Clinical Trial Protocol

	Document Number:	**c03032933-02**
BI Trial No.:	1270.15	
BI Investigational Product(s):	BI 836826	
Title:	A Phase Ib, Open label, Single Arm, Multi-center, Dose Escalation Trial of Intravenous BI 836826 in Combination with ibrutinib in Patients with Relapsed/Refractory Chronic Lymphocytic Leukemia	
Brief Title:	Intravenous BI 836826 in combination with ibrutinib in relapsed/refractory CLL patients who have been pre-treated with at least one prior line of systemic therapy, and who are eligible for treatment with ibrutinib	
Clinical Phase:	Phase Ib	
Trial Clinical Monitor:	Telephone: Fax:	
Coordinating Investigator:	Telephone: Fax:	
Status:	Final Protocol (Revised Protocol based on Global Amendment 1)	
Version and Date:	**Version: 2.0**	**Date: 18 Jul 2018**

CLINICAL TRIAL PROTOCOL SYNOPSIS

Name of company: **Boehringer Ingelheim**			
Name of finished product: NA			
Name of active ingredient: BI 836826			
Protocol date: 05 Nov 2015	**Trial number:** 1270.15		**Revision date:** 18 Jul 2018

Title of trial:	A Phase Ib, Open label, Single Arm, Multi-center, Dose Escalation Trial of Intravenous BI 836826 in Combination with ibrutinib in Patients with Relapsed/Refractory Chronic Lymphocytic Leukemia
Coordinating Investigator	Telephone: Fax:
Trial site(s):	Multicenter Trial conducted in the United States
Clinical phase:	Ib
Objective(s):	The primary objective is to determine the Recommended Phase 2 Dose (RP2D) of BI 836826 in combination with ibrutinib in relapsed/refractory CLL patients.
Methodology:	Open-label, single arm, dose escalation, Bayesian Logistic Regression Model (BLRM) with overdose control to confirm safety and to evaluate clinical efficacy.
No. of patients:	Approximately 20 patients
total entered:	Approximately 20 patients

Name of company: **Boehringer Ingelheim**			
Name of finished product: NA			
Name of active ingredient: BI 836826			
Protocol date: 05 Nov 2015	**Trial number:** 1270.15		**Revision date:** 18 Jul 2018

each treatment:	Dose finding: Approximately 20 patients
Diagnosis :	Patients with relapsed or refractory Chronic Lymphocytic Leukemia, who have been pre-treated with at least one prior line of systemic treatment and who qualify for treatment with ibrutinib.
Main criteria for inclusion:	Adult patients ≥ 18 years of age, diagnosed with either relapsed or refractory CLL with ECOG 0-2
Test product(s):	BI 836826
dose:	During the dose escalation phase, dose tiers of BI 836826 starting at 100 mg and escalating to the Maximum Tolerated Dose (MTD) in combination with ibrutinib will be evaluated. BI 836826 will be administered in 4-week cycles, every two weeks for the first 16 weeks (Cycles 1-4), and every 4 weeks starting at week 17 (Cycle 5) until Cycle 12. Patients experiencing a CR, CRi or a MRD negative Partial Response (PR) may continue BI 836826 every 4 weeks with 12 additional treatment cycles and receive up to a maximum of 24 treatment cycles.
mode of administration:	BI 836826 i.v. as a rate controlled infusion
Combination product:	ibrutinib
dose:	420 mg dose daily

Name of company: **Boehringer Ingelheim**			
Name of finished product: NA			
Name of active ingredient: BI 836826			
Protocol date: 05 Nov 2015	**Trial number:** 1270.15		**Revision date:** 18 Jul 2018

mode of administration:	Orally, daily
Duration of treatment:	Ibrutinib: Until progression or unacceptable toxicity BI 836826: All patients may receive 12 Cycles (18 infusions) unless progression, unacceptable toxicity, or withdrawal of consent occurs earlier. Patients with a CR, CRi or MRD negative PR after 12 Cycles may prolong therapy to Cycle 24.
Endpoints	Primary endpoints: - RP2D of BI 836826 in combination with ibrutinib and the number of patients with dose limiting toxicities in the first treatment cycle Secondary endpoint: - Maximum tolerated dose (MTD)
Safety criteria:	Maximum tolerated dose, incidence and severity of adverse events graded according to the common terminology criteria for adverse events (CTCAE, version 4.0). Incidence of dose limiting toxicity, laboratory parameters. In addition, hematological toxicity based on laboratory values using the criteria as described in IWCLL guidelines.
Statistical methods:	Descriptive statistics and exploratory data analysis Dose escalation is guided by a BLRM with overdose control that will be fitted to binary toxicity outcomes. The estimate of parameters will be updated as data are accumulated using the BLRM. The toxicity probability at each dose level will be calculated to determine the MTD.

FLOW CHART – SCREENING THROUGH CYCLE 12

Trial periods[1]	**Screening**	**Run -In**[2]	**Cycle 1**					**Cycle 2-12**[1]		**Response Evaluation at the End of Cycle 3, 6, 9 and 12**	**EOT**[3]	**End of Residual Effect Period Visit (EoR)**[4]	**FU for PD and Eof FU Visit**[5]	**End of Trial Status**[6]
Day of Cycle[1]	(-35 to -15)	(-14 to -1)	1	2	8	15	20 ±3[20]	1	15	21-28				
Informed consent	x													
Informed consent for pharmacogenetics and biobanking	x													
Demographics and baseline conditions	x													
Oncology history/Review of in-/exclusion criteria	x													
Review of pre BI 836826 dose laboratory values (Section 4.1.4)			x[9]											
BI 836826 Dose Assignment	x[10]													
LABS AND SAFETY ASSESSMENTS														
Physical examination (Incl Height[11])	x		x					x			x			
Vital signs[12]	x		x	x	x	x		x	x		x			
ECOG Performance score	x		x					x			x			
12 lead-ECG[13]	x							x			x			
Virology screening (HBV, HCV, CMV, HIV)	x													
HBV DNA monitoring, if applicable[14]								x			x			
Safety laboratory tests - Chemistry and Urine[15]	x		x	x	x	x		x	x		x			
CBC with Differentials[15]	x	x	x	x	x	x	x	x	x	x	x			
CMV monitoring[16]	x			x				x			x			
Pregnancy test if applicable[17]	x		x					x			x			
Adverse events	x	x	x	x	x	x	x	x	x	x	x	x		
Concomitant therapies	x	x	x	x	x	x	x	x	x	x	x	x		

Trial periods[1]	**Screening**	**Run -In[2]**	**Cycle 1**					**Cycle 2-12[1]**		**Response Evaluation at the End of Cycle 3, 6, 9 and 12**	**EOT[3]**	**End of Residual Effect Period Visit (EoR)[4]**	**FU for PD and Eof FU Visit[5]**	**End of Trial Status[6]**
Day of Cycle[1]	(-35 to -15)	(-14 to -1)	1	2	8	15	20 ±3[20]	1	15	21-28				
TRIAL MEDICATIONS[7]														
BI 836826 administration			pre-dose 10 mg	x (50%)[7]	x (50%)	x		x	x					
BACKBONE MEDICATION[19]														
Ibrutinib administration	Dosing instructions as per the package insert													
FULL DISEASE ASSESSMENTS[8, 26]														
Physical Exam	x	x												
MRD[234](blood)	x	x								x	x			

Trial periods[1]	**Screening**	**Run -In[2]**	**Cycle 1**					**Cycle 2-12[1]**		**Response Evaluation at the End of Cycle 3, 6, 9 and 12**	**EOT[3]**	**End of Residual Effect Period Visit (EoR)[4]**	**FU for PD and Eof FU Visit[5]**	**End of Trial Status[6]**
Day of Cycle[1]	(-35 to -15)	(-14 to -1)	1	2	8	15	20 ±3[20]	1	15	21-28				
Bone marrow examination (sample for MRD included in all BM obtained during the trial)	x										x			
Cross sectional imaging[24] (CT scan) Chest-Abdomen-Pelvis	x									x	x	x		
Survival Status (including disease progression, response)														x
Next line of therapy for CLL														x

[1]The planned duration of a treatment cycle is 28 days (4 weeks). Day 1 of a new cycle should take place on "Day 29" (see Section 6.0). Visit windows of -2/+14 days for Cycles 2-4 and -2/+14 days for Cycle 5 through Cycle 12 are permitted, unless otherwise specified. Beginning with Cycle 5, BI 836826 Infusions will be administered monthly on Day 1 of each cycle. Day 15 visits are not required. All assessments should be performed prior to the dose administration of BI 836826 on dosing days, unless otherwise specified.

