Clinical Trial Protocol

Doc. No.: c01568809-08

EudraCT No.:	2010-021488-34
BI Trial No.:	1270.1
BI Investigational Product(s):	BI 836826
Title:	A Phase I, open, dose escalation trial with BI 836826 in patients with advanced chronic lymphocytic leukaemia
Clinical Phase:	Phase I
Trial Clinical Monitor:	[redacted] Phone: [redacted] Fax: [redacted]
Coordinating Investigator:	[redacted] Phone: [redacted] Fax: [redacted]
Status, Version, and Date of Protocol:	Final Protocol, Version 1, 27 July 2010
Status, Version, and Date of Revised Protocol	Final Protocol, Version 2, 20 January 2011 Final Protocol, Version 3, 20 September 2011 Final Protocol, Version 4, 2 Aug 2012 Final Protocol, Version 5, 07 Aug 2013 **Final Protocol, Version 6, 04 March 2015**

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: 27 Jul 2010	**Trial number:** 1270.1		**Revision date:** 04 Mar 2015

Title of trial:	A Phase I, open, dose escalation trial with BI 836826 in patients with advanced chronic lymphocytic leukaemia
Coordinating Investigator:	[redacted]
Trial site(s) :	Multi-center trial
Clinical phase:	Phase I
Objective(s):	To investigate the maximum tolerated dose (MTD), safety and tolerability, [redacted] and efficacy of BI 836826 monotherapy in patients with chronic lymphocytic leukaemia (CLL).
Methodology:	Open-label dose escalation
No. of patients:	About 70
total entered:	About 60
Diagnosis :	Chronic lymphocytic leukaemia (CLL)
Main criteria for inclusion:	Adult patients with active CLL who have received at least two prior treatment regimens
Test product(s) :	BI 836826
dose:	The starting dose for BI 836826 will be 1 mg.
mode of admin. :	BI 836826 administered intravenously as one to three single doses within a 14 day course.
Comparator products:	Not applicable.
dose:	
mode of admin. :	
Duration of treatment:	Minimum of one 14-day treatment course. Patients are eligible for repeated courses as long as neither patient nor investigator requests treatment discontinuation.

Name of company: Boehringer Ingelheim		**Tabulated Trial Protocol**	
Name of finished product: Not applicable			
Name of active ingredient: BI 836826			
Protocol date: 27 Jul 2010	**Trial number:** 1270.1		**Revision date:** 04 Mar 2015
Criteria for efficacy, pharmacokinetics, pharmacodynamics:	Number of lymphocytes in the peripheral blood, [redacted], blood counts, best overall response, progression free survival, failure free survival, [redacted]		
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.		

FLOW CHARTS

Flow Chart Course 1, Dosing on Day 1 and Day 2

Trial Periods	Screen	Treatment**					EOT/FU
Course *		1					If no signs of progression please continue to Visit 1 Flow Chart Course 2-8 If the patient has disease progression or withdraws, please continue to EOT visit on Flow Chart Course 2-8
Visit *	Screen	1		2		3	
Days	-14 to -1	1	2	3	4	8	
Informed consent	x						
Demographics	x						
Medical history	x						
Review of in-/exclusion criteria	x	x					
12 lead-ECG	x						
[redacted]							
Height	x						
Physical examination, [redacted] ECOG performance status	x	x					
Vital signs	x	x	x	x	x	x	
Weight	x	x					
Dose assignment	x [1]						
Adverse events		x	x	x	x	x	
Concomitant therapy	x	x	x	x	x	x	
Administration of BI 836826		x	x				
General safety laboratory parameters [3]	x	x	x	x	x	x	
Screening for Tumour Lysis Syndrome [4]		x	x	x	x		
Serum pregnancy test [5]	x	x					
CMV monitoring [6]	x	x				x	
[redacted]							
Virology screening (HBV, HCV, HIV, CMV)	x						

EOT: End of treatment, performed 14 days (± 2 days) after the last administration of BI 836826
CMV: Cytomegalovirus
HBV: Hepatitis B Virus
HCV: Hepatitis C Virus
HIV: Human Immunodeficiency Virus
[redacted]

* 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 …
** the planned duration of a treatment course is 14 days

1 After informed consent, and review of in- and exclusion criteria, and before the first administration of the trial drug
[redacted]
3 For details refer to Section 5.2.3.1

4 **Screening for tumour lysis syndrome in between safety laboratory assessments (Section 5.2.3.2)**
5 **For women of childbearing potential only (please refer to Sections 3.3.3 (exclusion criterion 18) and 5.2.3.1)**
6 **Quantitative CMV DNA PCR or pp65 antigen Section 5.2.3.3.2**

[redacted]

Flow Chart Courses 2 - 8

Trial Periods	Treatment**				EOT	FU
Course *			2 - 8			
Visit *	1		2	3	EOT	
Days	1	2	3 (+2)	8 (+2)		
12 lead-ECG					x	
Physical examination, [redacted] ECOG performance status	x				x	x
Vital signs	x	x	x	x	x	x
Weight	x				x	x
Adverse events	x	x	x	x	x	x [1]
Concomitant therapy	x	x	x	x	x	x [2]
Disease / response assessment (blood, clinical)	x [8,9]				x	x
Administration of BI 836826	x					
Eligibility for further course	x [9]					
General safety laboratory parameters [3, 9]	x	x	x	x	x	x
Screening for Tumour Lysis Syndrome [4]	x	x				
Serum pregnancy test [5]	x				x	
CMV monitoring [6]	x			x	x	x
[redacted]						
End of active trial treatment					x	
Outcome (remission, progression, death)					x	x
Other therapy for CLL						x

EOT: End of treatment, performed 14 days (± 2 days) after the last administration of BI 836826
FU: Follow-up, starts after EOT, visits at least every 4 weeks until 6 months after EOT, details see Section 6.2.3.2
CMV: Cytomegalovirus
HBV: Hepatitis B Virus
HCV: Hepatitis C Virus
HIV: Human Immunodeficiency Virus
[redacted]

* 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 …
** the planned duration of a treatment course is 14 days

1 For AE assessment during FU refer to Sections 5.2.1 and Section 6.2.3.2
2 Concomitant therapy during FU only in case indicated for treatment of an AE (Section 4.2.1).
3 For details refer to Section 5.2.3.1
4 Screening for tumour lysis syndrome in between safety laboratory assessments (Section 5.2.3.2)
5 For women of childbearing potential only (please refer to Sections 3.3.3 (exclusion criterion 18) and 5.2.3.1)
6 Quantitative CMV DNA PCR or pp65 antigen (Section 5.2.3.3.2)
[redacted]

8 **Disease / response assessment (peripheral blood, clinical) has to be performed in the first treatment course prior to starting treatment, and at day 1 of subsequent courses prior to the next administration of BI 836826, may be performed 1 day earlier to allow for a timely continuation of the treatment or at day 1 of the next course prior to treatment administration.**

9 [redacted]

If patients continue beyond cycle 8 in agreement with investigator and BI, the same assessments will be done as applicable for cycle 5-8.

TABLE OF CONTENTS

ABBREVIATIONS

[redacted]	[redacted]
ADCC	Antibody dependent cellular cytotoxicity
AE	Adverse Event
ALT	Alanine amino transferase
ANC	Absolute Neutrophil Count
anti-HB	Hepatitis B surface antibody
anti-HBc	Hepatitis B core antibody
anti-HCV	Hepatitis C antibody
AP	Alkaline phosphatase
aPTT	Activated partial thromboplastin time
ASCT	Autologous stem cell transplant
AST	Aspartate amino transferase
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
BLQ	Below the lower limit of quantification
CA	Competent Authority
CD	Cluster of Differentiation
CDC	Complement dependent cytotoxicity
CI	Confidence Interval
[redacted]	[redacted]
CLL	Chronic Lymphocytic Leukaemia
[redacted]	[redacted]
CML	Clinical Monitor Local
CMV	Cytomegalovirus
CR	Complete Remission
CRi	Complete Remission with incomplete marrow recovery
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Clinical Research Organisation
CT	Computer tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTMF	Clinical Trial Master File
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
[redacted]	[redacted]
DILI	Drug-Induced Liver Injury

DLT	Dose Limiting Toxicity
[redacted]	[redacted]
DSMB	Data Safety Monitoring Board
eCRF	Electronic Case Report Form
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic Data Capture
[redacted]	[redacted]
EOT	End of active treatment
EudraCT	European Clinical Trials Database
FAS	Full Analysis Set
[redacted]	[redacted]
FDA	Food and Drug Administration
FFS	Failure free survival
GCP	Good Clinical Practice
G-CSF	Granulocyte colony stimulating factor
GFR	Glomerular filtration rate
HAHA	Human anti-human antibodies
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
IRB	Institutional Review Board
ISF	Investigator Site File
IUD	Intrauterine device
i.v.	intravenous
IWCLL	International Workshop on Chronic Lymphocytic Leukemia
LDH	Lactate dehydrogenase
MTD	Maximum Tolerated Dose
MedDRA	Medical Dictionary for Drug Regulatory Activities
[redacted]	[redacted]
NBE	New biological entity
NC	Not calculated
NHL	Non-Hodgkin-Lymphome
NOA	Not analyzed
[redacted]	[redacted]
OBD	Optimal Biological Dose
OPU	Operative Unit
[redacted]	[redacted]

PCR	Polymerase chain reaction
PD	Progressive disease
PFS	Progession free survival
[redacted]	[redacted]
PLT	Platelets
p.o.	per os (oral)
PR	Partial remission
PT	Prothrombin time
RBC	Red blood cell count
SAE	Serious Adverse Event
s.c.	subcutaneous
SD	Stable disease
SDV	Source data verification
SMIP	Small modular immuno pharmaceutical
SOP	Standard Operating Procedure
SPC	Summary of Product Characteristics
SUSAR	Suspected unexpected serious adverse reaction
[redacted]	[redacted]
TCM	Trial Clinical Monitor
TDMAP	Trial Data Management and Analysis Plan
[redacted]	[redacted]
TLS	Tumour lysis syndrome
[redacted]	[redacted]
TMM	Team Member Medicine
TMW	Trial Medical Writer
[redacted]	[redacted]
TSAP	Trial Statistical Analysis Plan
[redacted]	[redacted]
WBC	White blood cell count
WHO	World Health Organisation

1. INTRODUCTION

1.1 MEDICAL BACKGROUND

Chronic lymphocytic leukaemia (CLL) is the most common form of leukaemia in Europe and North America, accounting for approximately one third of all leukemias in these regions, with an estimated annual age-adjusted incidence of 3–5 per 100 000 persons. The disease is diagnosed most commonly in the elderly, with the median age at diagnosis of 65 to 70 years. CLL is characterized by the accumulation of non-proliferating, mature-appearing, monoclonal B-lymphocytes in the blood, bone marrow and lymphatic organs. Commonly used staging systems, e.g. the modified Rai- or the Binet-System, classify patients in three prognostic groups as low, intermediate or high risk.

CLL is considered incurable with standard therapy. Despite a high response rate of a first line therapy with rituximab, fludarabine and cyclophosphamide, most patients will eventually experience disease progression. After subsequent relapses treatment options become increasingly limited. This is particularly true in patients refractory to fludarabine, who have limited response to salvage therapy and poor survival (R10-4432).

As of today, three monoclonal antibodies have received a marketing authorisation by regulatory authorities for the treatment of relapsed or refractory CLL: Rituximab and ofatumumab (targeting CD20) and alemtuzumab (targeting CD52).

