures to ensure the quality of the data are described in detail in the trial data management and analysis plan (TDMAP) available in the CTMF. Coding of the data obtained will be done by using the medical dictionary for regulatory activities (MedDRA) and the WHO dictionary for concomitant medication. Data quality review meetings will be performed at regular intervals to evaluate the quality of the data collected. Discrepancies in data will be queried.

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.

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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 BI 836826 this is the current version of the Investigator's Brochure (c01715907-08). The current versions of these reference documents are provided in the ISF.

8.4.2 Expedited reporting to health authorities and IECs/IRBs

Expedited reporting of 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 IEC and the regulatory authority, *i.e.* the Paul-Ehrlich-Institute.

8.6 COMPLETION OF TRIAL

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

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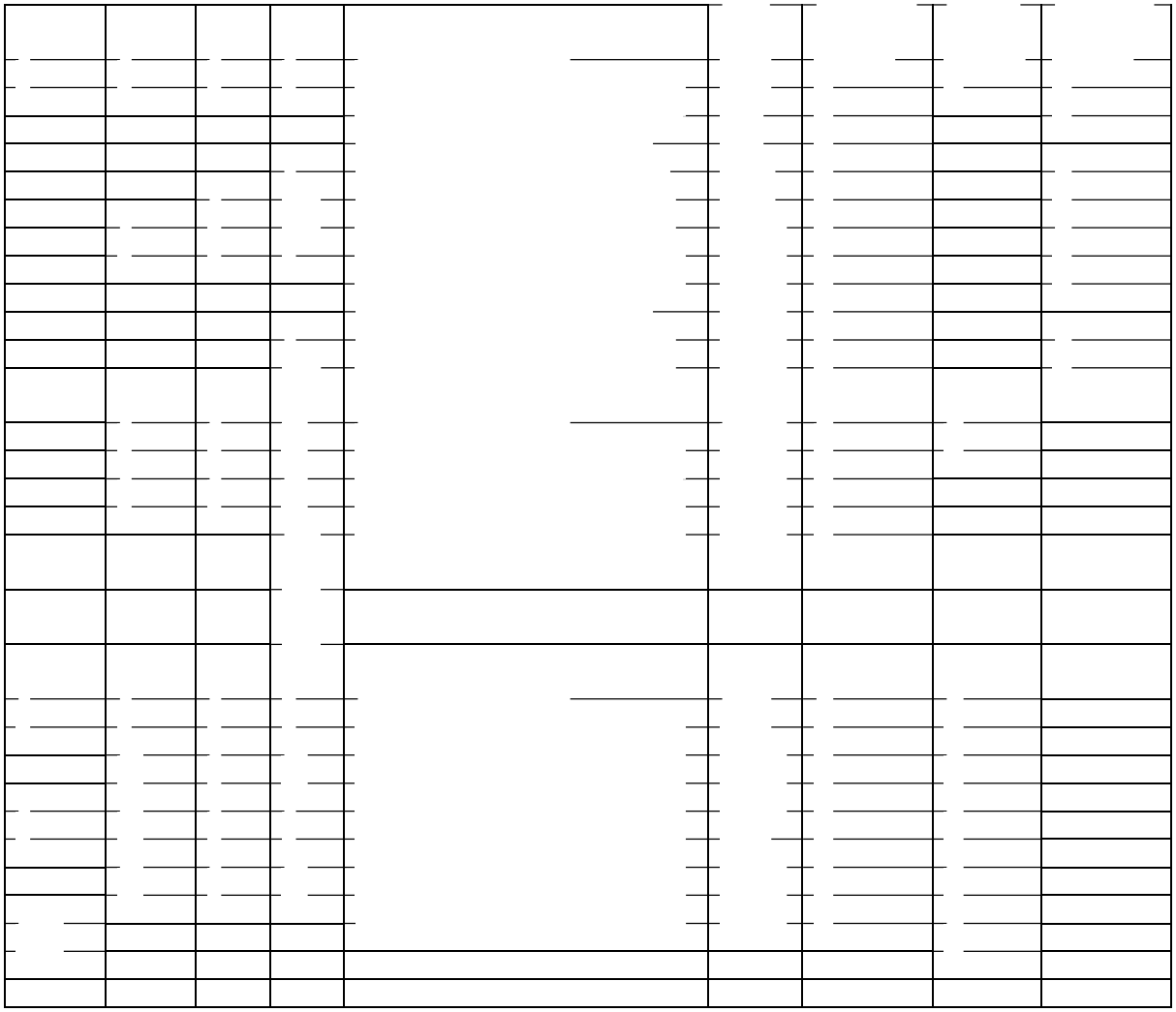
10. APPENDICES