[2]Run-In Phase: Begins with first dosing of ibrutinib. Duration of phase is two weeks (+/- 2 days). Disease assessments (peripheral blood evaluation and clinical evaluation) to be performed close to Day 1 of Cycle 1. Assessments can also be performed on Day 1 **prior** to start of 10 mg BI 836826 pre-dose.

[3]EOT visit: When the decision is taken to permanently discontinue the study medication. The EOT visit should be performed as soon as possible, but before a new CLL treatment is started. Assessments do not need to be repeated if the EOT is done within 14 days after a response assessment visit. For patients who complete Cycle 12 and terminate BI 836826 in the absence of PD, the assessments specified for EoT and EoR can be also combined at the time of EoR

[4]End of Residual Effect Period (EoR) Visit is to be completed 30 days after the EOT (+ 7 days). Information collected at this visit should include all new AEs and ConMeds that occurred since the EOT and follow-up of AEs ongoing at the time of the EOT. In case the patient completes Cycle 12 and terminates treatment with BI 836826 according to protocol in the absence of PD, the assessments indicated for the EOT and EoR visit in the flowchart may be performed once, at the time specified for the EoR visit

[5] Follow-up visits will no longer be required after approval of CTP Amendment 1.Follow-up for patients who terminate for any other reason at any time other than PD: Full response assessment at EOT or EoR;

[6]There will be an additional contact with regard to the End of Trial status as soon as the end of the whole trial is reached (see Section 8.6). Contact can be either a clinic visit or phone call. Visits will include vital status and anti-cancer treatment for CLL at the time of contact.

[7]Patients are **ONLY** required to be hospitalized overnight after the first 50% infusion of BI 836826 on Cycle 1 Day 2 if patient is at risk of TLS requiring monitoring and/or prophylactic treatments.

[8]Disease Assessment: Should be performed as close to the start date (within 7 days) of Ibrutinib during screening. Historical CT scans (up to 30 days prior to start of run-in phase) may be used at screening, if no other anti-CLL therapy (ies) have been given. Minimum of 7 days after BI 836826 administration (preferably between D 21 and D28 of Cycle 2 and 4); Subsequent 12 week Disease Assessments: >=21 days after BI 836826 administration and prior to start of next cycle (preferably between D21 and D28). Assessments to be performed every 12 weeks or 3 cycles from Cycle 1 Day 1 (C3, C6, C9, C12).

[9]Review of key laboratory values outlines in Section 4.1.4 prior to first pre-dose administration of BI 836826

[10]After Informed Consent is obtained and review of inclusion/exclusion

[11]In Cycle 1, done at Day 1, before start of BI 836826 infusion; Every 8 weeks during the treatment period, i.e. every other cycle (Cycle 2, 4, etc.) and EOT. PE to include weight. Height to be recorded at screening only.

[12]Vital signs (blood pressure, pulse rate and body temperature) will be recorded at every visit during screening, and treatment , before proceeding with any other protocol specific procedure and after at least 5 minutes of rest (See Section 5.3.2 and Section 6.1 for assessments)

[13]Single, resting 12 lead ECG to be performed at Screening, Day 1 of every Cycle and EOT, or whenever deemed necessary by the investigator (See Section 5.3.4).

[14]HBV DNA monitoring is only applicable to patients who are HBc antibody positive at screening (see Section 5.3.3.4.1). Patients who are HBc antibody positive at screening will be monitored for potential HBV reactivation by quantitative HBV DNA at visit 1 of every even course (Cycle 2, 4, 6, etc.…) and at the EOT.

[15]Safety lab tests (blood and urine) do not have to be repeated if previous tests are within 48 hours of visit. Safety lab tests will include screening for tumor lysis syndrome. An additional safety lab should be performed on Day 1 of Cycle 1, 1 to 3 hours after the end of infusion to check for tumor lysis syndrome. Additional safety labs may be performed as deemed necessary by the investigator. If neutropenia CTCAE Grade 3 or 4 is observed for more than 7 days, repeat until return to a Grade 2 or lower in order to capture the duration of severe neutropenia (see Section 5.3.3). Coagulation tests have only to be performed at screening, at every other cycle and at EOT visit.

[16]Quantitative CMV DNA PCR or pp65 antigen to be performed every other cycle (see Section 5.3.3.4.2).

[17]Urine Pregnancy test is mandatory for all female patients of childbearing potential. Test must be performed within 7 days prior to first treatment on C1 Day 1, at CxV1of every other cycle (i.e. Cycle 3, 5, etc.) and at EOT. However, in the first cycle, the test will be performed on C1D1. To ensure early detection of pregnancy, test might be repeated as necessary during the treatment period. (See Section 5.3.3.1)

[18]For AE/SAE assessment during FU, refer to Sections 5.3.7 and 6.2.3

[19]. Ibrutinib will be administered according to the package insert for CLL indication. Eligible patients must secure sourcing and be on stable ibrutinib dosing for 2 weeks (+/- 2 days) prior to planned first BI dose (Cycle 1 Day 1). Patients are to be provided a dosing diary (Run-In and Cycle 1 through Cycle 2 only) and instruct patients not to take ibrutinib dose at home on Day 1 of each Cycle during PK sample collection period and to bring their medicine to clinic for dosing. Diaries are to be reviewed by site staff to confirm compliance. Daily dosing of ibrutinib can continue as per the label and at the discretion of the investigator or physician.

[23]MRD in peripheral blood is to be performed at screening, prior to C1D1, at the end of Cycles 3,6, 9, 12, and at EOT. A bone marrow aspirate and biopsy, including MRD evaluation according to IWCLL guidelines is mandatory in patients who meet the criteria for CR based on physical examination, complete blood count (two consecutive CBCs matching the criteria for CR), and imaging (see Section 5.2.6).

[24]At screening, at the end of Cycle 3 (within Day 21 and 28); every 12 weeks if clinically indicated; in case of CR and within 21-28 days after the 12th cycle infusion with BI 836826. If a patient is in CR, CRi or PR (MRD negative) after a disease assessment, he/she may continue with the study treatment for up to a maximum of 24 cycles.

[25] Collection of End of Treatment samples will not be required after approval of CTP Amendment 1.

[26]Findings on physical examination with potential impact on response assessment should be confirmed by imaging.

[27]Sample collection will no longer be required after approval of CTP Amendment 1.

FLOW CHART – CYCLE 13 THROUGH CYCLE 24

Trial periods[1]	Day 1 Cycles 13- 24[1]	Response Evaluation at the End of Cycle 16, 20 and 24	EOT[2]	End of Residual Effect Period Visit (EoR)[3]	FU for PD and EofFU Visit[4]	End of Trial Status[5]
Day of Cycle[1]	1	21-28				
Physical examination (Including weight)[7]	x		x			
Vital signs	x		x			
ECOG Performance score	x		x			
12 lead-ECG[8]	x		x			
HBV DNA monitoring, if applicable[9]	x		x			
Safety laboratory tests - Chemistry and , Urine[10]	x		x			
CBC with Differentials[10]	x	x	x			
CMV monitoring[11]	x		x			
Pregnancy test if applicable[12]	x		x			
Adverse events	x	x	x	x		
Concomitant therapies	x	x	x	x		
OTHER ASSESSMENTS						
TRIAL MEDICATIONS						

Trial periods[1]	Day 1 Cycles 13- 24[1]	Response Evaluation at the End of Cycle 16, 20 and 24	EOT[2]	End of Residual Effect Period Visit (EoR)[3]	FU for PD and EofFU Visit[4]	End of Trial Status[5]
Day of Cycle[1]	1	21-28				
BI 836826 administration	x					
BACKBONE MEDICATION[6]						
Ibrutinib administration	Dosing instructions as per the package insert					
FULL DISEASE ASSESSMENTS[17,21]						
Physical Exam[21]		x				
MRD[18](blood)		x				
Cross sectional imaging[19] (CT scan) Chest-Abdomen-Pelvis		x	x	x		
Survival Status (including disease progression, response)						x
Next line of therapy for CLL						x

[1]The planned duration of a treatment cycle is 28 days (4 weeks). Day 1 of a new cycle should take place on "Day 29" (see Section 6). Visit windows of –2/+14 days for Cycles 13-24 are permitted, unless otherwise specified. **All** assessments should be performed prior to the dose administration of BI 836826 on dosing days, unless otherwise specified.