Rituximab has limited activity as monotherapy in CLL, however is effective in combination with cytotoxic chemotherapy. Rituximab is currently introduced into first-line treatment in combination with fludarabine containing regimens and it is not clear which patients should be re-exposed to rituximab for treatment of relapsed disease.

Ofatumumab is indicated for treatment of fludarabine and alemtuzumab refractory CLL and may be a treatment option for patients relapsing after rituximab containing regimens. Subgroup analyses in a limited number of patients have shown that treatment with Ofatumumab results in similar response rates in patients who had received prior rituximab containing regimens compared to those who have not. (R10-4435).

Treatment with alemtuzumab is effective in patients with unfavourable prognostic markers such as 17p deletion, 11p deletion, unmutated VH (R10-4434), however it has limited efficacy in patients with bulky nodal disease (R10-4433). Due to the ubiquitous expression of CD52 on lymphocytes and monocytes, alemtuzumab causes significant haematological adverse events and infectious complications. However, infectious complications are manageable with adequate antibiotic prophylaxis and treatment, and careful monitoring for CMV reactivation and other potential infections (R10-4430). Alemtuzumab has clinical activity in relapsed patients with del(17p13), who are resistant to most standard therapies. While only 5% of CLL patients have del(17p13) at diagnosis, up to half of patients acquire this abnormality as their disease progresses over time (R10-4505).

To broaden the spectrum of treatment options for subsequent relapses of this chronic disease, there is a high need to develop novel treatments targeting CLL-related antigens and pathways.

1.2 DRUG PROFILE

BI 836826 is a [redacted] antibody of the IgG1 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 majority of malignant cells in patients with B-NHL and CLL express the CD37 antigen (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).

[redacted]

[redacted]

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 IgG1 and attenuated T-cell mediated immune reactions (R09-5412). The majority of malignant cells in patients with B-NHL including CLL 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 10 mg/kg in patients with CLL, with predominantly haematological dose limiting toxicities (R10-2733).

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.

This trial will be the first administration of BI 836826 in humans.

2.2 TRIAL OBJECTIVES

The primary objective of this trial is to determine the MTD of BI 836826. As BI 836826 is a new biological entity (NBE) and the MTD may not be reached, an optimal biological dose (OBD) may be defined instead, presuming pharmacokinetic or pharmacodynamic markers or clinical response parameters will indicate that BI 836826 exerts a relevant biological effect, e.g. a relevant reduction of B-cells, at a dose level with a low probability of toxicity. Secondary objectives are to document the safety and tolerability of BI 836826, [redacted] and to evaluate parameters of efficacy.

2.3 BENEFIT - RISK ASSESSMENT

Although considerable progress has been achieved in understanding the aetiology and biologic behaviour of CLL and the development of more effective treatment regimens, most patients with advanced or refractory CLL may eventually not be amenable to established forms of treatment. In particular, patients with resistant disease, relapse after fludarabine and

alkylating agent containing regimens, a short time to progression after the first treatment, and/or leukemia cells with del (17p) should be offered participation in clinical trials testing investigative agents according to published recommendations (R10-4429).

Targeting CD37 in this patient population may potentially offer a benefit to these patients, because cross-resistance with prior therapies is not to be expected.

BI 836826 is a monoclonal antibody which specifically targets CD37. In-vitro, BI 836826 was able to induce apoptosis of the target cells which resulted in depletion of B-cells from blood and lymphatic organs. In the clinical setting, these effects may potentially result in antitumour activity as a monotherapy, but also as in combination with other monoclonal antibodies or cytotoxic drugs in patients with Non-Hodgkin-Lymphoma (NHL) of B-cell origin including CLL.

BI 836826 has not previously been used in humans. CD37 is not expressed outside of the haematopoietic and lymphatic system. [redacted]

Patients with CLL and active disease requiring treatment after at least two lines of therapy with limited or no standard treatment options may benefit from tumour cell reduction, tumour stabilization or improvement of tumour-related symptoms resulting from treatment with BI 836826. The potential benefit of therapy with BI 836826 is expected to outweigh the treatment-related risks.

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

This trial will be performed in patients suffering from advanced or refractory chronic lymphocytic leukemia (CLL) who have failed two prior lines of therapy. It will be performed in an open, non-randomized, modified 3+3 design.

Initially, patients will be treated at escalating dose levels to determine the MTD.

Single patient cohorts will be treated until either a drug-related adverse event of CTCAE grade 2 or higher occurs, or until a relevant pharmacodynamic effect (i.e. a reduction of B-lymphocytes in the blood by more than 50%) is documented in a patient during the first treatment course. As soon as one of these criteria applies, cohorts will be expanded to three to six patients according to a standard 3+3 design, following a fixed dose escalation design with dose de-escalation steps (R04-0569). The dose level will be escalated with each new cohort until at least one out of three patients of a cohort experiences a DLT (for definition see 5.2.1.1). If exactly one out of the three patients of the cohort experiences a DLT, three additional patients will be treated at the same dose level. If none of the three additional patients experiences a DLT, then the 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 deescalated until a dose level is reached in which at most one DLT out of six patients is observed (R01-0028). The MTD is defined as the dose of BI 836826 that is one dose cohort below the dose at which two or more out of six patients experienced DLT. At the maximum tolerated dose, no more than one patient out of six patients may experience DLT, i.e., the MTD is defined as the highest dose studied for which the incidence of dose-limiting toxicity is no more than 17% (i.e., 1/6 patients) during the first course.

During the dose escalation phase, each patient will receive up to 4 repeated treatment courses. In patients who show an unequivocal clinical benefit after 4 courses of treatment, the number of treatment courses on the same dose level may be increased to 8 in agreement between investigator and Clinical Monitor of Boehringer Ingelheim. 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 dose limiting toxicities (DLT).

After definition of the MTD, it is planned to enroll an expansion cohort of 12-30 patients to better characterize the safety and possibly adapt the dose recommended for phase II prior to starting the next trials. Patients enrolled in the expansion cohort may receive up to 8 repeated treatment courses, provided that 4 courses are considered safe based on the available data on safety and pharmacokinetic parameters from patients treated during the dose escalation phase.

During the dose escalation phase, enrolment into the same dose cohort will be allowed the earliest 7 days after the first administration of the first dose to the previous patient in this dose cohort. Enrolment into the next higher dose cohort is allowed after the previous dose cohort was found to be safe for the initial application of the last patient in this cohort, i.e. at

least 14 days after the first application of drug in this patient. Enrolment in this context refers to the day of administration of the first dose to a patient.

Once the MTD is defined, a dose for treatment of the expansion cohort will be determined, which will not exceed the MTD. In case the MTD will not be reached, an OBD may be defined instead. This dose will be discussed and agreed between Coordinating Investigator and the sponsor. The dose recommendation for the expansion cohort 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. During treatment of the expansion cohort, new patients may be enrolled at any time.

3.1.1 Administrative structure of the trial

Boehringer Ingelheim is the Sponsor of this trial. The Coordinating Investigator and participating investigators will be physicians experienced and specialized in the treatment of CLL 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 whether to continue, modify or to terminate 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.

Adult patients with CLL who experience a relapse after at least two prior treatment regimens are considered eligible for this trial. Treatment options in this population are limited, in particular in patients with adverse prognostic markers, such as deletion 17p, who frequently do not reach durable responses or a long progression free interval after standard chemotherapy based regimens.

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 or the documentation of a threshold pharmacodynamic activity as defined in Section 3.1, cohorts of single patients will be expanded to cohorts of at least 3 patients, and the trial design will follow a standard 3+3 design with dose escalation and de-escalation. Once the MTD has been defined, an expansion cohort of 12-30 patients is planned to be enrolled to better characterize the safety profile and tolerability of the MTD.

At screening, blood samples and a physical examination including a clinical assessment of CLL are done and the patient is evaluated for eligibility in the trial. Evaluation of bone

marrow and CT scan may be performed at the discretion of the investigator. Results should be reported in case these examinations have been performed within 4 weeks prior to screening.

A patient enrolled in a cohort during dose escalation may receive up to 4 courses of BI 836826. In patients who unequivocally show clinical benefit from the drug, the administration of 4 additional treatment courses may be possible in agreement between the investigator and the Clinical Monitor at Boehringer Ingelheim. Provided that the administration of 4 courses is considered safe, up to 8 courses may be administered for patients enrolled in the expansion cohort.

Each patient will be closely monitored for infusion-related reactions and tumour lysis syndrome.

Safety [redacted] will be performed at all visits during the treatment phase.

Disease status will be assessed every two weeks until the EOT visit, including physical examination, clinical assessment of CLL and blood samples. At the discretion of the investigator (i.e., if medically indicated), a CT scan and a bone marrow examination may be performed to confirm a CR 8 weeks after a patient for the first time meets the criteria of a CR. Results of any CT scan or bone marrow examination performed during the conduct of the trial should be reported in the eCRF.

During the follow-up phase, disease status evaluations (physical examination, clinical assessment of CLL, and blood samples) should be performed at least every 4 weeks for 6 months after the EOT visit. 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

Patients with chronic lymphocytic leukaemia will be eligible for this trial.

3.3.2 Inclusion criteria

1. Diagnosis of relapsed or refractory chronic lymphocytic leukaemia (according to the definition of the IWCLL (R10-4429))
2. Previous therapy of CLL with at least two prior treatment regimens
3. At least one of the following criteria for active disease as defined by the IWCLL
   (1) Evidence of progressive marrow failure as manifested by the development or worsening of anemia and/or thrombocytopenia
   (2) Massive (i.e. at least 6 cm below the left costal margin) or progressive or symptomatic splenomegaly as assessed by the investigator;
   (3) Massive nodes (i.e. at least 10 cm in longest diameter) or progressive or symptomatic lymphadenopathy as assessed by the investigator

(4) Progressive lymphocytosis with an increase of more than 50% over a 2-month period or a lymphocyte doubling time of less than 6 months
(5) Constitutional symptoms, defined as any one or more of the following disease-related symptoms or signs:
- Unintentional weight loss of 10% or more within the previous 6 months
- Fevers higher than 38.0°C for 2 or more weeks without other evidence of infection
- Night sweats for more than 1 month without evidence of infection

4. Absolute lymphocyte count lower than 200 x 10^9/l
5. ECOG Performance Status 0, 1 or 2
6. Age ≥ 18 years.
7. Written informed consent which is consistent with ICH-GCP guidelines and local legislation

3.3.3 Exclusion criteria

1. Prior treatment with anti CD 20 therapy within 4 weeks, or alemtuzumab within 8 weeks, or any **cytotoxic** antileukemia therapy within 2 weeks, **Ibrutinib or Idelalisib within 1 week** prior to the first administration of the trial drug
2. Prior allogeneic stem cell transplantation
3. Active autoimmune haemolytic anemia
4. Active autoimmune thrombocytopenia
5. Known transformation to an aggressive B-cell malignancy (e.g. large B-cell lymphoma, Richter's syndrome)
6. Concurrent treatment with systemic glucocorticosteroids at doses equivalent to prednisolone 20 mg/d or higher.
7. Prior history of malignancy other than CLL (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.
8. AST, and/or ALT > 2.5 x upper limit of normal (CTCAE grade 2 or higher)
9. Total bilirubin > 1.5 x upper limit of normal (CTCAE grade 2 or higher)
10. ANC < 1.0 x 10^9/L (without growth factor support).
11. Platelets < 25 x 10^9/L (without growth factor support or transfusions)
12. Estimated GFR <45 mL/min (see Section 10.3)
13. Proteinuria CTCAE grade 2 or higher
14. 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.
15. Any infectious disease requiring treatment at the time of enrolment or within the previous 2 weeks.
16. Active Hepatitis B or Hepatitis C, or laboratory evidence for a chronic infection.
17. HIV infection
18. CMV viremia
19. 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 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 are 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 post-menopausal for at least two years.