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10.2 AGGRESSIVE AND INDOLENT LYMPHOMA

Protocol defined aggressive lymphoma (de novo or transformation):

- Diffuse large B-cell lymphoma
- Mantle cell lymphoma
- Mediastinal large B-cell lymphoma
- Intravascular large B-cell lymphoma
  ALK positive large B-cell lymphoma
- Plasmablastic lymphoma
- Primary effusion lymphoma
- Burkitt lymphoma

Protocol defined indolent lymphoma:

- Follicular lymphoma
- Lymphoplasmacytic lymphoma
- Extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT)
- Splenic marginal zone lymphoma
- Nodal marginal zone lymphoma
- Primary cutaneous follicular center lymphoma

10.3 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

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10.4 ANN ARBOR STAGING

Stage	Definition
I	Involvement of one region and/or local involvement of one extra nodal site (I_E)
II	Involvement of >one region on the same site of diaphragma without or with one extra nodal site (II_E)
III	Involvement of regions on both sites of diaphragma, involvement of spleen without or with one extra nodal site (III_E)
IV	Diffuse or disseminated disease in extra nodal organs
A – without disease symptoms B – with symptoms like night sweats, weight loss >10% over 6 months, fever without infection E – extranodal disease	

Reference R10-6400

10.5 CALCULATION OF GLOMERULAR FILTRATION RATE

Glomerular filtration rate (GFR) may be estimated based on commonly used and accepted formulae, *i.e*

Cockroft Gault formula

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

Units: GFR [ml/min], age [years], weight [kg], serum creatinine [mg/dl], F_S is a correction Factor for Sex: in males $F_S = 1$, in females $F_S = 0.85$

Modification of Diet in Renal Disease (MDRD) formula

$$GFR = 170 \times Serum\ Creatinine^{-0.999} \times Age^{-0,176} \times BUN^{-0.170} \times Albumin^{+0.318} \times F_S$$

Units: GFR [ml/min], age [years], serum creatinine [mg/dl], F_S is a correction Factor for Sex: in males $F_S = 1$, in females $F_S = 0.762$

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Variations of the MDRD formula

$$GFR = 186 \times \text{Serum Creatinine}^{-1.154} \times \text{Age}^{-0,203} \times F_S$$

Units: GFR [ml/min], age [years], serum creatinine [mg/dl], F_S is a correction Factor for Sex: in males $F_S = 1$, in females $F_S = 0.742$

Alternative methods of calculation of GFR may be agreed between Investigator and the Trial Clinical Monitor at Boehringer Ingelheim.

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 Significant Adverse Events), 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 72hours. If ALT and/or AST ≥3 fold ULN combined with an elevation of total bilirubin ≥2 fold ULN are confirmed (if normal values at baseline/screening), or ALT and/or AST >5 fold ULN combined with an elevation of total bilirubin >2 fold ULN are confirmed (if elevated values at baseline/screening) 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 homeand work place exposure) according to the "DILI checklist" provided in the ISF;

and report these via the CRF.

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

Clinical chemistry

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

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Serology

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

Hormone

Thyroid stimulating hormone

Haematology

White blood count + differential, haemoglobin, thrombocytes

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

Initiate close observation of 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 or additional parameters identified, follow-up should be based on medical judgement and Good Clinical Practice (GCP).

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10.7 FLOWCHART FOR THE SPLIT FIRST DOSE ADMINISTRATION (LOW DOSE AND FULL DOSE)