[2]EOT visit – When the decision is taken to permanently discontinue the study medication for PD. The EOT visit should be performed as soon as possible, but before a new CLL treatment is started. Assessments do not need to be repeated if the EOT is done within 14 days after a response assessment visit. For patients who complete Cycle 24 and terminate BI 836826 in the absence of PD, the assessments specified for EoT and EoR can be also combined at the time of EoR.

[3]End of Residual Effect Period (EoR) Visit is to be completed 30 days after the EOT (+ 7 days). Information collected at this visit should include all new AEs and ConMeds that occurred since the EOT and follow-up of AEs ongoing at the time of the EOT. In case the patient completes Cycle 24 and terminates treatment with BI 836826 according to protocol in the absence of PD, the assessments indicated for the EOT and EoR visit in the flowchart may be performed once, at the time specified for the EoR visit

[5]There will be an additional contact with regard to the End of Trial status as soon as the end of the whole trial is reached (see Section 8.6). Contact can be either a clinic visit or phone call. Visits will include vital status and anti-cancer treatment for CLL at the time of contact.

[6]Ibrutinib will be administered according to the package insert for CLL indication. Patients must continue to secure sourcing of ibrutinib For patients with CR, CRi or PR (MRD negative) at each of the disease assessments, may continue with monthly infusions of BI 836826, until progression, undue toxicity or to the maximum of 24 cycles. Daily dosing of ibrutinib can continue as per the label and at the discretion of the investigator or physician.

[7]PE to be performed on Day 1 of every Cycle, before start of BI 836826 infusion and at EOT

[8]Single, resting 12 lead ECG to be performed on Day 1 of every Cycle and EOT, or whenever deemed necessary by the investigator (See Section 5.3.4).

[9]HBV DNA monitoring is only applicable to patients who are HBc antibody positive at screening (see Section 5.3.3.4.1). Patients who are HBc antibody positive at screening will be monitored for potential HBV reactivation by quantitative HBV DNA at visit 1 of every even course (Cycle 14, 16, 18, etc…) and at the EOT

[10]Safety lab tests (blood and urine) do not have to be repeated if previous tests are within 48 hours of visit. Additional safety labs may be performed as deemed necessary by the investigator. If neutropenia CTCAE Grade 3 or 4 is observed for more than 7 days, repeat until return to a Grade 2 or lower in order to capture the duration of severe neutropenia (see Section 5.3.3). Coagulation tests have only to be performed at every other cycle and at EOT visit.

[11]Quantitative CMV DNA PCR or pp65 antigen to be performed every other cycle, starting with Cycle 13 (see Section 5.3.3.4.2).

[12]Urine Pregnancy test is mandatory for all female patients of childbearing potential. Test must be performed within 7 days prior to first treatment on C1 Day 1, at CxV1of every other cycle starting with Cycle 13 (i.e. Cycle 15, 17, etc..) and at EOT. To ensure early detection of pregnancy, test might be repeated as necessary during the treatment period. (See Section 5.3.3.1)

[13] Follow-up visits and accompanying assessments will no longer be required after approval of CTP Amendment 1

[14] Follow-up visits will no longer be required after approval of CTP Amendment 1

[17]Disease assessment has to be performed prior to starting treatment at Day 1, >=21 days after BI 836826 administration and prior to start of next cycle (preferably between D21 and D28); Every 4 Cycles.

[18]MRD in peripheral blood is to be performed at the end of Cycles 16, 20, 24 and at EOT. A bone marrow aspirate and biopsy, including MRD evaluation according to IWCLL guidelines is mandatory in patients who meet the criteria for CR based on physical examination, complete blood count (two consecutive CBCs matching the criteria for CR), and imaging (see Section 5.2.6).

[19]Every 16 weeks if clinically indicated; If a patient is in CR after a disease assessment, he/she may continue with the study treatment for up to the maximum of 24 cycles. A CT should be performed whenever a CR is suspected for the first time, if none was performed in the previous last 4 weeks and at EOT if none was performed in the previous last 4 weeks

[20] Sample collection will no longer be required after approval of CTP Amendment 1

[21]Findings on physical examination with potential impact on response assessment should be confirmed by imaging.

[22] Follow-up visits and accompanying assessments will no longer be required after approval of CTP Amendment 1

TABLE OF CONTENTS

ABBREVIATIONS

ADA	Antidrug Antibodies
ADCC	Antibody-Dependent Cellular Cytotoxicity
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALC	Absolute Lymphocyte Counts
ALT	Alanine Aminotransferase
anti-HBs	Hepatitis B Surface Antibody
anti-HBcanti-	Hepatitis B Core Antibody
HIV	HIV Antibody
anti-HCV	Hepatitis C Antibody
AP	Alkaline Phosphatase
aPTT	Activated Partial Thromboplastin Time
AST	Aspartate Aminotransferase
AUC	Area under the Curve
BCR	B-cell Antigen Receptor
BIRDS	Boehringer Ingelheim Regulatory Documents for Submission
BLRM	Bayesian Logistic Regression Model
BLQ	Below the Limit of Qualification
BM	Bone Marrow
B-NHL	B-cell Non-Hodgkin's Lymphoma
BOR	Best Overall Response
BORBTK	Bruton's Tyrosine Kinase (inhibitor)
BUN	Blood Urea Nitrogen
C1D1	Cycle 1 Day 1
CA	Competent Authority
CBC	Complete Blood Count
CICL	Coordinating Investigator
CL	Clearance
CLL	Chronic Lymphocytic Leukaemia
CML	Local Clinical Monitor
CMV	Cytomegalovirus
CR	Complete Response
CRi	Complete Response with incomplete Marrow Recovery
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Contract Research Organization
CT	Computerized Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
DCR	Duration of Complete Response
DDI	Drug-Drug Interaction
DEDP	Drug Exposure During Pregnancy
DILI	Drug Induced Liver Injury

DLT	Dose Limiting Toxicity
DNA	Deoxyribonucleic Acid
DOR	Duration of Overall Response
ECOG	Eastern Cooperative Oncology Group
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDTA	Ethylenediaminetetraacetic Acid
ELISA	Enzyme-Linked Immuno Assay
EoFU	End of Follow-Up
EOT	End of Treatment
EoR	End of REP
ERIC	European Research Initiative on CLL
EU	European Union
EudraCT	European Clinical Trials Database
EWOC	Escalation With Overdose Control
FCGR	G Fragment C Receptors
FISH	Fluorescence In-Situ Hybridisation
GCP	Good Clinical Practice
G-CSF	Granulocyte Colony Stimulating Factor
GFR	Glomerular Filtration Rate
HBsAG	Hepatitis B Surface Antigen
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IGHV	Immunoglobulin Heavy Chain Variable
INR	International Normalized Ratio
IRB	Institutional Review Board
IRC	Independent Review Committee
IRR	Infusion-Related Reactions
IRT	Interactive Response Technology
ISF	Investigator Site File
i.v.	intravenous
IVRS	Interactive Voice Response System
IWCLL	International Workshop Chronic Lymphocytic Leukemia
IWRS	Interactive Web-based Response System
LCCD	Longest Cranio-caudal Diameter
LCMS	Liquid Chromatography Tandem Mass Spectrometry Assay
LD	Largest Diameter
LDH	Lactate Dehydrogenase