20. Pregnancy or breast feeding.
21. Known or suspected active alcohol or drug abuse.
22. Treatment with another investigational drug within the past four weeks before start of therapy or concomitantly with this trial.
23. Prior treatment with BI 836826.
24. Patients unable to comply with the protocol

3.3.4 Removal of patients from therapy or assessments

3.3.4.1 Removal of individual patients

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

- The patient withdraws consent. Patients are free to discontinue their participation in this trial at any time without the need to justify the decision.
- The patient needs concomitant drugs which may interfere with the investigational product (please refer to Section 4.2.2).
- The patient is no longer able to participate for other medical reasons (e.g. adverse events unrelated to therapy or disease progression, concomitant diagnoses, pregnancy, surgery or administrative reasons). The investigator may also stop a patient's participation if the patient is no longer able to attend trial visits.

A patient can be withdrawn 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 next scheduled visit and the EOT have to be performed if feasible. Every effort should be made to follow-up patients in case an AE is still ongoing at the time of withdrawal.

A patient has to discontinue trial drug administration in case

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

Patients who have not completed at least one course will be replaced. 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 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).

3.3.4.2.1 Trial stopping rules in case of unacceptable toxicities

All AEs, including SAEs and deaths will be carefully analyzed by the sponsor. Unacceptable toxicity will be defined as:

- **Clinically relevant adverse events that are unexpected considering the mode of action, and are not manifestations of underlying disease or background events typical of the study population**
    - **and/or are debilitating, non-reversible, not manageable**
    - **or lead to a fatal outcome**

  where evidence suggests that there was a reasonable possibility that the drug caused the adverse event

- **Higher than expected frequency of specific events (such as known consequences of the underlying disease or other events that commonly occur in the study population independent of drug therapy) that indicates those events occur more frequently in the drug treatment group than would be expected in the study population.**

If one or both of the above criteria are met the enrolment to the trial will be stopped to allow for in-depth analysis of the safety profile of BI836826. The risk-benefit profile of BI 836826 will be re-assessed by the sponsor's trial team, coordinating investigator and DSMB. The outcome of the analysis and the recommendations will be shared with all involved regulatory health authorities prior to a possible re-start of enrolment.

In case the benefit/risk assessment is no longer considered to be positive, the trial will be discontinued.

4. TREATMENTS

4.1 TREATMENTS TO BE ADMINISTERED

In course 1, the total dose will be divided into two portions administered on day 1 and 2 (please refer to the Flow Chart: Course 1, Dosing on Day 1 and Day 2).

The dose on day 1 will be 10% of the total dose, but not exceed 10 mg in case the total dose is higher than 100 mg. The dose on day 2 will be the planned total dose minus the dose administered on day 1. If adverse events which are related to the infusion schedule, e.g. infusion-related reactions or tumour lysis syndrome require administration of a lower dose on day 2, the total dose in course 1 may be divided into 3 smaller portions on day 1, 2 and 8. In this case, the dose on day 1 will remain as defined previously. The difference between day 1 and the planned total dose level will be equally divided between day 2 and 8 (reference to appendix 10.6). The distribution of the planned total dose in course 1 to two, or if needed to three smaller portions will be based on safety data from the previous cohort and will be assessed and may be modified by the DSMB. If supported by the DSMB, the same rules may be applied to course 2 in case infusion-related adverse events can be controlled by the above measures in course 1 but occur in course 2.

In all subsequent treatment courses, BI 836826 will be administered as a rate-controlled intravenous infusion on day 1 of each 14-day course.

The first and second infusion will be started at a rate of 10 mL/h. The infusion rate should be increased every 30 (+/-10) minutes by 10 mL/h to a maximum of 80 mL/h as long as tolerated by the patient. If considered safe by the investigator, the stepwise increase of infusion rate during the third and subsequent infusions may be faster or steps may be omitted, but the maximum infusion rate must not exceed 120 mL/h. If symptoms of an infusion related reaction occur, the infusion should be temporarily stopped. Upon recovery, it should be 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 reasons, 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.

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(s)

4.1.1.1 BI 836826

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:	One to three single doses within a 14 day course
Route of administration:	Intravenous
Posology:	Rate controlled infusion See Section 4.1.6

4.1.2 Method of assigning patients to treatment groups

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

4.1.3 Selection of doses in the trial

BI 836826 will be administered as a rate-controlled, intravenous infusion on day 1, 2 and possibly day 8 in course 1 and on day 1 in the subsequent courses.

A fixed dose of 1 mg BI 836826 per patient was determined 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 of CLL patients. For details please refer to the Investigator's Brochure, Section 5.6.3 (U10-1892-01).

The dose is planned to be escalated in cohorts at pre-defined dose levels based on a multiplication factor of approximately 3 in the low dose range, and a factor of 2 at doses higher than 25 mg. The dose levels per treatment course are 1 mg, 3 mg, 9 mg, 25 mg, 50 mg, 100 mg, 200 mg **…**, up to 1400 mg. At doses higher than 200 mg, the next dose cohort will be enrolled at a dose which is at maximum two times of the previous dose.

Every time a dose escalation is to be performed, the data of all previous dose cohorts will be reviewed and discussed between the Coordinating Investigator and the sponsor. The same data and the recommendation of the Sponsor and Coordinating investigator will be provided to the DSMB who will be asked to provide an independent assessment including a 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

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. 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. [redacted]

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/or prophylactic drugs according to local standards or published guidelines (R10-4517).

Premedication to prevent infusion-related reactions is obligatory 30 - 120 minutes prior to the first and second administration of BI 836826, unless a contraindication for premedication exists, and should include

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

If BI 836826 has been well tolerated without signs of infusion-related reactions in the first and second course, glucocorticoid premedication may be reduced to 50% of the dose in the previous course starting with the third course. In case the patient has tolerated the 4th treatment course without infusion-related reactions after premedication with doses equivalent to prednisolone 25 mg, the investigator may individually decide whether to administer premedication in courses 5-8.

During the dose-escalation phase, up to 4 courses may be administered. In case of evidence of clinical benefit as judged by the investigator (e.g. PR, CR, disease stabilization, amelioration of CLL related symptoms), treatment with BI 836826 can be continued for another 4 courses after discussion between the Investigator and the Clinical Monitor of the sponsor. During treatment of the expansion cohort, a maximum of 8 courses may be offered to all patients. In the dose-escalation phase as well as in the expansion cohort, in patients who experience sustained benefit and tolerate treatment well, treatment may be continued beyond 8 courses on a case by case basis after discussion between the Investigator and the Clinical Monitor of the sponsor. If patients continue beyond cycle 8, the same assessments will be done as applicable for cycles 5-8. At the end of each treatment course, adverse events and safety laboratory will be assessed. To continue treatment with further courses, **all** of the following criteria must be met:

(1) Neutrophils ≥ 500 /µL (0.5 x 10^9/L) and platelets ≥ 25.000 /µL (25 x 10^9/L), with or without growth-factor support or transfusions.

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

In case criterion 1 and/or 2 is not fulfilled, blood counts and/or the adverse event should be re-evaluated for up to three weeks. Any case of a delay in treatment course should be communicated to the Clinical Monitor at Boehringer Ingelheim. As soon as criterion 1 is 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). 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 may be considered in agreement between investigator and sponsor for selected patients. It is restricted to patients who have received at least 4 treatment courses and tolerate the treatment well at the time of dose escalation. Intra-patient dose escalation can only be performed at a time when the next higher dose cohort has been reviewed and considered safe by the DSMB. The dose escalation step is limited the dose which has been administered to the next higher cohort. The treatment courses at the increased dose have to follow the instructions as outlined for course 5-8 in the Flow Chart and the protocol. In addition, after the first dose at the higher dose level, patients have to be monitored for at least 24 hours after the end of the infusion, including safety laboratory for tumour lysis syndrome.

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, single arm design. It will recruit patients with relapsed and refractory CLL and active disease. 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

[redacted]

For details of packaging and the description of the label, refer to the Investigator Site File (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 (U10-1892-01) 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.

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(s). 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(s) received from the sponsor.

4.2 CONCOMITANT THERAPY, RESTRICTIONS, AND RESCUE TREATMENT

4.2.1 Rescue medication, emergency procedures, and additional treatments

Rescue medication to reverse the action of BI 836826 is not available. Potential side effects of BI 836826 have to be treated symptomatically. Patients should receive supportive care according to local guidelines regarding treatment of infusion-related reactions, blood product support, antibiotics, antivirals, 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. The use of growth factors such as granulocyte colony stimulating factor (G-CSF) will be allowed, but growth factors should be avoided in the first treatment course for better assessment of safety and response parameters.

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

All concomitant non-antileukaemia therapies to provide adequate care may be given as clinically necessary. 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 anaesthesia, it will be sufficient to indicate '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.

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

Prior antileukemia therapy must have been discontinued **in line with the requirement per exclusion criterion 1** and the patient must have recovered from all clinically relevant reversible toxicities. A time interval of at least 4 weeks must have elapsed from the last administration of any other investigational treatment for CLL to the first administration of BI 836826.

No anti-neoplastic therapy concomitantly is allowed.

Short term glucocorticoid medications may be used as clinically indicated to treat infusion-related reactions at any dose. Daily oral steroid treatment may be administered at doses equivalent to prednisolone 20 mg per day. All other indications for steroids have to be discussed and agreed upon between investigator and sponsor.

Immunoglobulins should be avoided during treatment with BI 836826. However, if medically indicated, e.g. for substitution of immunoglobulin deficiency, immunoglobulins may be used. Administration within a time window of 2 days before and after the infusion of BI 836826 should be avoided.

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

5. VARIABLES AND THEIR ASSESSMENT

5.1 EFFICACY - PHARMACODYNAMICS

5.1.1 Endpoints of efficacy

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

Secondary endpoints of efficacy are:

- Number of lymphocytes in the peripheral blood
- [redacted]
- Blood counts (red blood cells, haemoglobin, platelets, neutrophils)
- Best overall response according to IWCLL criteria (R10-4429)
- Progression free survival
- Failure free survival

[redacted]

5.1.2 Assessment of efficacy

5.1.2.1 Number of lymphocytes in the peripheral blood

In most patients with relapsed or refractory CLL, malignant B-cells represent the majority of lymphocytes in the peripheral blood. Reduction of B-cells can be assessed in the peripheral blood by blood cell counts, differential WBC analysis and flow cytometry, which will be performed at the time points specified in the Flow Chart. [redacted]

[redacted]

[redacted]

5.1.2.3 Blood counts (red blood cells, haemoglobin, platelets, neutrophils)

- Blood counts including a differential will be done at all visits. In patients with blood counts below the limits of normal pre-treatment, improvement in blood counts during therapy may indicate a benefit for the patient.

5.1.2.4 Assessment and definition of overall best response

Response will be assessed according to the IWCLL guidelines based on laboratory data from the peripheral blood and clinical examination after each course prior to administration of the next dose of BI 836826, at the EOT-visit and at all follow-up visits. Bone marrow examination will be performed at the discretion of the investigator, e.g. in case clinical and laboratory examinations of peripheral blood demonstrate that a CR has been achieved, or for assessment of persistent neutropenia, anemia or thrombocytopenia.