10.7.1 Flowchart for Course 1

Trial Periods	**Screen**	**Treatment and observation/rest**													EOT	FU
Course *		**1**														
Week		**1**				**2**			**3**		**4**	**5**	**6**	**7**		
Visit **	**Screen**	**1**			**2**	**3**		**4**	**5**	**6**	**7**	**8**	**9**	**10**		
Days	**-14 to -1**	**1**	**2**	**3**	**4 + 2**	**8**	**9**	**10 +2**	**15**	**17 +2**	**22**	**29 ±2**	**36 ± 2**	**43 ±2**		
Informed consent	x															
Demographics	x															
Medical history	x															
Review of in-/exclusion criteria	x	x [1]														
Eligibility for trial	x															
12-lead ECG	x															
	x															
		x														
Height	x															
Weight	x	x	x			x	x		x		x			x		
Physical examination, incl. tumour size (lymph nodes, spleen, liver),	x	x									x			x		
Vital signs [2]	x	x	x	x	x	x	x	x	x	x	x	x	x	x		
Dose assignment	x [3]															
Concomitant therapy	x	x	x	x	x	x	x	x	x	x	x	x	x	x		
General safety laboratory parameters [4]	x	x	x	x	x	x	x	x	x	x	x	x	x	x		
Administration of BI 836826		x	x			x			x		x					
Screening for Tumour Lysis Syndrome [5]		x	x	x		x	x									
Adverse events		x	x	x	x	x	x	x	x	x	x	x	x	x		
Disease/response assessm. (clinical/imaging)	x	x [6]									x [6]			x [6]		
Serum pregnancy test [7]	x	x									x					
CMV monitoring [8]	x	x							x		x	x	x	x		
Lymphocyte typing (B/T/NK cells)		x			x	x		x	x	x	x	x	x	x		
Anti-drug antibodies [9]		x							x							
Virology screening [10] (HBV, HCV, HIV, CMV)	x															
	x															
CT scan of neck, thorax, abdomen and pelvis	x [11]															

If no signs of progression and agreement on further treatment for the patient, please continue to Visit 1 on Flowchart for Course 2

If the patient has disease progression or withdraws, please continue to EOT visit on Flowchart for Course 3

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EOT: End of treatment visit, to be performed at withdrawal from further treatment (<12 administrations) or at the latest 8 weeks after the last administration of BI 836826 (12 administrations)
FU: Follow-up visits (starts after EOT) at least every 6 weeks until 6 months after EOT visit, details see section 6.2.3.2
CMV: Cytomegalovirus
HBV: Hepatitis B virus
HCV: Hepatitis C virus
HIV: Human immunodeficiency virus

* the planned duration of course 1 is 7 weeks (49 days)
** the visit number follows the course number, i.e. visit 2 course 1 will read C1_V2 and visit 2 course 2 will read C2_V2 …

1 Review of eligibility
2 For details during and after infusion of BI 836826, refer to section 5.2.5.1
3 After informed consent, and review of in- and exclusion criteria, and before the first administration of the trial drug
4 For details refer to section 5.2.3.1
5 Screening for tumour lysis syndrome in between safety laboratory assessments (section 5.2.3.2)
6 Disease / response assessment will be based on clinical judgement when recent CT is not available
7 For women of childbearing potential only (please refer to sections 3.3.3 (exclusion criterion 20) and 5.2.3.1)
8 Quantitative CMV DNA PCR (section 5.2.3.3.2)
9 Sampling at the time points specified in table 10.1.1 (Appendix 10.1)
10 Please refer to section 5.2.3.3.1
11 CT scan may be performed up to 4 weeks prior to first infusion according to the standard of care in this patient population

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11. DESCRIPTION OF GLOBAL AMENDMENTS

Summary of Clinical Trial Protocol Modifications Sheet (SOMS)

Number of global amendment		1
Date of CTP revision		*21 May 2012*
EudraCT number		*2010-024456-29*
BI Trial number		*1270.2*
BI Investigational Product(s)		*BI 836826*
Title of protocol		A Phase I, Open-Label, Dose-Escalation Trial with BI 836826 in Patients with Relapsed or Refractory non-Hodgkin Lymphoma of B cell Origin
To be implemented only after approval of the IRB/IEC/Competent Authorities		☒
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		☐
Can be implemented without IRB/IEC/ Competent Authority approval as changes involve logistical or administrative aspects only		☐
Section to be changed		Change 1: Trial Clinical Monitor Change 2: Protocol Synopsis Change 3: Flow Chart Change 4: TABLE OF CONTENTS Change 5: ABBREVIATIONS Change 6: Section 3.1

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Number of global amendment		1
		Change 7: Section 3.2 Change 8: Section 3.2 Change 9: Section 3.3.2 Change 10: Section 3.3.3 Change 11: Section 3.3.3 Change 12: Section 4.1.4.1.3 Change 13:Section 4.1.7 Change 14: Section 5.2.2.1 Change 15: Section 5.2.2.2 Change 16: Section 5.2.3.1 Change 17: Section 5.2.3.2 Change 18: Section 5.2.3.2 Change 19: Section 5.2.3.3.2 Change 20: Section 5.2.3.4 Change 21: Section 5.2.5.1 Change 25: Section 6.1 Change 26: Section 6.2.1 Change 28: Section 10.2