LDT	Lymphocyte Doubling Time
LLN	Lower Limit of Normal
LUC	Large Unstained Cells
Mab	Monoclonal Antibody
MedDRA	Medical Dictionary for Drug Regulatory Activities
MRD	Minimal Residual Disease
MRI	Magnetic Resonance Imaging
MRT	Mean Residence Time
MS	Mass Spectrometry
MTD	Maximum Tolerated Dose
NCICTC	National Cancer Institute – Common Terminology Criteria
NE	Non Evaluable
NHL	Non-Hodgkin's Lymphoma
NIMP	Non-investigational Product
NK	Natural Killer
NOA	Not Analysed
NOR	No Valid Result
NOS	No Sample Available
OR	Overall Response
ORR	Overall Response Rate
OS	Overall Survival
PC	Patient Completion
PCR	Polymerase Chain Reaction
PD	Progressive Disease; Pharmacodynamics
PFS	Progression Free Survival
PGx	Pharmacogenetics
PK	Pharmacokinetics
PLD	Perpendicular Diameter
PLT	Platelets
p.o.	per os (oral)
PR	Partial Response
PR-L	Partial Response w/ Lymphocytosis
PT	Prothrombin Time
RBC	Red Blood Cell Count
RDC	Remote Data Capture
REP	Residual Effect Period
RP2D	Recommended Phase 2 Dose
RNA	Ribonucleic Acid
SAE	Serious Adverse Event
SCT	Stem Cell Transplant
SD	Stable Disease
SLL	Small Lymphocytic Lymphoma
SLP	Single Lesion Product
SOP	Standard Operating Procedures
SRC	Safety Review Committee
SUSAR	Suspected Unexpected Serious Adverse Reactions
TCM	Trial Clinical Monitor

TCR	Time to Complete Response
TNF	Tumor Necrosis Factor Alpha
TTF	Time to Treatment Failure
TLS	Tumor Lysis Syndrome
TSAP	Trial Statistical Analysis Plan
ULN	Upper Limit of Normal
USPI	United States Product Insert
Vdss/F	Distribution at Steady State
WBC	White Blood Cell Count

1. INTRODUCTION

Chronic lymphocytic leukemia (CLL) is the most common form of leukemia in western countries and accounts for approximately one third of all leukemias in these regions, with an estimated annual age-adjusted incidence of 3–5 per 100 000 people. The disease is diagnosed most commonly in the elderly, with the median age at diagnosis of 72 years [P14-17458], Typically CLL affects more frequently males than females (ratio: 1.7:1) R14-3818]. The incidence rate rises with age, and almost 70% of patients are older than 65 years [P14-17458] at the time of diagnosis. It is expected that with aging population the prevalence and mortality of CLL are likely to increase in the years to come.

1.1 MEDICAL BACKGROUND

The absence of curative treatments (with the exception of allogeneic stem cell transplantation) has led to "wait and watch" approach for initially diagnosed and asymptomatic patients. Once the need for treatment arises the combination of anti CD20 antibody with chemotherapy (called chemo-immunotherapy) is considered a standard treatment in the first line [R14-3280] [R14-2573].

However, many patients will relapse within first few years after initial treatment. Especially, the relapse is imminent within <2 years in patients who harbor high risk disease as defined by deletion on chromosome 17 (del17p), or carrying mutations in TP53, NOTCH1, or SF3B1 [R15-0126]. Recently, two kinase inhibitors targeting B-cell receptor signaling pathways have gained FDA approval in the US for treatment of patients with relapsed CLL: Idelalisib (PI3Kδ inhibitor) which is indicated in combination with Rituximab for patients for whom rituximab alone would be considered appropriate due to other co-morbidities, and ibrutinib (BTK inhibitor) which is indicated for CLL patients who have received at least one prior therapy. Both drugs are very effective with an Overall Response Rate (ORR) of 39% and 42.6% respectively; median Progression Free Survival (PFS) was not reached in both registration studies, but at 6 months PFS was 88% for patients on ibrutinib. Moreover, the responses are achieved irrespective of the presence of the classic high risk disease markers, (e.g. del17p or TP53 mutation). Interestingly, patients treated with ibrutinib or idelalisib frequently experience rapid improvement of CLL related symptoms, e.g. decrease in lymphadenopathy. This is typically accompanied by an increase in peripheral Absolute Lymphocyte Counts (ALC). This transient lymphocytosis is now viewed as a class effect of kinase inhibitors targeting the B cell receptor signaling pathway [R15-0125], and is not considered a sign of progression of disease. Despite durable disease control, most responses on those inhibitors are PR, and it is conceivable that the persistence of residual disease will eventually lead to progression or transformation. This concern, together with recently described acquired mutations in Bruton's Tyrosine Kinase (BTK) and phospholipase C gamma gene (PLC2γ) [R15-0127], [R15-0124], in CLL patients progressing on ibrutinib, demonstrate the first examples that resistance to ibrutinib has to be expected. Combining ibrutinib with other agents (chemotherapy, or monoclonal antibodies (Mab)) might therefore offer advantages over monotherapy by increasing the depth of response, and potentially

reducing the treatment duration. The first results of such combinations have proven safe, but available limited data although encouraging, are still inconclusive in regard to added benefit [R15-0151], [R15-0130]. The search for the best partner for such combinations still continues. This study will evaluate BI 836826, a novel CD37 antibody engineered for enhanced antibody-dependent cellular cytotoxicity (ADCC) activity in combination with ibrutinib. Besides safety of the combination, this Phase Ib/study will evaluate early signals of response, and the depth of response in relapsed/refractory CLL patients who have failed at least one prior line of systemic therapy.

1.2 DRUG PROFILE

1.2.1 BI 836826

General information:
BI 836826 is a mouse human chimeric Mab against human CD37. BI 836826 has a cytotoxic mode of action by directly inducing apoptosis upon binding to the target cell independent of Immunoglobulin G (IgG) cross-linking. In addition, BI 836826 harbors a mutation in the Fc portion of the molecule which conveys increased ADCC. BI 836826 is an investigational compound currently in clinical development in mature B-cell neoplasms, including CLL.

CD37 Antigen:
CD37, a member of the tetraspanin superfamily, is a glycosylated cell surface protein with four transmembrane domains and two extracellular loops. CD37 is predominantly expressed on B cells with highest expression levels on mature peripheral blood B cells and reduced levels on plasma cells (R08-2979, R08-2943). Low level expression of CD37 has been reported for monocytes, T cells, macrophages, and granulocytes (R08-2979, R09-4740, and R09-4739). The physiological function of CD37 in humans remains largely 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 Immunoglobulin A (IgA) response (R09-4740, R09-5414). The majority of malignant cells in patients with B-cell Non-Hodgkin's Lymphoma (B-NHL) and CLL express the CD37 antigen (R08-2979, R08-2943, R08-2981, R08-2945, R08-2942). Recent data provide evidence that CD37 can function as a death receptor on B cells, which can mediate dual signal transduction through its N- and C-terminal intracellular domain (R12-2850).

Preclinical pharmacology and toxicology:
In vitro assays demonstrated that BI 836826 specifically recognizes human CD37 and binds with high affinity to this antigen. BI 836826 is a potent inducer of apoptosis and ADCC on Ramos Burkitt lymphoma in vitro, but lacks CDC activity. The pro-apoptotic activity of BI 836826 does not depend on IgG cross-linking. Moreover, BI 836826 is able to deplete endogenous, normal B cells, spiked Ramos Burkitt lymphoma cells and CLL cells from human blood without affecting endogenous T cells and monocytes [R10-6346], [R11-4834], [R11-4833].

The combination of BI 836826 with chemotherapeutics (bendamustine, chlorambucil, fludarabine) or with the CD20 antibody rituximab results in additive or synergistic apoptosis induction on lymphoma cell lines and primary CLL cells [R12-4648].

Due to the lack of cross-reactivity of BI 836826 with CD37 in any preclinical species tested, the preclinical safety of BI 836826 was investigated in two toxicologically relevant models: 1) Transgenic mouse model, in which the human CD37 protein instead of the murine CD37 protein is expressed (HuCD37 transgenic mice) and 2) Cynomolgus monkeys, in which an anti-macaque CD37 surrogate antibody (BI 836847) was used.