5.1.2.4.1 Complete remission (CR)

CR requires all of the following criteria for a period of at least 2 months:

A1 Peripheral blood lymphocytes (evaluated by WBC and differential count) below 4×10^9/L.
A2 Absence of significant lymphadenopathy, i.e. no lymph nodes > 1.5 cm.
A3 No hepatomegaly.
A4 No splenomegaly.
A5 Bone marrow aspirate and biopsy demonstrate absence of residual disease.
B1 Platelets more than 100×10^9/L (without exogenous growth factors or transfusion).
B2 Hemoglobin more than 110 g/L (without exogenous growth factors or transfusions)
B3 Neutrophils more than 1.5×10^9/L (without exogenous growth factors).
C Absence of disease-related constitutional symptoms.
4.
Group A criteria define the tumor load, group B criteria define the function of the hematopoietic system. In case all criteria A and C are met, but a patient has a persistent anemia or thrombocytopenia or neutropenia apparently unrelated to CLL, but related to drug toxicity, the patient should be categorized as CR with incomplete marrow recovery (CRi).

5.1.2.4.2 Nodular partial remission (nodular PR)

In case lymphoid nodules are found in the bone marrow, but all other criteria for CR are met, the case should be classified as nodular PR

5.1.2.4.3 Partial remission (PR)

To define a PR, at least 2 criteria of category A and 1 criterion of category B have to be met for a period of at least 2 months.

A1 Decrease in the number of blood lymphocytes by 50% or more compared to the pre-treatment value.
A2 Reduction in lymphadenopathy by 50% or more, defined as
a decrease in lymph node size by 50% or more, either in the sum products of up to 6 lymph nodes or in the largest diameter of the enlarged lymph nodes detected prior to therapy, AND
no increase in any lymph node, and no new enlarged lymph node. In small lymph nodes (<2cm) an increase of less than 25% is not considered to be significant.
A3 Decrease in hepatomegaly by 50% or more
A4 Decrease in splenomegaly by 50% or more.
A5 Reduction by 50% or more in bone marrow infiltration, or B-lymphoid nodules.
B1 Platelets more than 100 x 10^9/L or 50% improvement over baseline (without exogenous growth factors or transfusion).
B2 Hemoglobin more than 110 g/L or 50% improvement over baseline (without exogenous growth factors or transfusions).
B3 Neutrophils more than 1.5 x 10^9/L or 50% improvement over baseline (without exogenous growth factors).

5.1.2.4.4 Progressive disease (PD)

At least one of the following criteria is required:

A1 An increase in the number of blood lymphocytes by 50% or more over baseline with an absolute number of B-lymphocytes of at least 5 x 10^9/L.
A2 Progression of lymphadenopathy, defined as appearance of any new lymph node > 1.5 cm or an increase by 50% or more in the greatest determined diameter of any previous site, or appearance of a new organ infiltrate other then hepatomegaly or splenomegaly.
A3 An increase in the previously noted enlargement of the liver by 50% or more or new appearance of hepatomegaly.
A4 An increase in the previously noted enlargement of the spleen by 50% or more or new appearance of splenomegaly.
B1 Decrease of platelet counts by more than 50% or to less than 100 x 10^9/L secondary to CLL and unrelated to autoimmune cytopenia
B2 Decrease of hemoglobin levels by more than 20 g/L or to less than 100 g/L secondary to CLL and unrelated to autoimmune cytopenia
T Transformation to a more aggressive histology, e.g. Richter syndrome.

During therapy, cytopenia cannot be used to define disease progression. The progression of any cytopenia unrelated to autoimmune cytopenia as defined by criteria B1 and B2 which

occurs at least 3 months after treatment, defines disease progression, if the marrow biopsy demonstrates an infiltrate of clonal CLL cells.

5.1.2.4.5 Stable disease (SD)

Patients who have not achieved a CR or a PR, and who have not exhibited PD, will be considered to have stable disease.

5.1.2.5 Progression free survival (PFS)

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

5.1.2.6 Failure free survival (FFS)

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

[redacted]

[redacted]

5.2 SAFETY

5.2.1 Endpoints of safety

As this trial is the first in human use of BI 836826, the primary objective is to assess the safety of the drug in humans and to determine the MTD of BI 836826. For details on determination of MTD, please refer to Sections 3.1, 5.2.1.1 and 7.3.1.

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 (DLT)

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.

The additional following haematologic adverse events will be considered DLT:

- **Grade 4 neutropenia lasting more than 7 days.**
- **Febrile neutropenia not resolving within 48 hrs with appropriate treatment (antibiotics, antivirals, antifungals, growth factor support)**

- **Grade 4 thrombocytopenia lasting more than 7 days, or grade 3-4 thrombocytopenia with clinically significant bleeding**
- **Grade 4 anemia**

Less severe haematological adverse events are frequently pre-existing in CLL patients, are usually manageable with routine supportive measures and are therefore not considered as adverse events relevant for DLT definition. Nevertheless, haematological adverse events 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 treatment course**.** However, for those patients who receive more than one dose 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.

All DLTs, occurring during the first or repeated treatment course will be reported as significant adverse events.

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 event

A 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 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,
- Drug-induced liver injury (DILI)
  Although rare, 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 10.5 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 Appendix 10.5 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.

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 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.

Changes in vital signs, ECG, 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 and non-serious, occurring during the course of the clinical trial (i.e., from signing the informed consent onwards through the observational phase (=6 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, 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.

Table 5.2.2.2:1 AE/SAE reporting requirements

Time Period	Reporting requirements
From signature of informed consent until 6 weeks (42 days) after last administration of study drug	Report all AEs, SAEs regardless of relatedness. This includes all deaths.
Post treatment (>42 days after last administration of study drug) until end of follow-up (6 months after the EOT visit)	Report AEs and SAEs which are considered related to study drug or study design / procedures. Please note: Death should always be reported as SAE in this trial.

Patients may be hospitalized during selected phases of the study as required per protocol, e.g., monitoring of trial drug administration, [redacted], 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.

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

The SAE form is to be forwarded to the defined unique entry point identified for the BI OPU (country-specific contact details will be provided in the Investigator Site File). This immediate report is required irrespective of whether the investigational product has been administered or not and irrespective of causal relationship. It also applies if new information to existing SAEs or 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 Flow Chart. **Blood samples should be collected more frequently in case of relevant toxicities; e.g. in case of grade 4 neutropenia or thrombocytopenia, to document as accurately as possible the duration of the AE**. 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 Screening, Visit 1, Day 1 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 Screening, Visit 1, Day 1 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) where indicated (e.g. treatment with vitamin K antagonists)
Urine	pH, glucose, erythrocytes, leukocytes, protein, nitrite will be analysed by dipstick and reported as semiquantitative measurements. In case of pathological findings, further evaluation should be performed and results documented.
Pregnancy test	A serum pregnancy test needs to be obtained at the time points indicated in the Flow Chart in patients of childbearing potential.

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

Tumor lysis syndrome (TLS) is characterized by a group of metabolic derangements caused by the massive and abrupt release of cellular components into the blood after rapid lysis of malignant cells. The release of intracellular metabolites, including nucleic acids, proteins, phosphorus, and potassium, 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). 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).

To allow for early treatment in case TLS develops, vigilant monitoring is recommended. Between the first and the second infusion, during the first 48 hours after the start of the second infusion of BI 836826 in course 1 and during the first 24 hours after the start of the infusion(s) in course 2, in between timepoints at which a complete safety laboratory has to be performed, i.e. every 4-8 hours, the following laboratory parameters need to be determined to screen for evidence of a tumour lysis syndrome. In case the schedule as outlined in Section 10.6 is used, monitoring for TLS has to be performed for 24 hours also after the infusion on day 8.

Sampling for TLS in course 3 and subsequent courses should be performed as clinically indicated.

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) with differential, platelets (PLT)
Biochemistry	uric acid, potassium, calcium, inorganic phosphate, lactate dehydrogenase (LDH), creatinine, urea

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. 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 Flow Chart according to local standards. Quantitative PCR assays to detect CMV DNA and quantitative assays of the pp65 antigen are considered acceptable for the purpose of this trial. The same method should be used for all patients treated at the same investigational site. Results have to be reported in the eCRF.

[redacted]

[redacted]

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.

5.2.5 Assessment of other safety parameters

5.2.5.1 Vital signs

Vital signs (blood pressure, pulse rate and body temperature) will be recorded at every visit during screening, treatment and follow-up. Additional time points for blood pressure and heart rate at the day of administration of BI 836826 are: prior to the start of premedication and infusion, then every 30 (±10) minutes after start of the infusion of BI 836826 and 60 (±10) minutes after the end of the infusion. At least during the first two courses blood pressure, pulse rate and body temperature should be measured every 4-8 hours until at least 24 hours after the start of the infusion. In case of an infusion-related reaction, the investigator should decide whether to intensify or prolong monitoring of vital signs of the patient. Continuous cardiac monitoring should be performed during the first and second infusion of BI 836826, patient surveillance may be modified by the investigator according to tolerability of the infusion during subsequent applications.

5.2.5.2 Physical examination

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

[redacted]

[redacted]

[redacted]

5.4 APPROPRIATENESS OF MEASUREMENTS

Determination of MTD 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 (R10-4429) are well established and scientifically accepted.

[redacted]

[redacted]

[redacted]

[redacted]

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

During the treatment phase, after administration of BI 836826, patients are required to be hospitalized under close surveillance with access to intensive care for at least 48 hours after the second dose of BI 836826 in course 1 to allow close monitoring for infusion-related reactions, tumour lysis syndrome or other adverse events. After good tolerability of the first two doses in course 1 of BI 836826 the investigator may evaluate the risk for an infusion-related reaction and other adverse events in view of relevant comorbidities or CLL-related symptoms, and as a result, shorten the duration of surveillance to 24 hours.

In case the patient demonstrated benefit after 4 treatment courses, and the investigator in agreement with the sponsor decided to administer 4 additional courses, the decision whether to hospitalize the patient for application of courses 5-8 is left to the discretion of the investigator.

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

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

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

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

6.2.1 Screening period

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.