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Number of global amendment		1
		Change 29: Section 10.6
Description of change		Change 1:Tria Clinical Monitor change Change 2: Deletion of "conducted in one country". Change 4: 10.6 was added in table of content Change 5: DILI was added in the abbreviations Change 6: Full stop was added Change 7: The part "(may be performed up to 8 weeks (preferably 4 weeks) prior to first infusion)" was added. Change 8: The sentence "If the CT scans are not possible or available, magnetic resonance imaging can be used instead. However the same imaging methods should be used consistently throughout the trial" was added. Change 9: "1" was added."1" was replaced by "2". Change 10: "NHL" was replaced by "a mature B cell neoplasm according to WHO classification (R10-6296)". Change 11:"prednisolone or equivalent" was added. Change 12: "CTCAE 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 (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)." was added.

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Number of global amendment		1
		Change 13: "CRA" was added. Change 14: "protocol-specified" and "DILI Although rare, drug-induced liver injury (DILI) is under constant surveillance bysponsors and regulators and is considered a protocol-specified significant adverse event. Timely detection, evaluation, and follow-up of laboratory alterations of selected liver laboratory parameters to distinguish an effect of the underlying malignancy on liver function from other causes such as DILI are important for patient safety. The following are considered as Protocol-specified significant events: Hepatic injury defined by the following alterations of liver parameters: • For patients with normal liver function (ALT, AST and bilirubin within normal limits) at baseline an elevation of AST and/or ALT ≥3 fold ULN combined with an elevation of bilirubin ≥2 fold ULN measured in the same blood draw sample. Patients showing these lab abnormalities need to be followed up according to Appendix 10.6 of this clinical trial protocol and the "DILI checklist" provided in the ISF. • For patients with impaired liver function at baseline an elevation of AST and/or ALT >5 fold ULN combined with an elevation of total bilirubin >2 fold ULN measured in the same blood draw sample. Patients showing these lab abnormalities need to be followed up according to Appenddix 10.6 of this clinical trial protocol and the “DILI checklist” provided in ISF" . Protocol-specified significant adverse events are to be reported in an expedited manner similar to Serious Adverse Events, even if they do not meet

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Number of global amendment		1
		any of the seriousness criteria - for details see section 5.2.2.2. If the investigator determines any protocol-specific significant adverse event is related to study drug, the administration of the study drug must be managed according to section 4.1.4 of the protocol." were added "the" was add. "Expected fluctuations or expected deterioration of the underlying disease and other pre-existing conditions should not be recorded as an AE unless at least one of the following criteria is met: • the worsening of the disease constitutes an SAE • the investigational drug is discontinued or the dose is reduced • additional treatment is required, *i.e.* concomitant medication is added or changed • an unexpected deterioration from baseline has occurred in the opinion of the investigator" was replaced by "Worsening of the underlying disease or of other pre-existing conditions will be recorded as an (S)AE in the (e)CRF." "with the term Neoplasm Progression" was added. "Changes in vital signs including blood pressure, pulse rate, electrocardiogram (ECG), physical examination, and laboratory tests will be only then recorded as AEs if they are not associated with an already reported AE, symptom or diagnosis, and the investigational drug is either discontinued, reduced or increased, or additional treatment is required, *i.e.* concomitant medication is added or changed" was replaced by "Changes in vital signs, ECG, physical examination and laboratory test results will be recorded as an (S)AE in the (e)CRF , if they are judged clinically relevant by the investigator." Change 15: "protocol-specified" was added. Change 16:"total" and "(if elevated provide direct bilirubin)"was added.

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Number of global amendment		1
		Change 17: "of the second infusion in course 1" and "Monitoring for TLS of the second infusion of course 2 and the first and second infusion of course 3 are be performed while the patient is in hospital" were added. Change 18: "+differential" was added. Change 19: "The same method should always be used for all treated patients in the same investigational site" was added. Change 20: "in the laboratory at the investigational" was replaced by "in a specialized laboratory either at the investigational site or at a centralized laboratory. Detailed instructions are included in the laboratory manual in the ISF." Change 21:"appropiate" was replaced by "appropriate". Change 25: "please inform the clinical monitor or the CRA" was added. Change 26:"has" was replaced by "should".