The majority of effects observed in the general toxicity studies with BI 836826 in HuCD37 mice and with the surrogate BI 836847 (an anti-macaque CD37 surrogate antibody) in cynomolgus monkeys were directly related or secondary to the pharmacological activity of BI 836826 and BI 836847. The main target organs following repeat intravenous (i.v.) exposure to BI 836826 in HuCD37 mice and to the surrogate BI 836847 (an anti-macaque CD37 surrogate antibody) in cynomolgus monkeys were the blood and lymphoid system. BI 836826 induced B- but also T-cell reduction in HuCD37 mice in peripheral blood and lymphoid organs at all dose levels with the histopathological correlate of lymphoid depletion in B-cell areas in spleen and lymph nodes. In contrast, the surrogate BI 836847 induced reduction of lymphocytes, predominantly B cells and NK cells at low to moderate doses. T cells, granulocytes and Platelets (PLT) were reduced at higher doses. Severe and sustained immunosuppression in monkeys treated with high doses led to several cases of septicaemia. Furthermore, anti-drug antibodies were documented in both animal models. They were of neutralizing nature allowing recovery of the pharmacodynamic effects in mice within the 5-week study duration and resulted in an immune-complex mediated glomerulopathy and uveitis in monkeys. However, anti-drug antibodies in the transgenic mouse and the cynomolgus monkey are not considered to be predictive for the immunogenic effect in humans. Cytokine release studies demonstrated a transient and dose dependent increase in interleukin 6 and interleukin 8 in monkeys and of IL-6 and TNFα in the in vitro study using the human blood solid phase assay.

Clinical trials in CLL:
Preliminary data from the ongoing Phase 1, first in human, dose escalation trial 1270.1 in patients with CLL are available. As of June 2015, 36 patients were exposed to BI 836826, administered intravenously at escalating doses in a 2 week schedule. The median age of patients was 68 years (range: 44-80 years). BI 836826 was administered at the following dose tiers (n) 1 mg (3), 3 mg (3), 9 mg (6), 25 mg (6), 50 mg (3), 100 mg (3), 200 mg (6), 400 mg (3) and 800 mg (3). The initial treatment schedule employed at dose tiers of 1 mg, 3 mg and 9 mg contained one i.v. infusion of BI 836826 at a fixed rate over 3 hours on day 1 of a 14-day treatment course. Due to occurrence of infusion related reactions of maximum Grade 2 the infusion schedule was amended to increase tolerability. The amendment included a slow increase of the infusion rate and division of the first dose into two portions delivered on two consecutive treatment days (Day 1 and 2 of course 1) to mitigate the risk for severe

Infusion-Related Reactions (IRRs). This schedule was applied to 3 additional patients at 9 mg, and all patients treated at dose tiers of 25 mg and above. During the dose escalation all patients were scheduled to receive 4 treatment courses, and upon clinical benefit were allowed to proceed to 8 treatment courses. Those with sustained clinical benefit were offered prolonged therapy. Eighteen of 36 patients have initiated 8 or more treatment courses.

Infusion-related reaction (IRR) was the most frequent AE, reported in 25 patients (69%). With mandatory premedication and an infusion schedule using a split of the first dose over two consecutive treatment days and a slowly increasing infusion rate the IRRs reported have been manageable at all dose tiers. The majority of IRRs was grade 1 or 2; only 3 patients experienced a grade 3 reaction.

Decrease in leukocytes, neutrophils, thrombocytes and haemoglobin have frequently been reported in patients. Drug related neutropenia was reported in 42% (15/36) of the patients, with a worst Common Terminology Criteria for Adverse Events (CTCAE) grade 3 or 4 in 14/36 patients (39%). Drug related thrombocytopenia was reported in 31% (11/36), with a worst CTCAE grade of 3 or 4 in 8 patients (22%). Corresponding laboratory data showed that neutrophils and thrombocytes declined immediately after the infusion, with recovery by day 8 in the majority of patients. Anemia was considered drug related in 28% of the patients and highest grade was CTCAE grade 3. A drug related increase of Alanine Aminotransferase (ALT) was reported in 4 patients (11%), of Aspartate Aminotransferase (AST) in 5 patients (14%). ALT and AST elevations were grade 1 and 2 in all patients except for one patient with a grade 3 ALT elevation. The corresponding laboratory data in these patients showed short lasting, reversible elevations of AST and/or ALT without concomitant bilirubin elevation. Prior to the next administration of BI 836826, ALT and AST had returned spontaneously to normal or pre-treatment values.

Efficacy was observed at doses ≥9 mg. The ORR was 40% (12/30 patients), all responses were PRs. In addition, the decline in ALC was analyzed to assess effect of BI 836826 on CLL tumor load in 25 patients treated at doses ≥9 mg, who had an elevated ALC at baseline and received at least one full dose of BI 836826 at the respective dose tier. A decline in ALC by 50% or more as compared to baseline was observed in 80% (20/25 patients) and a reduction to $< 4 \times 10^9$/L in 56% (14/25 patients).

The preliminary Pharmacokinetics (PK) data from a Phase I study 1270.1 concludes to an increase of Area Under the Curve (AUC) with dose and a Clearance (CL) decrease with dose suggesting target mediated drug disposition. No accumulation after repeated dosing was observed. Moreover, a quick elimination of BI 836826 from blood was also observed.

For a more detailed description of the drug profile, including data on an ongoing trial in Non-Hodgkin's lymphoma, please refer to the current Investigator's Brochure (c01715907-08) which is included in the Investigator Site File (ISF).

1.2.2 Ibrutinib (Imbruvica®)

Ibrutinib (Imbruvica) is a small molecule inhibitor of BTK inhibitor approved by FDA. Ibrutinib forms a covalent bond with a cysteine residue in the BTK active site, leading to inhibition of BTK enzymatic activity. BTK is a signaling molecule of the B-cell Antigen Receptor (BCR) and cytokine receptor pathways. BTK's role in signaling through the B-cell surface receptors results in activation of pathways necessary for B-cell trafficking, chemotaxis, and adhesion. Nonclinical studies show that ibrutinib inhibits malignant B-cell proliferation and survival in vivo as well as cell migration and substrate adhesion in vitro. In patients with recurrent B-cell lymphoma > 90% occupancy of the BTK active site in peripheral blood mononuclear cells was observed up to 24 hours after ibrutinib doses of ≥ 2.5 mg/kg/day (≥ 175 mg/day for average weight of 70 kg). Ibrutinib is absorbed after oral administration with a median T_{max} of 1 to 2 hours. Ibrutinib exposure increases with doses up to 840 mg. The steady-state AUC (mean ± standard deviation) observed in patients at 560 mg is 953 ± 705 ng·h/mL and in patients at 420 mg is 680 ± 517 ng·h/mL. Administration with food increased ibrutinib Cmax and AUC by approximately 2 to 4-and 2-fold, respectively, compared with administration of ibrutinib after overnight fasting. Reversible binding of ibrutinib to human plasma protein in vitro was 97.3% with no concentration dependence in the range of 50 to 1000 ng/mL. The apparent volume of Distribution at Steady State (Vd, ss/F) is approximately 10000 L. Metabolism is the main route of elimination for ibrutinib. It is metabolized to several metabolites primarily by cytochrome P450, CYP3A, and to a minor extent by CYP2D6. The active metabolite, PCI-45227, is a dihydrodiol metabolite with inhibitory activity towards BTK approximately 15 times lower than that of ibrutinib. The range of the mean metabolite to parent ratio for PCI-45227 at steady-state is 1 to 2.8. Apparent clearance (CL/F) is approximately 1000 L/h. The half-life of ibrutinib is 4 to 6 hours.

Ibrutinib, mainly in the form of metabolites, is eliminated primarily via feces. After a single oral administration of radiolabeled [14C]-ibrutinib in healthy subjects, approximately 90% of radioactivity was excreted within 168 hours, with the majority (80%) excreted in the feces and less than 10% accounted for in urine. Unchanged ibrutinib accounted for approximately 1% of the radiolabeled excretion product in feces and none in urine, with the remainder of the dose being metabolites. Due to potential DDI, ibrutinib should not be used with strong CYP3A inhibitors- for detailed description (See Section 4.2.2.1

Ibrutinib should not be administered to pregnant women (due to teratogenicity) and to nursing mothers. The safety and effectiveness in pediatric populations has not been established.