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

- Informed consent
- Demographics (sex, birth date, race)
- Medical history (oncological and relevant non-oncological)
- Review of inclusion and exclusion criteria (patient eligibility)
- 12-lead ECG
- Informed consent for pharmacogenetics
- Physical examination, body height, weight, vital signs and ECOG performance score

- Disease assessment: [redacted]
- Safety laboratory (haematology, biochemistry including serum immunoglobulin levels and direct antiglobulin test, coagulation, urine; for details please refer to Section 5.2.3.1)
- Serum pregnancy test in women of childbearing potential
- Virology screening (HBV, HCV, HIV, CMV) and CMV monitoring, for details refer to Section 5.2.3.3
- [redacted]
- Dose assignment (during dose escalation phase only, before the first administration of the trial drug and after informed consent and review of in- and exclusion criteria)
- Concomitant therapy

6.2.2 Treatment periods

6.2.2.1 Visit 1 - day 1 (day 1 of a treatment course)

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

- Review of inclusion and exclusion criteria (patient eligibility), in the first cycle only
- Blood samples for pharmacogenetic investigations (optional, only after signature of separate informed consent)
- Physical examination, weight [redacted]
- Vital signs at time points specified in Section 5.2.5.1
- Adverse events (AEs)
- Changes in concomitant therapies
- Administration of BI 836826 after final confirmation of dose tier
- Safety lab parameters before trial drug administration as specified in Section 5.2.3.1
- [redacted]
- Blood samples to screen for evidence of tumour lysis syndrome (see Section 5.2.3.2)
- Serum pregnancy test in women of childbearing potential (does not have to be repeated in case pregnancy test has been performed within the last 3 days)
- CMV monitoring (see Section 5.2.3.3.2)

- [redacted]
- Response assessment (blood and clinical assessment) at the end of each treatment course prior to next administration of BI 836826, may be performed at day 1 of the next course prior to treatment administration or up to 1 day earlier to allow for a timely continuation of the treatment.
- Assessment of eligibility for further courses in all treatment courses except for course 1

6.2.2.2 Visit 1 - day 2 (day 2 of a treatment course)

On the day after the treatment, the following parameters and investigations will be obtained/performed

- Administration of BI 836826 only in course 1
- Vital signs at time points specified in Section 5.2.5.1
- Adverse events
- Concomitant therapy
- Safety lab parameters as specified in Section 5.2.3.1
- Blood samples to screen for evidence of tumour lysis syndrome (see Section 5.2.3.2)
- [redacted]

6.2.2.3 Visit 2 - day 3 (day 3 in course 1 or day 3 (+2) in course 2-8)

On visit 2, the following parameters and investigations will be obtained/performed

- Vital signs (see Section 5.2.5.1)
- Adverse events
- Concomitant therapy
- Safety lab parameters as specified in Section 5.2.3.1
- [redacted]

6.2.2.4 Visit 2 - day 4 (day 4 only in course 1)

- Vital signs (see Section 5.2.5.1)
- Adverse events
- Concomitant therapy
- Safety lab parameters as specified in Section 5.2.3.1
- [redacted]

6.2.2.5 Visit 3 - day 8 (**day 8 in course 1** and day 8 (+2) in course 2-8)

On visit 3, the following parameters and investigations will be obtained/performed

- Administration of BI 836826 only in course 1, if treatment schedule according to Section 10.6 is used
- Vital signs (see Section 5.2.5.1)
- Adverse events
- Concomitant therapy
- Safety lab parameters as specified in Section 5.2.3.1
- Blood samples to screen for evidence of tumour lysis syndrome only in course 1, if treatment schedule according to section 10.6 is used
- [redacted]
- CMV monitoring (see Section 5.2.3.3.2)

6.2.2.6 Visit 3 - day 9 (day 9 only in course 1, if treatment schedule according to Section 10.6 is used)

On visit 3, the following parameters and investigations will be obtained/performed

- Vital signs (see Section 5.2.5.1)
- Adverse events
- Concomitant therapy
- Safety lab parameters as specified in Section 5.2.3.1
- Blood samples to screen for evidence of tumour lysis syndrome
- [redacted]

6.2.3 End of trial and follow-up period

6.2.3.1 End of treatment

The end of treatment (EOT) visit should be performed 14 days (± 2 days) after the last administration of BI 836826. If the patient concludes the trial within a treatment cycle not at the end of a treatment cycle, the information required to be collected at the EOT visit should be obtained immediately.

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

- Physical examination, weight [redacted]
- Vital signs (see Section 5.2.5.1)
- 12-lead ECG
- Adverse events (AEs)

- Changes in concomitant therapies
- Response assessment (blood and clinical assessment)
- Safety lab parameters as specified in Section 5.2.3.1
- [redacted]
- Serum pregnancy test in women of childbearing potential (does not have to be repeated in case pregnancy test has been performed within the last 3 days)
- CMV monitoring (see Section 5.2.3.3.2)
- [redacted]
- Completion of trial treatment (including reason for conclusion or if applicable premature discontinuation of trial, date of last administration of the trial drug)
- Outcome: in case the patient had PD the date of first diagnosis of PD has to be recorded

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-neoplastic therapy or in case the investigator and sponsor agree not to pursue further follow up visits. Follow-up visits should be performed at 4 weeks intervals or earlier 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 for 6 months after the EOT-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:

- Physical examination, [redacted] vital signs and weight
- [redacted]
- Safety laboratory (haematology, biochemistry including serum immunoglobulin levels and direct antiglobulin test, coagulation, urine; for details please refer to Section 5.2.3.1)
- Response assessment (blood and clinical assessment)
- CMV monitoring (see Section 5.2.3.3.2)
- [redacted]

- AEs since last visit in case they occurred during the observational period (6 weeks after the last trial drug administration) or are considered drug-related (see Section 5.2.1)
- concomitant therapy indicated for treatment of an AE
- Follow-up of AEs in case they were not yet recovered at EOT
- [redacted]
- Outcome: date death (if applicable), date of progression (in case, the patient experienced PD)
- [redacted]

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. 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.

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.). After the MTD has been determined, up to 30 patients are additionally entered at a dose level supposed to be recommended for Phase II.

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). In order to identify the MTD, the number of DLTs at each dose level must be presented. For the analysis of tolerability and safety, please refer to Section 7.3.3.

7.3.2 Secondary analyses

7.3.2.1 Number of lymphocytes in the peripheral blood

The number and the change of lymphocytes in the peripheral blood will be analysed descriptively by time point. The maximal reduction of lymphocytes with respect to all time points after baseline will be analysed.

[redacted]

7.3.2.4 Blood counts

Blood counts will be analysed as part of the laboratory tests (see Section 7.3.3)

7.3.2.5 Best overall response

Best overall response is the best response (CR, PR, SD or PD in this order) with respect to all time points. Remission rate is the rate of patients that either have CR 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.

7.3.2.6 Progression-free survival, [redacted], failure-free survival, [redacted]

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.

[redacted]

7.3.3 Safety analyses

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.

Incidence and intensity of adverse events

The severity, and timing of adverse events will indicate how well the treatment regimen is tolerated. Toxicities 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 treatment schedules. Serious adverse events will be tabulated. In addition, events leading to dose reduction or treatment discontinuation will be examined, but may not be reported as individual tables, depending upon the extent of overlap with the occurrence of DLT.

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 started

within the period starting with first administration of the trial drug and ending six 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 and the DSMB will perform interim safety evaluations as considered necessary.

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

If considered necessary, as soon as the MTD is determined an evaluation of the safety aspects will be performed. Results of this evaluation will be documented and archived. If applicable such an analysis will be defined in more detail in the Statistical Analysis Plan.

[redacted]

[redacted]

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.

Together with an assumed number of up to 30 additional patients for the expansion cohort this leads to an expected sample size of 60 entered patients. Note that in general, the sample size is induced by the 3+3 design and is subject to different random factors.

8. INFORMED CONSENT, DATA PROTECTION, TRIAL RECORDS

The trial will be carried out in compliance with the protocol, the principles laid down in the Declaration of Helsinki, version as of October 1996 (as long as local laws do not require to follow other versions), 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 (CA) according to national and international regulations. The same applies for the implementation of changes introduced by amendments.

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

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

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

8.2 DATA QUALITY ASSURANCE

The trial will be conducted in compliance with the protocol, the principles laid down in the Declaration of Helsinki version 1996 (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.

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.

8.3 RECORDS

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

8.3.1 Source documents

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

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

For eCRFs all data must be derived from source documents.

8.3.2 Direct access to source data and documents

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

8.4 LISTEDNESS AND EXPEDITED REPORTING OF ADVERSE EVENTS

8.4.1 Listedness

To fulfil the regulatory requirements for expedited safety reporting, the sponsor evaluates whether a particular adverse event is "listed", i.e. is a known side effect of the drug or not. Therefore a unique reference document for the evaluation of listedness needs to be provided. For BI 836826 this is the current version of the Investigator's Brochure (U10-1892-01). 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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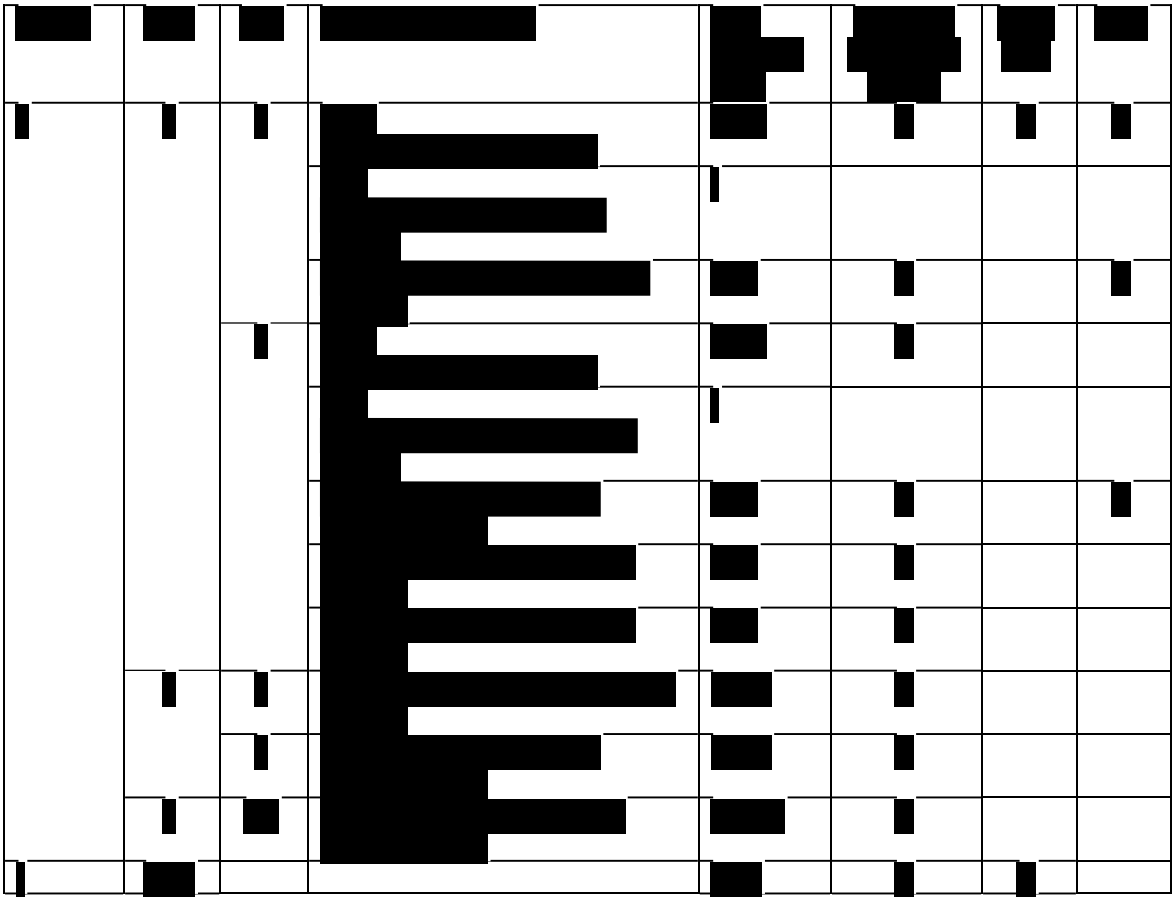
10. APPENDICES

[redacted]

[redacted]

[redacted]



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10.4 EASTERN COOPERATIVE ONCOLOGY GROUP (ECOG) PERFORMANCE SCORE

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

Reference R01-0787

10.5 CLINICAL EVALUATION OF LIVER INJURY

10.5.1 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:

10.5.2 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.