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Number of global amendment		1
		"preferably" was added. "If the patient has not receive any anti lymphoma treatments and regarded a clinical stable by the investigator, the pre trial CT scan within 8 weeks before visit 1 can be employed." was added. Change 28: "(de novo or transformation):"was added. Change 29: The whole section 10.6 was added.
Rationale for change		Change 1: Change of personnel. Change 2: The trial may be conducted in other countries as well. Change 4: Explanation of abbreviation. Change 5: Clarification of Liver Injury. Change 6:Typo. Change 7: Clarification of CT scan time frame prior to treatment. Change 8: Other imaging than CT scan is allowed to enable patients to enroll where additional radiation exposure else would be limiting for enrolment. Change 9: ECOG status 2 was added to allow patients with lower performance status to be included as the performance status may be related to underlying disease and not per se considered an increase risk for the patient.

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Number of global amendment		1
		Change 10: To precisely define which previous B cell neoplasms are allowed. Change 11: To clarify on the dose and to allow other steroid than prednisolone. Change 12: Definition of which TLS classification will be used. Change 13: Addition of CRA as a second contact person. Change 14: Clarification that significant AEs are the defined protocol specific AEs and Liver injury (DILI) was added. (S)AE reporting change required by regulatory authority. Change 15: Clarification of (S)AE reporting. Change 16: Clarification that total bilirubin value is to be obtained. In case bilirubin is elevated, direct bilirubin will be needed for clinical interpretation. Change 17: Clarification of the screening schedule of tumour lysis syndrome to be consistent with the sampling indicated in the flowcharts. Change 18: Additional pharmacodynamic and safety evaluation without changing blood sampling. Change 19: Emphasizing the need that a standard method should be applied through out the study. Change 20: To ensure comparability of lymphocyte testing, only a limited number of diagnostic instruments and protocols should be used. Therefore, method and qualification of laboratories at the sites will be assessed and decision taken by the sponsor whether measurement can be performed at the site or should be delegated to a central laboratory.

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Number of global amendment		1
		Change 21:Typo. Change 25: Clarification of the operation process. Change 26: Expansion of the time window for pre trial CT scan to minimize the use of CT scan where these are not considered indicated for documentation of disease status. Change 28: Clarification that subtypes of aggressive lymphoma can be as a de novo lymphoma or as transformation of another mature B cell malignancy. Change 29: Procedure of Clinical Evaluation on case of Liver Injury.

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Number of global amendment		2
Date of CTP revision		*14 Feb 2013*
EudraCT number		*2010-024456-29*
BI Trial number		*1270.2*
BI Investigational Product(s)		*BI 836826*
Title of protocol		A Phase I, Open-Label, Dose-Escalation Trial with BI 836826 in Patients with Relapsed or Refractory non-Hodgkin Lymphoma of B cell Origin
To be implemented only after approval of the IRB/IEC/Competent Authorities		☒
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		☐
Can be implemented without IRB/IEC/ Competent Authority approval as changes involve logistical or administrative aspects only		☐
Section to be changed		Change 1: Synopsis Change 2: Section 3.1 Change 3: Section 3.2 Change 4: Section 3.3.1 Change 5: Section 3.3.3 Change 6: Section 4.1 Change 7: Section 4.1.1 Change 8: Section 4.1.4.1.2

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Number of global amendment		2
		Change 9: Section 4.1.4.2 Change 10: Section 5.2.3.2 Change 11: Section 5.2.5.1 Change 12: Section 6.1 Change 13: Section 6.2.2.1 Change 14: Section 7.1 Change 15: Section 7.6
Description of change		Change 1: Total patient number adapted Change 2: • 836286 was replaced by 836826 • "Over 3 hours" was deleted • "Unless the first administration will be split (refer section 4.1). " was added • "Coordinating Investigator" and "The data will be discussed and aligned with the coordinating investigator" were deleted. • Patient number changed • Patient population of expansion cohort defined Change 3: Patient population of expansion cohort was defined. "an expansion cohort of up to 20 patients is planned to be enrolled to better characterize the safety profile and tolerability of the MTD." was deleted. Change 4: "a minority" was replaced by "minorities"