Clinical experience with ibrutinib:
The clinical efficacy of ibrutinib was tested in a randomized, multicenter, open-label Phase 3 study. Patients with CLL or Small Lymphocytic Lymphoma (SLL) (n=391) were randomly assigned to receive either ibrutinib at 420mg orally daily until disease progression, or unacceptable toxicity, or ofatumumab at an initial dose of 300 mg, followed one week later by a dose of 2000 mg weekly for 7 doses and then every 4

weeks for 4 additional doses. Fifty seven patients randomized to ofatumumab crossed over following progression to receive ibrutinib. The median age was 67 years (range, 30 to 88 years), 68% were male, and 90% were Caucasian. All patients had a baseline Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. The trial enrolled 373 patients with CLL and 18 patients with SLL. The median time since diagnosis was 91 months and the median number of prior treatments was 2 (range, 1 to 13 treatments). At baseline, 58% of patients had at least one tumor ≥ 5 cm. Thirty-two percent of patients had 17p deletion. Adverse reactions and laboratory abnormalities reflect exposure to ibrutinib with a median duration of 8.6 months. The most common non hematologic adverse reactions (with a cut off of 20%) in this study occurring in 195 patients assigned to receive ibrutinib were: diarrhea 48%, nausea 26%, fatigue 28%, pyrexia 24%, rash 24%, and musculo-skeletal pain 28%. The following treatment emergent laboratory abnormalities per International Workshop Chronic Lymphocytic Leukemia (IWCLL) criteria were observed: neutrophils decreased 51% (23% G3-4), PLT decreased 52% (5% G3-4), and hemoglobin decreased 36% (no G3-4). Approximately five percent of patients receiving ibrutinib discontinued treatment due to Adverse Events (AEs). These included infections, subdural hematomas and diarrhea. AEs leading to dose reduction occurred in approximately 6% of patients. Additional adverse reactions have been observed in patients taking ibrutinib: hemorrhage, infections, cytopenias, atrial fibrillation, and second malignancies.

PFS as assessed by Independent Review Committee (IRC) according to IWCLL criteria indicated a 78% statistically significant reduction in the risk of death or progression. Analysis of Overall Survival (OS) demonstrated a 57% statistically significant reduction in the risk of death for patients in the ibrutinib arm. The study included 127 CLL patients with del 17p. The ORR 63 patients with del17p treated with ibrutinib was 47.6%, and the median PFS was not reached in this group. Interestingly, upon initiation of ibrutinib, an increase in lymphocyte counts (i.e., ≥ 50% increase from baseline and above ALC of 5,000/mcL) occurred in 77% of CLL patients. The onset of isolated lymphocytosis occurs during the first month of ibrutinib therapy and resolves by a median of 23 weeks (range 1 -104+ weeks). This study led to approval of ibrutinib (Imbruvica) by FDA for the treatment of patients with CLL who have received at least one prior therapy and for the treatment of patients with CLL with 17p deletion regardless of prior lines of treatment.

2. RATIONALE, OBJECTIVES, AND BENEFIT - RISK ASSESSMENT

2.1 RATIONALE FOR PERFORMING THE TRIAL

There has been significant progress in treatment of CLL patients since the recent approval of two small molecules that inhibit BCR-associated kinases: ibrutinib, and idelalisib. Both agents are highly active in treating B-cell malignancies. Treatment with ibrutinib results in ORR of 42.6% in CLL patients, and in longer PFS when compared to ofatumumab, even in patients with high risk CLL (ie del17p). However, in most cases patients treated with ibrutinib achieve PRs, and only very few patients achieve Complete Response (CR), or Minimal Residual Disease (MRD) [R15-0129] negativity on monotherapy. In order to maintain responses continuous treatment with inhibitors of BCR-associated kinases seems necessary. Besides high cost of such treatment, emerging resistance mechanisms are a growing concern that long term exposure to the drug will ultimately result in relapse [R15-0127], with very few therapeutic options left for the patient. Historical experience with CLL indicates that depth of response is important for the outcome of therapy, i.e. prolongation of PFS and OS [R15-0128]. A combination approach has been undertaken in several smaller studies examining the therapeutic potential of ibrutinib with rituximab, or ibrutinib with chemotherapy. So far only limited data are available, and the CR rate reported in those trials is low. Therefore, while the combination treatments with ibrutinib remain a very attractive option to increase the depth of response in CLL patients- the choice of the best combination partner remains a challenge. CD20-targeting monoclonal antibodies: rituximab, ofatumumab, obinutuzumab, have proven effective in CLL in combination with cytotoxic agents. Thus, the majority of CLL patients will be pre-treated with CD20 antibodies as part of their first line treatment. Given the dim CD20 expression on CLL cells, the modest single agent activity of rituximab in relapsed CLL, and low CR rate generated by rituximab plus ibrutinib combinations, exploration of combination partners outside of rituximab is warranted.

In addition, due to advanced age of typical CLL patients and frequent comorbidities, chemotherapy-free combinations are preferred.

This study will be generating first set of data on the combination of ibrutinib with anti CD37 antibody.

BI 836826 is a novel anti-CD37 (chimeric mouse) antibody with intrinsic ADCC activity. Strong expression of CD37 (stronger than CD20) has been demonstrated in samples derived from CLL patients [R11-4833]. Data available so far from the ongoing first in human phase I study in patients with relapsed/refractory CLL demonstrate an OR rate of 40% (12/30 patients treated at doses ≥9 mg). This encouraging monotherapy activity allows generating a hypothesis that BI 836826 has a potential to deepen the response when combined with ibrutinib in CLL patients.

This is a single arm, open-label phase Ib study to explore safety and efficacy of combining ibrutinib with BI 836826. The study will be conducted in patients with relapsed/refractory CLL who have been pre-treated with at least one prior line of systemic therapy, and who would otherwise qualify for treatment with ibrutinib. The study will consist of dose escalation

where standard dose of ibrutinib will be combined with escalating doses of BI 836826 in cohorts of a minimum of 3 patients until an MTD for the combination is established. During dose escalation, the Safety Review Committee (SRC) will define a RP2D .

Note: Following a company decision, further development of BI 836826 has been discontinued. Recruitment of trial participants will be stopped; however, current subjects on treatment will be allowed to complete the trial as per the protocol. Trial procedures and endpoint analysis has been amended due to the early termination of the trial.

2.2 TRIAL OBJECTIVES

The primary objective of this trial is to determine the RP2D of BI 836826 in combination with ibrutinib in relapsed/refractory CLL patients, which may either be the MTD, or a lower dose. In case a formal MTD cannot be determined after dose escalation to the highest protocol defined dose, an appropriate clinically active and safe dose will be determined on the basis of all relevant study data relating to safety, pharmacodynamics, PK, and signs of clinical efficacy. Determination of the MTD is a secondary objective.

2.3 BENEFIT - RISK ASSESSMENT

BI 836826 is a Mab which specifically targets CD37 positive cells through direct apoptosis induction and ADCC [R10-6345].

CD37 is not expressed outside of the haematopoietic and lymphatic system. The anticipated side effect profile of BI 836826 based on preclinical studies comprised predominantly hematological AEs such as neutropenia and thrombocytopenia. In the ongoing Phase I trial in patients, IRRs, neutropenia and thrombocytopenia were among the most frequently observed AEs.

Infusion Related Reactions:
Infusion Related Reactions (IRRs) in patients with hematological diseases are considered associated with cytokine release and measures for risk mitigation typically include premedication, slow infusion rates, patient monitoring and interruption of infusions at the occurrence of first symptoms. IRRs have been manageable in the ongoing Phase I CLL trial, with 3 out of a total of 36 patients terminating treatment early due to IRRs.