[redacted]

10.6 FLOW CHART [redacted] FOR COURSE 1, IN CASE THE TOTAL DOSE IN THIS COURSE IS DIVIDED INTO THREE PORTIONS ADMINISTERED ON DAY 1, DAY 2 AND DAY 8

Flow Chart for Course 1 with administration on Day 1, Day 2 and Day 8

Trial Periods	Screen	Treatment**						EOT	FU
Course *		1						If no signs of progression please continue to Visit 1 Flow Chart Course 2-8	
Visit *	Screen	1				2			
Days	-14 to -1	1	2	3	4	8	9		
Informed consent	x								
Demographics	x								
Medical history	x								
Review of in-/exclusion criteria	x	x							
12 lead-ECG	x								
[redacted]								If the patient has disease progression or withdraws, please continue to EOT visit on Flow Chart Course 2-8	
Height	x								
Physical examination, [redacted] ECOG performance status	x	x							
Vital signs	x	x	x	x	x	x	x		
Weight	x	x							
Dose assignment	x [1]								
Adverse events		x	x	x	x	x	x		
Concomitant therapy	x	x	x	x	x	x	x		
Administration of BI 836826		x	x			x			
General safety laboratory parameters [3]	x	x	x	x	x	x	x		
Screening for Tumour Lysis Syndrome [4]		x	x	x	x	x	x		
Serum pregnancy test [5]	x	x							
CMV monitoring [6]	x	x				x			
[redacted]									
Virology screening (HBV, HCV, HIV, CMV)	x								

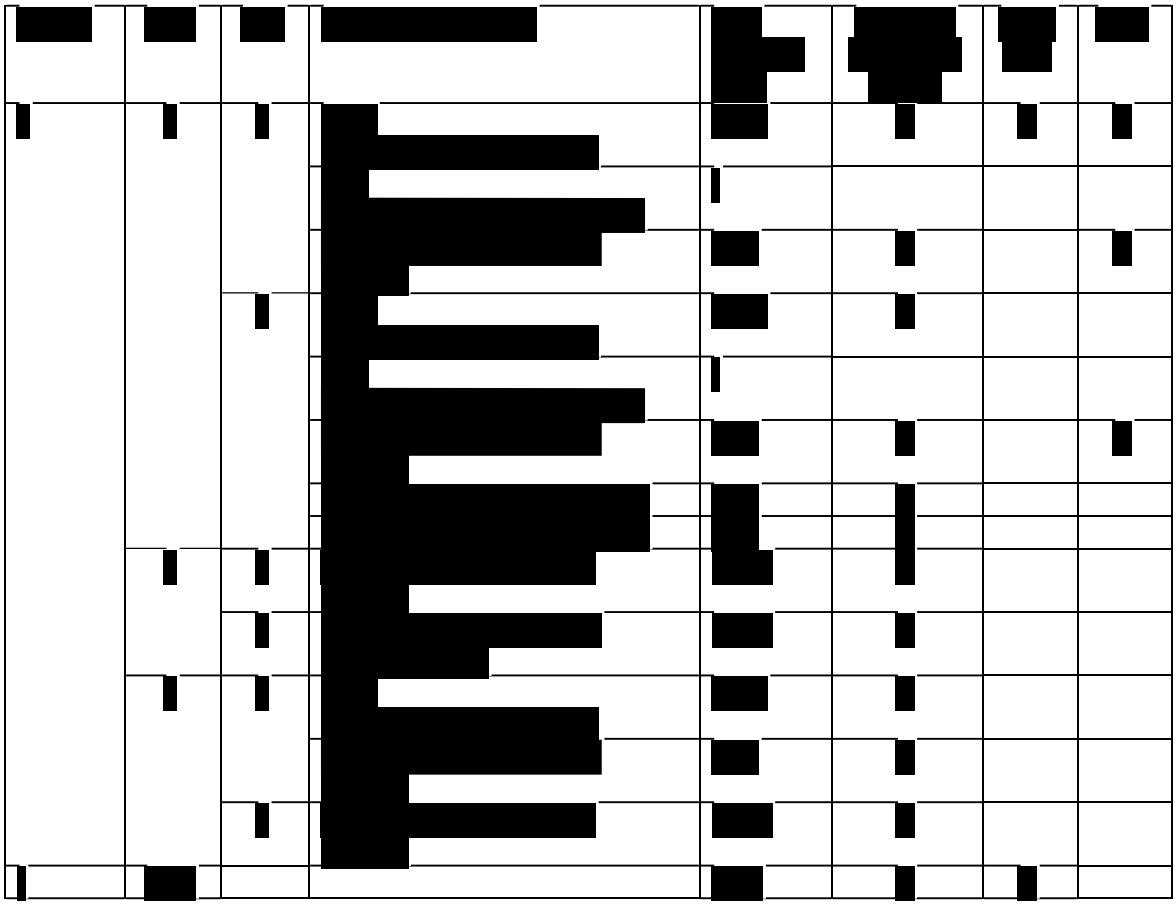
EOT: End of treatment, performed 14 days (± 2 days) after the last administration of BI 836826
FU: Follow-up, starts after EOT, visits at least every 4 weeks until 6 months after EOT, details see Section 6.2.3.2
CMV: Cytomegalovirus

HBV: Hepatitis B Virus
HCV: Hepatitis C Virus
HIV: Human Immunodeficiency Virus
[redacted]

* 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 …
** the planned duration of a treatment course is 14 days

1 After informed consent, and review of in- and exclusion criteria, and before the first administration of the trial drug
[redacted]
3 For details refer to Section 5.2.3.1
4 Screening for tumour lysis syndrome in between safety laboratory assessments (Section 5.2.3.2)
5 For women of childbearing potential only (please refer to Sections 3.3.3 (exclusion criterion 18) and 5.2.3.1)
6 Quantitative CMV DNA PCR or pp65 antigen (Section 5.2.3.3.2)
7 Sampling at the time points specified in (see below)
[redacted]

[redacted]



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11. SUMMARY OF CLINICAL TRIAL PROTOCOL MODIFICATIONS

Summary of Clinical Trial Protocol Modifications Sheet (SOMS)

Number of CTP modification		1
Date of CTP modification		*20 Jan 2011*
EudraCT number		*2010-021488-34*
BI Trial number		*1270.1*
BI Investigational Product(s)		*BI 836826*
Title of protocol		A Phase I, open, dose escalation trial with BI 836826 in patients with advanced chronic lymphocytic leukaemia
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: Sections 3.1 and 4.1.3* *Change 2: Section 4.1.4* *Change 3: Sections 5.2.1, 5.2.2.1, 5.2.2.2, 5.4 and 9.1*
Description of change		*Change 1: Description of sequential enrolment transferred from Section 4.1.3 to Section 3.1* *Change 2: 25,000 corrected to 25.000*

		Change 3: CTCAE, version 3.0 changed to CTCAE, version 4.0, including update of published reference
Rationale for change		*Change 1: Clarification of trial design in Section 3.1, which now includes a description of sequential enrolment which has been previously included in Section 4.1.3.* *Change 2: Correction of a typing error.* *Change 3: Implementation of the current version 4.0 of Common Terminology Criteria for Adverse Events (CTCAE).*

Number of CTP modification		2
Date of CTP modification		*20 Sep 2011*
EudraCT number		*2010-021488-34*
BI Trial number		*1270.1*
BI Investigational Product(s)		*BI 836826*
Title of protocol		A Phase I, open, dose escalation trial with BI 836826 in patients with advanced chronic lymphocytic leukaemia
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: Protocol Synopsis* *Change 4: Flow Chart* *Change 5: Flow Chart, Section 6.2.2.2, 6.2.2.3, 6.2.2.4* *Change 6: Section 3.1* *Change 7: Section 3.1.1* *Change 8: Section 3.3.2*

		Change 9: Section 3.3.3 *Change 10: Section 4.1.4* *Change 11: Section 4.1.4* *Change 12: Section 4.1.7* *Change 13: Section 5.2.2.1* *Change 14: Section 5.2.3.2* *Change 15: Section 5.2.3.3.2* *Change 16: Section 5.2.3.4* *Change 17: Section 5.3.3* *Change 18: Section 5.5.2* *Change 19: Section 5.6.3.1 and Flow Chart* *Change 20: Section 5.6.3.2* *Change 21: Section 5.6.3.3* *Change 22: Section 5.6.3.3* *Change 23: Section 10.1* *Change 24: Section 9.1 and Section 10.4*
Description of change		*Change 1: Trial Clinical Monitor changed from* [redacted] *to* [redacted] *Change 2: Deletion of "conducted in one country"* *Change 3: CTCAE version 3.0 changed to version 4.0* *Change 4: Addition of footnote 14* *Change 5: Timepoints for assessment of weight indicated in a separate row in the Flow Chart. Measurements which are not needed are deleted from visit 1, day 2, visit 2 and visit 3.*

		Change 6: Addition of missing words "the first dose to" *Change 7: Name of Coordinating Investigator deleted from protocol text, addition of "and".* *Change 8: Modification of inclusion criterion 4 from "White blood cell count (WBC) between 20 x 10^9/l and 150 x 10^9/l" to "Absolute lymphocyte count between 5 x 10^9/l and 150 x 10^9/l"* *Change 9: Addition of "and/or" to exclusion criterion 8.* *Change 10: "and Allopurinol" replaced by "and/or prophylactic drugs" and "available" by "published"* *Change 11: "Acetaminophen/Paracetamole" replaced by "Analgetic/Antipyretic, equivalent to Acetaminophen or Paracetamole".* *Change 12: Clinical Research Associate (CRA) added as contact in case of storage conditions outside the specified range.* *Change 13: "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 or increased,* • *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."* *is replaced by "Worsening of the underlying disease or of other pre-existing conditions will be recorded as an (S)AE in the (e)CRF."* *and*

		"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." *is 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 14: Addition of "Day 1" to specify timepoint in Visit 1 at which reticulocytes, serum immunoglobulin levels and direct antiglobulin test have to be obtained.* *Change 15: Addition of " The same method should be used for all patients treated at the same investigational site."* [redacted] [redacted] *Change 18: "For the early time points on the day of drug administration" replaced by "During the administration of trial drug"* [redacted] [redacted]

		[redacted] [redacted] *Change 23: Revision of Table 10.1:1 to specify whether timepoints are relative to start or end of infusion.* *Change 24: Addition of definitions of Eastern Cooperative Group (ECOG) Performance Score and corresponding reference*

Rationale for change		*Change 1: Change of responsibilities* *Change 2: The trial may be conducted in more than one country in the future* *Change 3: Change from CTCAE version 3.0 to 4.0 has been implemented in previous amendment, but without correction of the Synopsis which is implemented in this version.* [redacted] *Change 5: Clarification that body weight has to be obtained only at day 1 of each treatment course.* *Change 6: Correction of typo by addition of missing words "the first dose to" in paragraph 6.* *Change 7: Administrative change. The name of the Coordinating Investigator is deleted from theprotocol text because it is mentioned on the Title and the Signature page, thus a repetition in this protocol section is not needed. In addition, a*

		clarification on the qualification of all investigators is included by addition of "and". *Change 8: Lymphocytes represent the majority of white blood cells in active CLL, and the number of circulating lymphocytes rather than the total number of white blood cells will be used to characterize the population. Patients with a lymphocyte count of 5 x 10^9/l will be evaluable for all endpoints and are expected to be comparable to patients with a white blood count of 20 x 10^9/l regarding the risk for adverse reactions.* *Change 9: Clarification of Exclusion Criterion 8.* *Change 10: Standards for phrophylaxis of tumour lysis syndrome vary, and allopurinol may not be considered standard in all countries. To allow prophylaxis according to local standards and published guidelines accross countries, the wording was modified.* *Change 11: Acetaminophen or Paracetamol may not be available in all countries for premedication. In this case, an equivalent other analgesic and antipyretic drugs should be administered.* *Change 12: Addition of the CRA as a second contact person in case of storage conditions outside the specified range.* *Change 13: Clarification of (S)AE reporting.* *Change 14: Clarification at which day during Visit 1 reticulocytes, immunoglobulin levels and direct antiglobulin test have to be measured.* *Change 15: Clarification that the same method of quantitative CMV testing should be applied to all patients treated at each investigational site.* [redacted]