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Number of global amendment		2
		Change 5: Addition of exclusion criterion Change 6: • "over 3 hours" was deleted and "unless the split first dose administration described below will be implemented" was added. • "The first infusion in each course should be started at a rate of 10 mL/h. The infusion rate can be increased every 30 (+/-10) minutes by 10 mL/h to a maximum of 80 mL/h as long as tolerated by the patient. If considered safe by the investigator, the subsequent infusions may be given with shorter interval for increasing the rate, but the maximum rate should not exceed 120 mL/h. If adverse events which are considered related to the infusion schedule, e.g. infusion-related reaction, are not well controlled by the above schedule an alternative administration will be used. The first administration in course 1 will be split into two infusions, a low dose on day 1 followed by the full dose on the day 2. The first part of the administration will be 10% of the full dose, but not exceeding 10 mg given on day 1. The day after the second part of the administration will be the full planned dose for the patient (please refer the flowchart in section 10.7). The same infusion schedule should be employed as described above, starting with a rate of 10 mL/h. Premedication is mandatory before both infusions as they will be considered as the first administration (section 4.1.4.1.1.). The potential change of the first infusion into two infusions will be assessed and may be modified by the DSMB. In subsequent administrations, the full dose of BI 836826 will be administered as a rate-controlled intravenous infusion on day 1. If symptoms of an infusion related

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Number of global amendment		2
		reaction occur, the infusion should be temporarily stopped. Upon recovery, it should be resumed at 50% of the rate at which the reaction occurred for at least 30 minutes. Lower rates may be selected if clinically indicated. Depending on the time of occurrence and the severity of the reaction, the investigator may consider administering additional supportive medication, e.g. corticosteroids. A stepwise re-increase of the infusion rate to a maximum of 80 mL/h is possible. For medical reason" was added. • "In case a patient experiences an adverse event during the infusion" was deleted. Change 7: • "or split dose (2 doses) only applicable for course 1"was added. • "Infusion over 3 hours" was replaced by "Rate controlled infusion". • "coordination investigator" and "Rate: 83.4 mL/h" was deleted. Change 8: "If the split first dose administration is employed patients are required to be hospitalized under close surveillance with access to intensive care for at least 72 hours for the 1st visit in course 1 and at least 24 hours during the second infusion in course 2. Hospitalization is required for at least 24 hours during the first infusion in course 2. In case of no relevant infusion-related adverse events, the decision to hospitalize the patient is left to the discretion of the investigator." was added. Change 9: "8" was replaced by "24". Change 10: "In case of the split first dose administration the same parameters need to be determined during the first 72 hours after the start of the low dose of BI 836826 in course 1, and for other infusions the monitoring should be as above described" was added.

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Number of global amendment		2
		Change 11: "In case of prolongation of the infusion time additional measures have to be documented every 30 minutes. In case of the split first dose administration monitoring has to be at least 72 hours after the start of the low dose."was added. Change 12: "In case of the split first dose administration patients are required to be hospitalized for at least 72 hours after the start of the low dose of BI 836826" was added. Change 13: "In case of the split first dose administration patients are required to be hospitalized under close surveillance with access to intensive care for at least 72 hours after the start of the low dose of BI 836826 to allow close monitoring for infusion-related reactions. Please refer the flowchart in section 10.7 for clinical disease, safety was added. Change 14: "up to 20 patients are additionally entered at a dose level supposed to be recommended for later studies." was replaced by "an expansion cohort of up to 20 patients with an aggressive NHL and up to 20 patient with indolent NHL are additionally entered at a dose level supposed to be recommended for later studies." Change 15: " with an aggressive NHL and up to 20 patients with indolent NHL" was added. "50" was replaced by "70". "enrolled" was deleted.
Rationale for change		Change 1: Please refer Section 10 Change 2:

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Number of global amendment		2
		• Typo • Clarification of Infusion schedule • Clarification of Infusion schedule • Clarification of Responsibility • Please refer Change 14 concerning the number • To ensure enrolment of both indolent and aggressive lymphomas Change 3: Please refer to Change 14 Change 4:Typo Change 5: The prohibited use of immunoglobulin already described in section 4.2.2.1 is added as an exclusion criterion for clarity. Change 6: Clarification of Infusion time and split of administration to reduce the risk and grade of infusion related reaction. Change 7: Clarification of infusion scheme and agreement of further treatment. Change 8: Clarification of Hospitalization. Change 9: Change to maximal allowed Infusion time. Change 10: Clarification of Safety Monitoring Period. Change 11: Clarification of Vital Signs Monitoring Period. Change 12: Clarification of Hospitalization. Change 13: Clarification of Course 1 in case of split dosing. Change 14: An expansion cohort of up to 20 patients with an aggressive NHL and up to 20 patient with indolent NHL are planned to be enrolled to better characterize the safety profile

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Number of global amendment		2
		and tolerability of BI 836826 in the respective lymphoma types. Change 15: Please refer Change 14.