Neutropenia:
Hematologic AEs, in particular neutropenia, are frequently reported in patients with CLL and may be due to the underlying disease infiltrating the bone marrow, previous and current treatments or combination of these. A decline in neutrophils has been observed immediately

after infusion of BI 836826, lasting up to several days in CLL patients. Due to the rapid onset after infusion, this effect of BI 836826 on neutrophils is considered to be likely an effect on circulating mature cells, possibly related to re-distribution of cells, rather than a cytotoxic effect on bone marrow precursor cells.

Thrombocytopenia:
A decline in PLT, with onset immediately after infusion of BI 836826, and recovery within few days has been observed.

Neutropenia and thrombocytopenia have been observed in patients treated with ibrutinib. There is a potential risk that frequency or severity of neutropenia and/or thrombocytopenia might be increased compared to each single agent when BI 836826 and ibrutinib are combined. In order to mitigate the risks associated with neutropenia and/or thrombocytopenia, patients' blood counts will be frequently monitored, and prophylactic measures will be instituted when clinically appropriate. An active surveillance for signs of infections will be performed at each clinic visit, and treatment will be instituted immediately if patients develop infections. Patients will be provided with supportive care (transfusions, growth factors support) if necessary.

Tumor Lysis Syndrome:
In patients with a high tumor burden who are exposed to a highly effective therapy, there is a risk of rapid tumor destruction resulting in Tumor Lysis Syndrome (TLS). Prophylaxis, close monitoring and appropriate interventions are the key to preventing and managing TLS. Instructions and reference to published guidelines on TLS are included in this protocol as a prophylactic measure (see Section 4.2.1.2.2).

Drug-Drug Interaction (DDI) potential of ibrutinib:
Ibrutinib is metabolized to a great extent by 3A enzyme of p450 complex. Strong CYP3A inhibitors have been demonstrated to increase Cmax and AUC of ibrutinib by 29-and 24-fold. Patients and investigators will be advised to avoid strong and moderate CYP3A inhibitors.

Drug induced liver toxicity:
Although rare, a potential for drug-induced liver injury is under constant surveillance by sponsors and regulators. Therefore, this trial requires timely detection, evaluation, and follow- up of laboratory alterations in selected liver laboratory parameters to ensure patients´ safety, see also Section 5.3.6.1.

Ongoing safety analysis:
An ongoing safety evaluation will be performed by a SRC composed of members from the sponsor together with the Coordinating Investigator (CI) and participating investigators in regular intervals after completion of MTD observation period (Cycle 1) for all patients in each dose escalation cohort.

Overall the risk benefit is considered positive for the combination of BI 836826 and ibrutinib. Moreover, if proven safe, this combination has the potential to improve the CR rate compared to historical data for ibrutinib alone, and to introduce treatment free intervals, which in turn might prevent development of drug resistance in CLL patients. Considering the chronic

nature of CLL and the need for repeated treatment, this potential benefit of therapy with BI 836826 in combination with ibrutinib is expected to outweigh the treatment-related risks.

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

This is a single arm, open label, phase Ib dose escalation study. Approximately 20 relapsed/refractory CLL patients who have been pre-treated with at least one prior line of systemic treatment and who qualify for treatment with ibrutinib will be treated with a combination of BI 836826 and ibrutinib in this trial.

Ibrutinib is to be dosed at a fixed, approved dose of 420mg daily in all patients. Stepwise dose escalation of BI 836826 will be performed. BI 836826 will be administered on cycle 1 on following days: D1 (10mg), D2 and D8 (50% of the assigned dose on each day), D15 (100% dose). In C2-4 BI 836826 will be administered on days: 1 and 15 of each cycle at 100% of the assigned dose.

Dose-escalation of BI 836826 will be guided by a BLRM with overdose control (refer to Section 7). The BLRM estimates the MTD by updating estimates of the probability of observing a DLT in the first cycle for each dose level in the study as patient information becomes available. At any time in the trial, it will not be permitted to escalate to a dose which does not fulfil the Escalation With Overdose Control (EWOC) criterion (refer to Section 7). Dose-increments will be $\leq$100% of the previous dose level tested in prior cohort.

For any dose-escalation cohort, at least 3 patients will be required (Section 7). However, in the case that only 2 patients are evaluable and neither has experienced a dose- limiting toxicity within the first cycle (28 days) of the combination treatment, then dose-escalation can occur based on these 2 patients.

A patient will be considered evaluable for DLT in cycle 1 (D1 to D28 of combination treatment)

- if the patient has been observed for at least one cycle and has had sufficient exposure to both study drugs, i.e. 4 infusions of BI 836826 (10 mg, 50% of target dose x 2, and 100% of target dose x1) and $\geq$ 80 % (22 of 28 doses) of ibrutinib doses.
- if the patient has experienced a DLT independent of exposure time in cycle 1.

Patients who do not meet at least one of the above criteria will be considered for the safety analysis, but will be replaced by an additional patient for DLT assessment.

After all patients in a cohort have either experienced a DLT or have been observed for at least one cycle (28 days) without experiencing a DLT, the Bayesian model will be updated with the newly accumulated data. The overdose risk will then be calculated for each dose, and escalation will be permitted to all doses which fulfil the EWOC criterion and the additional 100% escalation rule
If DLTs are observed in the first two consecutive patients of a previously untested dose level, subsequent enrollment to that cohort will be stopped. The BLRM will be re-run to confirm that the dose-level still fulfils the EWOC criterion. Based on this information, the SRC will

evaluate whether the next patients will be enrolled on the same dose level, or if they will be enrolled to a lower dose level.

Based on the model and on additional information, if available (PK, PD, patient profiles), the members of the SRC will reach a joint decision on the next dose level to be investigated. The SRC may also provide a recommendation for the size for the next dose cohort. However, the final decision on the next cohort size will be agreed mutually between the Sponsor and the CI.

The SRC may recommend stopping the dose finding phase after the criterion for MTD (see Section 7.1) is fulfilled. Further patients may be included to confirm this MTD estimate.

If a MTD is determined during dose escalation, the RP2D may be either the MTD or a lower dose. If no MTD is observed after escalation to the highest possible dose of 1400 mg, 1400mg or a dose below 1400 mg may be selected as RP2D. The RP2D will be a safe dose at which the intended clinical efficacy (e.g. one or more of the following are observed: ALC lowering effect, clinical CR, MRD negativity, effect on biomarkers). A minimum of 6 patients need to be evaluated at the RP2D..

During dose escalation, enrollment into the first dose cohort will be allowed only after the first patient in the cohort is evaluable for safety for a minimum of 3 days from the first administration (10 mg pre-dose) of BI 836826. Subsequent patients within this cohort and subsequent cohorts may be enrolled at any time.

Enrollment into the next higher dose cohort is allowed after the previous dose cohort is found to be safe for all patients in this cohort by the SRC. For the purposes of determining dose escalation, DLTs will be assessed based on safety data from cycle 1. However, AEs including those qualifying for DLT will be monitored beyond cycle 1 and throughout the trial.

Treatment:
Ibrutinib is going to be dosed at fixed, approved dose of 420mg daily in all patients. Stepwise dose escalation of BI 836826 will be performed. BI 836826 will be administered in Cycle 1 on the following days: D1 (10mg), D2 and D8 (50% of the assigned dose on each day), D15 (100% of the assigned dose). In Cycle 2-4 BI 836826 will be administered at the assigned dose on days 1 and 15 of each cycle. In Cycle 5-12 BI 836826 will be administered at the assigned dose on day 1 only. Patients will continue the study treatment till disease progression, unacceptable toxicity, or withdrawal of consent. Continued monthly treatments beyond cycle 12 are possible for patients with a CR, CRi, or MRD negative PR in the response assessment at the end of Cycle 12. In such cases, patients may continue treatment with 12 additional cycles of combination treatment up to a maximum and total of 24 treatment cycles.

Patients will take two weeks of ibrutinib during the run-in phase, prior to start of BI 836826 and will continue ibrutinib throughout the whole duration of the study. After completion of the study the continued treatment with ibrutinib is left to the decision of the investigator or patient's physician, depending on patients' disease status, and the need for further treatment.

For selection of doses please refer to Section 4.1.3.

For dose adaptation in case of AEs please refer to Section 4.1.4.5.