		[redacted]
		Change 23: In case of adverse events, the

		administration of BI 836826 may be extendend to 8 hours. [redacted] *Change 24: Clarification of definitions of ECOG Performance Score.*

Number of CTP modification		*3*
Date of CTP modification		*2 August 2012*
EudraCT number		*2010-021488-34*
BI Trial number		*1270.1*
BI Investigational Product(s)		*BI 836826*
Title of protocol		*A Phase I, open, dose escalation trial with BI 836826 in patients with advanced chronic lymphocytic leukaemia*
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: Flow Chart* *Change 3: Table of Contents* *Change 4: Abbreviations*

		Change 5: Section 3.1 *Change 6: Section 3.2* *Change 7: Section 3.3.2* *Change 8: Section 4.1* *Change 9: Section 4.1.1* *Change 10: Section 4.1.3* *Change 11: Section 4.1.4* *Change 12: Section 5.2.2.1* *Change 13: Section 5.2.2.2* *Change 14: Section 5.2.3.1* *Change 15: Section 5.2.3.2* *Change 16: Section 5.2.3.2* *Change 17: Section 5.3.2.1* *Change 18: Section 5.5.1* *Change 19:Section 5.5.2* *Change 20: Section 5.6.3.4* *Change 21: Section 6.1* *Change 22: Section 6.2.2.* *Change 23: Section 7.6* *Change 24: Section 10.1* *Change 25: Section 10.5* *Change 26:Section 10.6*
Description of change		*Change 1: "over 3 hours as single agent treatment on day 1 of each 14-day course" was replaced by "as one to three single doses within a 14 day course"*

		Change 2: Flow Chart and Footnote was deleted *Flow Chart Course 1, Dosing on Day 1 and Day 2 and Footnote was added* *Flow Chart Courses 2 - 8 and Footnote was added* *Change 3: Table of Contents was updated* *Change 4: Abbreviations were updated* *Change 5: "Enrolment in this context refers to the day of administration of the first dose to a patient" was added* *Change 6: "Intra-patient dose escalation will not be allowed." was deleted."* [redacted] *Change 8: "BI 836826 will be administered as an intravenous infusion over a period of 3 hours on day 1 of each 14-day course. In case a patient experiences an adverse event during the infusion" was replaced by " In course 1, the total dose will be divided into two portions administered on day 1 and 2 (please refer to the Flow Chart: Course 1, Dosing on Day 1 and Day 2). The dose on day 1 will be 10% of the total dose, but not exceed 10 mg in case the total dose is higher than 100 mg. The dose on day 2 will be the planned total dose minus the dose administered on day 1. If adverse events which are related to the infusion schedule, e.g. infusion-related reactions or tumour lysis syndrome require administration of a lower dose on day 2, the total dose in course 1 may be divided into 3 smaller portions on day 1, 2 and 8. In this case, the dose on day 1 will remain as defined previously. The difference between day 1 and the planned total dose level will be equally divided between day 2 and 8 (reference to section 10.6). The distribution of the planned total dose in course 1 to two, or if needed to three smaller portions will be based on safety data from the previous cohort and will be assessed and may be modified by the DSMB. If supported by the*

		DSMB, the same rules may be applied to course 2 in case infusion-related adverse events can be controlled by the above measures in course 1 but occur in course 2. *In all subsequent treatment courses, BI 836826 will be administered as a rate-controlled intravenous infusion on day 1 of each 14-day course.* *The first and second infusion will be started at a rate of 10 mL/h. The infusion rate should be increased every 30 (+/-10) minutes by 10 mL/h to a maximum of 80 mL/h as long as tolerated by the patient. If considered safe by the investigator, the stepwise increase of infusion rate during the third and subsequent infusions may be faster or steps may be omitted, but the maximum infusion rate must not exceed 120 mL/h. If symptoms of an infusion related reaction occur, the infusion should be temporarily stopped. Upon recovery, it should be 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.* *"In case a patient experiences an adverse event during the infusion" was replaced by "For medical reasons"* *Change 9:"Single dose on day 1 of in a 14 day course" was replaced by " One to three single doses within a 14 day course"* *"Infusion over 4 hours" and "Rate: 83,4 mL/h" was deleted and replaced by "Rate controlled infusion"* *Change 10:"over 3 hours on day 1 of each course" was replaced by " on day 1, 2 and possibly day 8 in course 1 and on day 1 in the*

		subsequent courses" *"per treatment course" was added* *Change 11: "Intra-patient dose escalation of BI 836826 will not be allowed in this trial " was replaced by "Intra-patient dose escalation may be considered in agreement between investigator and sponsor for selected patients. It is restricted to patients who have received at least 4 treatment courses and tolerate the treatment well at the time of dose escalation. Intra-patient dose escalation can only be performed at a time when the next higher dose cohort has been reviewed and considered safe by the DSMB. The dose escalation step is limited the dose which has been administered to the next higher cohort. The treatment courses at the increased dose have to follow the instructions as outlined for course 5-8 in the Flow Chart and the protocol. In addition, after the first dose at the higher dose level, patients have to be monitored for at least 24 hours after the end of the infusion, including safety laboratory for tumour lysis syndrome."* *Change 12: "Protocol-specified" and "Drug induced liver injury (DILI) Although rare, 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 10.5 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 Appendix 10.5 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." were added.* *Change 13: "BI has set up a list of AEs which are defined to be always serious. In order to support the investigator with the identification of these "always serious adverse events", if a non serious AE is identified to be serious per BI definition, a query will be raised. The investigator must verify the description and seriousness of the event. If the event description is correct, the item "serious" needs to be ticked and an SAE has to be reported in expedited fashion following the same procedure as above. The list of these adverse events can be found via the RDC-system." Was added* *Change 14: "Screening"," total" and "(if elevated direct bilirubin)" were added* *Change 15: "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)." *"Between the first and the second infusion", "the second", "i.e. every 4-8 hours" and "In case the schedule as outlined in Section 10.6 is used, monitoring for TLS has to be performed for 24 hours also after the infusion on day 8. Sampling for TLS in course 3 and subsequent courses should be performed as clinically indicated." were added* *Change 16: "with differential" was added* *Change 17: "ethnicity, if it is not prohibited by the local laws" was added* *Change 18: "from 0 to the last quantifiable plasma concentration" and "$_t$" were added* *Change 19:"and in Appendix 10.6" was added* [redacted] *Change 21:"the first and second" and " in course 1" were added* *"administration" was replaced "by two courses"* [redacted] *"Administration of BI 836826 only in course1" was added* *"The actual date and time of blood sampling must be recorded in the eCRF." was deleted* *"of a treatment course" was replaced by "day 3 day 3 in course 1"and " in course 2-8"* *"The actual date and time of blood sampling must be recorded in the eCRF." was deleted*

		"6.2.2.4 Visit 2 - day 4 (day 4 only in course 1) • *Vital signs (see Section 5.2.5.1)* □ *Adverse events* • *Concomitant therapy* • *Safety lab parameters as specified in Section 5.2.3.1* • [redacted] *"of a treatment course" was replaced by "day 8 day 8 in course 1 or" and " in course 2-8"* *"Administration of BI 836826 only in course 1, if treatment schedule according to section 10.6 is used" and "Blood samples to screen for evidence of tumour lysis syndrome only in course 1, if treatment schedule according to section 10.6 is used" were added* *"The actual date and time of blood sampling must be recorded in the eCRF." was deleted* *"6.2.2.6 Visit 3 - day 9 (day 9 only in course 1, if treatment schedule according to section 10.6 is used)* *On visit 3, the following parameters and investigations will be obtained/performed* • *Vital signs (see Section 5.2.5.1)* • *Adverse events* • *Concomitant therapy* • *Safety lab parameters as specified in Section 5.2.3.1* • *Blood samples to screen for evidence of tumour lysis syndrome* • [redacted] *Change 23: "n" was added*

		Change 24: Flow Chart was replaced by Course 1, Dosing on Day 1 and Day 2 and Course 2-8 *"If no signs of progression please continue to Visit 1 Flow Chart Course 2-8. If the patient has disease progression or withdraws, please continue to EOT." was added* *"The time for infusion may vary, depending on infusion rate and occurrence of infusion-related reactions. The exact start and end time of the infusion should be recorded. The assumed planned time of 5 hours is based on a stepwise increase of the rate every 30 (+/-10) minutes by 10 mL/h to a maximum of 80 mL/h without any interruptions." was added* *"If the time for infusion prolongs is longer than 3 hours, e.g. in case of infusion related reactions, the exact start and end time should be recorded. If the infusion is interrupted, the stop time and the time when it is re-started need to be documented " was deleted* [redacted] *Change 25:The whole section 10.5 was added* *Change 26:The whole section 10.6 was added*

Rationale for change		*Changes 1, 2, 8, 9, 10, 24, 26: To prevent infusion related reactions or tumour lysis syndrome after the first infusion, the infusion schedule for course 1 will be modified. Modification will include two elements: a small dose on day 1 to lower the risk for reactions related to the first infusion and to improve tolerability of a larger dose on day 2, and a slower infusion rate.* *The total dose in course 1 will be divided into 2 smaller portions. The dose on day 1 will be reduced to 10% of the planned dose and will not exceed 10 mg at planned doses of 100 mg and*

		above. The planned dose minus the dose administered on day 1 will be given on day 2. In case infusion related adverse events on day 2 would require also a modification of the infusion on day 2, the dose in course 1 may be distributed to days 1, 2 and 8 in agreement with the DSMB. Due to the change in the infusion scheme the Flow Chart was split in course 1 and course 2-8 (change 2), and a separate Flow Chart for the distribution of the total dose to 3 portions was provided (change 25). The infusion will remain rate controlled, but the infusion rate will be increased in small steps as tolerated by the patient not only in course 1 but in all treatment courses. Therefore the time for infusion will be longer than 3 hours and time for infusion will vary. *Change 3: Clarification and update of Table of Contents* *Change 4: Explanation of abbreviation* *Change 5: Clarification of definition of sequential enrolment* *Changes 6 and 11: Intra-patient dose escalation will be allowed for selected patients in case the next higher dose cohort is free of DLT and considered safe. This is not considered a safety risk because it will be restricted to patients who have tolerated four courses of BI 836826 at the time of dose escalation and may offer a potential benefit to patients enrolled at a lower dose.* *Change 7: 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 increased risk for the patient.* *Change 12: Clarification that the significant AEs are the defined protocol specific AEs and Liver injury (DILI) was added. (S)AE reporting change required by regulatory authority.* *Change 13: Clarification of serious adverse event*

		reporting. *Change 14: Clarification of the timepoints for safety laboratory values. Clarification that total bilirubin value is to be obtained. In case bilirubin is elevated, direct bilirubin will be needed for clinical interpretation.* *Change 15: Definition of classification of tumor lysis syndrome which will be used. Clarification of blood sampling for monitoring of tumour lysis syndrome.* [redacted] *Change 17: Adaptation to local laws* *Change 18: Clarification* *Change 19: Clarification of Sample Collection* [redacted] *Changes 21 and 22: Adaptation of hospital surveillance and visit schedule to the modified infusion schedule.* *Change 23: Correction of typo* *Change 25:Procedure of Clinical Evaluation in case of Liver Injury*