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Number of global amendment		3
Date of CTP revision		*07 Aug 2013*
EudraCT number		*2010-024456-29*
BI Trial number		*1270.2*
BI Investigational Product(s)		*BI 836826*
Title of protocol		A Phase I, Open-Label, Dose-Escalation Trial with BI 836826 in Patients with Relapsed or Refractory non-Hodgkin Lymphoma of B cell Origin
To be implemented only after approval of the IRB/IEC/Competent Authorities		☒
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		☐
Can be implemented without IRB/IEC/ Competent Authority approval as changes involve logistical or administrative aspects only		☐
Section to be changed		Change 1: Section 3.3.3 Change 2: Section 4.1.1 Change 3: Section 4.1.4.3 Change 4: Section 4.2.1.2.1 Change 5: Section 5.2.5.1
Description of change		Change 1: "GFR<60mL/min" was replaced by "GFR<45 mL/min". Change 2: ”Volume: 250 mL” was replaced by “See section 4.1.6”

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Number of global amendment		3
		Change 3: "and only with a reduced dose of BI 836826" was replaced by "or pre-treatment value "; "new" was replaced by "future"; "The reduced dose will be valid for all following treatment courses in the individual patient" was deleted; "In case, a patient experiences a second episode of DLT with the reduced BI 836826 dose, the treatment has to be permanently discontinued. Likewise, treatment" was replaced by "Treatment". Change 4: "Prophylactic antiviral therapy (e.g. nucleoside reverse transcriptase inhibitor) and/or monitoring of hepatitis B DNA in the blood is recommended for patients with a history of hepatitis B infection." was added. Change 5: "60 (±10), 90 (±10), 120 (±10), 150 (±10) and 180 (±10)" was replaced by "every"; "In case of prolongation of the infusion time additional measures have to be documented every 30 minutes" was deleted.
Rationale for change		Change 1: GFR decreases with age. In view of the average age of NHL patients, exclusion criterion 13 was modified to exclude only patients with a GFR<45 mL/min. Change 2: Volume of 250 mL was replaced by reference to section 4.1.6 for clarification Change 3: Clarification of handling of DLT to

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Number of global amendment		3
		allow for risk/benefit assessment for the patient receiving BI 836826. Change 4: Recommendation for prophylaxis/monitoring for patients with prior hepatitis B infection. Change 5: Vital Signs Clarification.

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Number of global amendment		4
Date of CTP revision		*01 Oct 2015*
EudraCT number		*2010-024456-29*
BI Trial number		*1270.2*
BI Investigational Product(s)		*BI 836826*
Title of protocol		A Phase I, Open-Label, Dose-Escalation Trial with BI 836826 in Patients with Relapsed or Refractory non-Hodgkin Lymphoma of B cell Origin
To be implemented only after approval of the IRB/IEC/Competent Authorities		☒
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		☐
Can be implemented without IRB/IEC/ Competent Authority approval as changes involve logistical or administrative aspects only		☐
Section to be changed		Change 1: Trial Responsibility for Trial Clinical Monitor changed from to Change 2: Synopsis – No of patients changed from approx. 80 to approx. 66, no of entered patients changed from approx. 70 to approx. 53, treatment was modified in order to display the required number of Korean patients for both treatment dosages (50 and 75mg) Change 3: Section 1.2 DRUG PROFILE – currently performed trials in B-NHL malignancies and chronic lymphocytic leukemia were added.

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Number of global amendment		4
		Change 4: Section 2.2 TRIAL OBJECTIVES – addition of results, which were generated in this trial and analysed after an interim database lock, to display changed recruitment expectation based on the safety analyses. Change 5: 2-3 BENEFIT-RISK ASSESSMENT – further in vitro, in vivo and first in human experiences with treatment of BI 836826 were added. Furthermore the risk of increased neutropenia was added and the information, that infections should be treated in an early stage. Change 6: Section 3.2 DISCUSSION OF TRIAL DESIGN, INCLUDING THE CHOICE OF CONTROL GROUP – modified trial design concerning inclusion of Asian patients. Change 7: Section 3.3.3 EXCLUSION CRITERIA – criterion 26 was deleted as already reflected by criterion #4. Change 8: Section 4.1.1 IDENTITY OF BI INVESTIGATIONAL PRODUCT AND COMPARATOR PRODUCT – Exact volume of infusion was deleted and instead a reference to section 4.1.6 with detailed explanation included. Change 9: Section 4.1.3 SELECTION OF DOSES IN THE TRIAL – MTD doses as examined in Caucasian patients was added and the new possible doses for Asian patients added. Change 10: Section 4.1.4.3 New section added 'MANAGEMENT OF INFECTIONS' to establish a standardized process in case of infections due to additional safety precaution. Change 11: Section 4.1.4.4 CONTINUATION OF TREATMENT DURING A COURSE - Criteria for re-start of trial medication were expanded by two criteria ('no active infection' and 'no evidence of progressive disease') .

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Number of global amendment		4
		Change 12: Section 4.2.1.2 SUPPORTIVE CARE – infections were added in order to take supportive care infections. Change 13: Section 4.2.1.2.1 ANTIBIOTICS AND ANTIVIRALS – more detailed procedure for how to treat infections was added. Change 14: Section 4.2.2.1 RESTRICTIONS REGARDING CONCOMITANT TREATMENT – typo was corrected. Change 15: Section 5.2.2.2 ADVERSE EVENT AND SERIOUS ADVERSE EVENT REPORTING – According to internal guidelines, clarification of SAE follow-up was included. Change 16: Section 5.5.3 ANALYTICAL DETERMINATION – description of the analysation method was corrected. Change 18: Section 7.3.2.1 TUMOUR SIZE size was deleted Change 19: Section 7.3.2.3 BLOOD COUNTS – complete section was deleted as it will not be followed anymore. Change 20: Section 7.3.2.4 BEST OVERALL RESPONSE - Analysation of CRu was added Change 21: Section 7.3.4. INTERIM ANALYSES – adaptation to reflect the result of the interim analyse with regard to MTD.

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Number of global amendment		4
		Change 23: Section 7.6 DETERMINATION OF SAMPLE SIZE – explanation was added, what is statistical rationale for determination of the chosen sample size.

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Number of global amendment		5
Date of CTP revision		*13 Apr 2016*
EudraCT number		*2010-024456-29*
BI Trial number		*1270.2*
BI Investigational Product(s)		*BI 836826*
Title of protocol		A Phase I, Open-Label, Dose-Escalation Trial with BI 836826 in Patients with Relapsed or Refractory non-Hodgkin Lymphoma of B cell Origin
To be implemented only after approval of the IRB/IEC/Competent Authorities		☒
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		☐
Can be implemented without IRB/IEC/ Competent Authority approval as changes involve logistical or administrative aspects only		☐
Section to be changed		Change 1: Section 2.2 Trial Objectives – 'Three out of 4 Korean patients have developed significant toxicities (infections) which lead to the need of exploring a lower dose levels (50 and 75mg) in a designated escalation cohort of Korean patients to further characterize safety and efficacy of BI 836826 (c02337389-01).' This was added to clarify that a new patient in Korea is not part of the expansion cohort. Change 2: Section 2.3 Benefit - Risk Assessment – Percentage of patients with mantle cell lymphoma corrected to 6 (14.6%) Change 3: Section 2.3 Benefit Risk Assessment – 'As a result the enrollment into the trial 1270.2

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Number of global amendment		5
		has been halted, and this current amendment is submitted to allow for testing lower dose of 50 and 75mg in Korean patients in an escalation cohort for Asian patients.' This was added to clarify that a new patient in Korea is not part of the expansion cohort. Change 4: Section 3.1 Overall trial design and plan – 'Instead, lower dose escalation cohorts of 50mg and 75 mg will be open to test the safety,…'. This was clarified to stress the escalation status of Korean patients on 50 and 75mg. Change 5: Section 3.3.2 – Clarification of inclusion criteria 3 and 6. Change 6: Section 4.1.4.1.1 Premedication 'Acetaminophen/paracetamol 1000 mg p.o. or a clinically comparable dose, or equivalent' was modified to reflect slight flexibility concerning the dose of paracetamol. Change 7: Section 4.1.4.4 – Correction of neutrophil count in brackets and correction of administrative mistake in former protocol. Change 8: 4.2.2.1 - Correction of administrative mistake in former protocol Change 9: 5.1.2.10 – Correction of mistake in former protocol.

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APPROVAL / SIGNATURE PAGE

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Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Author-Statistician		13 Apr 2016 14:53 CEST
Author-Trial Clinical Monitor		13 Apr 2016 16:38 CEST
Approval-Therapeutic Area		13 Apr 2016 23:25 CEST
Approval-Team Member Medicine		20 Apr 2016 12:57 CEST
		25 Apr 2016 17:16 CEST
Verification-Paper Signature Completion		27 Apr 2016 07:32 CEST

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