Number of CTP modification		*4*
Date of CTP modification		*7 Aug 2013*
EudraCT number		*2010-021488-34*
BI Trial number		*1270.1*
BI Investigational Product(s)		*BI 836826*
Title of protocol		*A Phase I, open, dose escalation trial with BI 836826 in patients with advanced chronic lymphocytic leukaemia*
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: Title page* *Change 2: Synopsis* *Change 3: Synopsis and section 4.1.4* *Change 4: Flow Chart course 1*

		Change 5: Flow Chart course 1 *Change 6: Flow Chart courses 1* *Change 7: Flow Chart course 1* *Change 8 : Flow Chart course 1* *Change 9 : Flow Chart, courses 2-8* *Change 10 : Flow Chart, courses 2-8* *Change 11 : Flow Chart, courses 2-8* *Change 12 : Flow Chart, courses 2-8* *Change 13 : Abbreviations* *Change 14: Section 3.1* *Change 15: Section 3.2* *Change 16: Section 3.2* *Change 17: Sections 3.3.2, 5.1.1 and 5.1.2* *Change 18: Section 3.3.2* *Change 19: Section 3.3.3* *Change 20: Section 3.3.3* *Change 21: Section 4.1.1* *Change 22 : Section 4.1.4* *Change 23: Section 4.2.2.1* *Change 24 : Section 5.1.2.4* *Change 25 : Section 5.2.5.1* *Change 26: Section 5.3.4.2 and 5.5.1* *Change 27 : Sections 5.6.3.2 and 5.6.3.3* *Change 28 : Section 6.1* *Change 29: Section 6.2.1*

		Change 30 : Section 6.2.2.1 *Change 31 Section 6.2.2.5* *Change 32:Section 6.2.3.2* *Change 33: Section 7.1* *Change 34 : Section 7.6* *Change 35: Section 10.1, Table 10.1 :1* *Change 36: Section 10.1, Table 10.1 :1* *Change 37: Section 10.6* *Change 38 : Section 10.6* *Change 39: Section 10.6* *Change 40: Section 10.6* *Change 41: Section 10.6*
Description of change		*Change 1:* [redacted] *was replaced by* [redacted] *and* [redacted] *by* [redacted]. *Change 2: "60" was replaced by "70" and "50" by "60".* *Change 3: synopsis:"up to 8" was deleted.Section 4.1.4:"coordinating" was deleted, "In the dose-escalation phase as well as in the expansion cohort" and "If patients continue beyond cycle 8, the same assessments will be done as applicable for cycle 5-8" were added.* *Change 4: +2 was added to day 8.* *Change 5: Screening for TLS: cross on day 4 was added (48 h monitoring).* *Change 6, 40: Some assessments were deleted.* *Change 7, 41: Some footnotes were deleted and the numbering was changed* [redacted]

		[redacted] *Change 9: +2 was added to day 8.* *Change 10: Footnote 8: "may be performed up to 3 days earlier" was replaced by "may be performed 1 day earlier".*  *Change 12*: "*If patients continue beyond cycle 8 in agreement with investigator and BI, the same assessments will be done as applicable for cycle 5-8" was added.* *Change 13: NCI was replaced by IWCLL, NCIWG deleted and IWCLL added to abbreviations.* *Change 14: 12-20 was replaced by 12-30.* *Change 15: 12-20 was replaced by 12-30.* *Change 16: "doses" was replaced by "courses".* *Change 17: NCI was replaced by IWCLL.* *Change 18: "between 5 x 10^9/l and 150" was replaced by "lower than 200".* *Change 19: "Treatment with anti CD 20 therapy within 28 days or alemtuzumab within 8 weeks prior to enrolment" was modified to "Prior treatment with anti CD 20 therapy within 4 weeks or alemtuzumab within 8 weeks, or any other antileukemia therapy within 2 weeks prior to the first administration of the trial drug".*

		Change 20: GFR<60mL/min was replaced by GFR<45 mL/min. *Change 21:" Volume: 250 mL" was replaced by "See section 4.1.6"* *Change 22: "or pre-treatment value" and "future" were added."and only with a reduced dose of BI 836826", "new", "The reduced dose will be valid for all following treatment courses in the individual patient", "In case, a patient experiences a second episode of DLT with the reduced BI 836826 dose, the treatment has to be permanently discontinued." and "Likewise" were deleted.* *Change 23: "may not be used within 4 weeks prior to the first trial infusion and 2 weeks after the last infusion of BI 836826" was replaced by "should be avoided during treatment with BI 836826. However, if medically indicated, e.g. for substitution of immunoglobulin deficiency, immunoglobulins may be used. Administration within a time window of 2 days before and after the infusion of BI 836826 should be avoided."* *Change 24: "or 50% improvement over baseline" was added.*  

		[redacted] [redacted] *Change 28: "after administration of BI 836826" was added, "first and" was deleted and "courses" was replaced by "doses in course 1".* [redacted] [redacted] *Change 31: +2 was added to day 8, "and" was added. "day 8", "or day 8(+1)" were deleted.* *Change 32: "receives new anti-neoplastic therapy" was added.* *Change 33: "20" was replaced by "30".* *Change 34: "12-20" was replaced by "up to 30" and "42-50" was replaced by "60".* *Change 35: Horizontal line was added.* [redacted] *Change 37: Screening for TLS: cross on days 3 and 4 was added (48 h monitoring).*

		Change 38: Crosses struck out from the EOT and FU visit assessments.

Rationale for change		*Change 1: Contact details of new TCM were added.* *Changes 2, 14, 15, 33, 34: The option to recruit more patients in the expansion cohort (from 12-20 to 12-30) was added. This is to obtain more safety information on the monotherapy MTD as subsequent development of BI 836826 will be based on combination treatment.* *Change 3: To add a clarification that individual prolongation of treatment beyond 8 courses is possible and how this prolongation is agreed.* *Changes 4, 9, 31: To allow some flexibility in the courses, a visit window +2 days was added on day 8.* *Change 5, 37: Correction: Screening for TLS: Crosses were added to be in line with 48 hours close monitoring.* *Changes 6, 40: Correction: The deleted assessments were not necessary since the Flow Chart is for course 1.* *Changes 7, 41: Correction: The deleted footnotes were not necessary since the Flow Chart is for course 1. The numbering of the remaining footnotes had to be changed accordingly.* [redacted]

		[redacted] *Change 12: Clarification of the assessments beyond cycle 8.* *Changes 13, 17: In-text reference to citation R10-4429 was corrected.* *Change 16: Correction of wording due to schedule change in amendment 3.* *Change 18: Inclusion criterion 4 modified to include patients with a lymphocyte count up to 200 x 10^9/L. Lymphocyte counts between 150 and 200 x 10^9/L are common in relapsed/refractory CLL. This modification is considered to allow more patients to be enrolled without additional safety risk.* *Change 19: Concomitant therapy restriction already existing in the Restriction section 4.2.2.1 was added into the exclusion criteria as a clarification.* *Change 20: GFR decreases with age. In view of the average age of CLL patients, exclusion criterion 12 was modified to exclude only patients with a GFR<45 mL/min.* *Change 21: Clarification: Volume of 250 mL was replaced by reference to section 4.1.6.* *Change 22: Clarification of handling of DLT to allow for risk benefit assessment for the patient receiving BI 836826.* *Change 23: Immunoglobulins deficiency in relapsed CLL is commonly treated by immunoglobulin substitution to decrease the risk of infections. Use of immunoglobulins as a concomitant medication was modified to allow medically indicated use of immunoglobulins in patients which otherwise would have to be removed from the protocol and to provide*

		guidance when to administer in relation to trial drug. *Change 24: Correction of PR criterion B3.* *Change 25: Correction due to new infusion scheme after last amendment and clarification to allow more flexibility concerning vital signs measurement.* [redacted] *Change 28: Correction for clarification.* *Change 32: Clarification of the end of follow-up period. Follow-up will end once new anti-neoplastic therapy starts.* *Change 35: Correction of table formatting* *Change 38: Correction of mistake: EOT/FU assessments are defined in the Flow Chart for courses 2-8.*

Number of CTP modification		*5*
Date of CTP modification		*04 March 2015*
EudraCT number		*2010-021488-34*
BI Trial number		*1270.1*
BI Investigational Product(s)		*BI 836826*
Title of protocol		*A Phase I, open, dose escalation trial with BI 836826 in patients with advanced chronic lymphocytic leukaemia*
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: Flowchart for Course 1 and Section 6.2.2.5 Visit 3, Day 8* *Change 2: 3.3.3 Exclusion criterion 1 and 4.2.2 Restrictions* *Change 3: Section 3.3.4.2.1: Trial stopping rules* *Change 4: Section 5.2.1.1: Dose limiting toxicity*

		(DLT) *Change 5: Section 5.2.3.1: General safety laboratory parameters* [redacted]
Description of change		*Change 1: Deletion of visit window: Course 1, Day 8* *Change 2: Exclusion criterion 1 was changed from "…or any other antileukemia therapy within 2 weeks, …" to "…or any cytotoxic antileukemia therapy within 2 weeks, Ibrutinib or Idelalisib within 1 week…." The restrictions section was changed from: "Prior antileukemia therapy must have been discontinued at least two weeks before the first administration of the trial drug…" to "Prior antileukemia therapy must have been discontinued in line with the requirements per exclusion criterion 1…"* *Change 3: Sub-section 3.3.4.2.1 was added describing Trial stopping rules* *Change 4: The following was added: "The additional following haematologic adverse events will be considered DLT:* • *Grade 4 neutropenia lasting more than 7 days.* • *Febrile neutropenia not resolving within 48 hrs with appropriate treatment (antibiotics, antivirals, antifungals, growth factor support)* • *Grade 4 thrombocytopenia lasting more than 7 days, or grade 3-4 thrombocytopenia with clinically significant bleeding* • *Grade 4 anemia"* *The following was deleted: "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."*

		Change 5: "Blood samples should be collected more frequently in case of relevant toxicities; e.g. in case of grade 4 neutropenia or thrombocytopenia, to document as accurately as possible the duration of the AE." was added. [redacted]

Rationale for change		*Change 1: To ensure that all patients can be assessed for duration of neutropenia and thrombocytopenia on the same day during the MTD evaluation period* *Change 2: Ibrutinib and Idelalisib were recently approved in the countries in which the trial is recruiting patients. Both drugs have a short half live and should be eliminated after 7 days after the last dose, therefore not posing additional risks for interaction with trial medication. Patients should not receive the first dose of BI 836826 earlier than 1 week after the last dose of Ibrutinib or Idelalisib to ensure elimination prior to starting BI 836826, while also allowing expeditious access to the investigational treatment for patients in need of treatment options.* *Change 3: Trial stopping rules were described in more details according to FDA recommendations* *Change 4: The DLT definition was refined to include specific haematologic adverse events according to FDA recommendations* *Change 5: More frequent measurements in case of relevant findings, e.g. to quantify the duration of Grade 4 neutropenia and/or thrombocytopenia* [redacted]

APPROVAL / SIGNATURE PAGE

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Signatures (obtained electronically)

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Meaning of Signature	Signed by	Date Signed