3.1.1 Administrative structure of the trial

Boehringer Ingelheim is the Sponsor of this trial. The CI for this trial will be of the . The CI and participating Investigators will be physicians experienced and specialized in the treatment of CLL and in the conduct of Phase I/II trials. Relevant documentation on the participating (Principal) Investigators and other important participants, including their curricula vitae, will be filed in BIRDS.

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

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

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

The SRC will consist of the CI, participating investigators, BI Clinical Program Leader, BI TCM and the BI Statistician. Additional experts may be invited as needed. Details will be specified in a SRC charter. The information on the overdose risk will be presented by the trial statistician to the SRC. Additional information, such as lower grade AEs, PD and PK information, individual patient profiles or data listings and other relevant information will also be presented. Based on this information, the members of the SRC will reach a joint decision on the next dose level to be investigated. This dose level may be above, below or identical to the currently investigated dose level. The SRC will also recommend the size for the next cohort. However, the final decision on the next cohort size will be made by a mutual decision between the Clinical Program Lead and the CI. Minutes of the SRC meetings and recommendations will be documented and archived by the TCM.

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

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

There has been significant progress in treatment of CLL patients since the recent approval of two small molecule inhibitors: ibrutinib, and idelalisib. Both agents are highly active in treating B-cell malignancies. Treatment with ibrutinib may result in long PFS, however, in most cases it is achieved through durable PRs, while very few patients achieve a CR, or MRD negativity on monotherapy. Data from large randomized phase 3 trials in untreated CLL indicates that depth of response is important for the best ultimate outcome which is

prolongation of OS. Therefore combining of novel CD37 antibody BI 836826 which has demonstrated single agent activity in CLL with ibrutinib provides the opportunity for improving the response quality in patients treated with ibrutinib.

This is a single arm, open-label phase Ib study to explore safety and efficacy of combining ibrutinib with BI 836826. The study will be conducted in relapsed/refractory CLL patients who would otherwise qualify for treatment with ibrutinib as standard of care. The study will consist of dose escalation where standard dose of ibrutinib will be combined with escalating doses of BI 836826 in cohorts of minimum of three patients. Dose escalation and cohort size will be determined based on the recommendation of the SRC, guided by a Bayesian Model with overdose control. An EWOC design will increase the chance of treating patients at efficacious doses while reducing the risk of overdosing. This design is based on practical experience and is an efficient algorithmic method due to its ability to identify the dose with a desired toxicity rate and its allocation of a greater proportion of patients to doses at, or close to, that dose (R13-4802, R13-4804, R13-4805).

3.3 SELECTION OF TRIAL POPULATION

Approximately 20 relapsed/refractory CLL patients will enter combination treatment at an estimated number of 4 US sites (approximately 20 patients/ 5 patients per site).

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

3.3.1 Main diagnosis for trial entry

Patients must be diagnosed with CLL, have relapsed/refractory disease pre-treated with at least one prior line of systemic treatment and qualify for treatment with ibrutinib.

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

3.3.2 Inclusion criteria

1. Diagnosis of CLL established according to IWCLL criteria (R10-4429) and documented within medical records.

2. Relapsed or refractory CLL pre-treated with at least one prior line of systemic therapy for CLL.

3. Indication for treatment consistent with IWCLL criteria, i.e. at least one of the following criteria should be met

    a) Evidence of progressive marrow failure as manifested by the development of, or worsening of, anaemia and/or thrombocytopenia.

b) Massive (i.e., lower edge of spleen ≥ 6 cm below the left costal margin) or progressive or symptomatic splenomegaly.
c) Massive nodes (i.e., ≥ 10 cm in longest diameter) or progressive or symptomatic lymphadenopathy.
d) Progressive lymphocytosis in the absence of infection, with an increase in blood ALC ≥50% over a 2-month period, or a lymphocyte doubling time (LDT) of <6 months (as long as initial ALC was ≥30000/µl).
e) Autoimmune anaemia and/or thrombocytopenia that is poorly responsive to corticosteroids or other standard therapy.
f) Constitutional symptoms, defined as any one or more of the following disease-related symptoms or signs:
   i. unintentional weight loss of 10% or more within the previous 6 months
   ii. significant fatigue (i.e. ECOG PS 2 or worse; inability to work or perform usual activities)
   iii. fevers higher than 100.5°F or 38.0°C for ≥2 weeks without other evidence of infection
   iv. night sweats for > 1 month without evidence of infection

4. Clinically quantifiable disease burden defined as at least one of the following:
   a) either ALC >10 000/ μ L, or
   b) measurable lymphadenopathy (at least one node > 1.5 cm in short diameter on CT or Magnetic Resonance Imaging (MRI) or
   c) quantifiable bone marrow infiltration documented in a bone marrow biopsy during screening

5. Minimum interval to prior CLL treatment in line with the following requirements:
   a) Last dose of a cytotoxic drug, a monoclonal antibody targeting CD20, or an investigational drug to treat CLL at least 1 week prior to the first dose of ibrutinib.
   b) Last dose of idelalisib at least 48 hours prior to the first dose of ibrutinib.
   c) Last dose of alemtuzumab at least 4 weeks prior to the first dose of ibrutinib.

6. Resolution of all clinically relevant acute non-hematologic toxic effects of any prior antitumor therapy resolved to Grade ≤1 with the exception of alopecia or neurotoxicity (Grade 1 or 2 neurotoxicity permitted)

7. Must have baseline laboratory data as defined in Table 3.3.2:1

Table 3.3.2:1 Baseline laboratory parameters

Parameter	Value required for study entry
Hb	≥8g/dL
ANC	≥1000/µL
PLT	≥25000/µL
GFR or Creatinine Clearance (See Appendix 10.5)	≥30ml/min
AST and ALT	<3 x ULN
Bilirubin (total) (Exceptions: patients with diagnosed Gilbert's syndrome)	<1.5 x ULN
aPTT PT or INR	≤1.5 x ULN PT ≤1.5 x ULN, INR ≤1.5

8. Male or female patients. Women of childbearing potential* must agree to use highly effective methods of birth control per International Conference on Harmonisation (ICH) M3(R2) that result in a low failure rate of less than 1% per year when used consistently and correctly, during the trial and for at least 1 year after the last dose of BI 836826 and 1 month after the last dose of ibrutinib. A list of contraception methods meeting these criteria is provided in the patient information. Male patients having a partner of childbearing potential must use condoms and ensure their partner is using a highly effective method of birth control as described above, during the trial and for at least 1 year after the last dose of BI 836826 and 3 months after the last dose of ibrutinib.

   *Women of childbearing potential are defined as:
   Any female who has experienced menarche and does not meet the criteria for "women not of childbearing potential" as described below.

   Women not of childbearing potential are defined as:
   Women who are postmenopausal (12 months with no menses without an alternative medical cause) or who are permanently sterilized (e.g., tubal occlusion, hysterectomy, bilateral oophorectomy or bilateral salpingectomy).

9. Eastern Cooperative Oncology Group (ECOG),[R01-0787] performance score of 0 to 2

10. Age 18 years and older

11. Eligible and able to secure sourcing for ibrutinib

12. Written Informed Consent consistent with ICH-GCP and local legislation

3.3.3 Exclusion criteria

1. Known transformation of CLL to an aggressive B-cell malignancy at the time of screening (e.g. large B-cell lymphoma, Richter's syndrome). Patients with Richter's Syndrome that has resolved ≥ 2 years from signing are eligible.

2. Prior allogeneic stem cell transplant within one year or active graft vs. host disease.

3. History of a non-CLL malignancy except for adequately treated in situ, stage 1 or 2 carcinoma in CR after appropriate treatment, or any other cancer that has been in CR for ≥2 years after end of cancer treatment.

4. Active, uncontrolled autoimmune cytopenia. Patients with autoimmune cytopenia which is controlled with corticosteroids at doses of ≤20 mg prednisolone or equivalent may be enrolled.

5. Previous CLL treatment with a CD37-targeting antibody or a CD37-antibody drug conjugate.

6. Previous treatment with ibrutinib

7. Previous treatment with another BTK-inhibitor than ibrutinib.

8. Ongoing systemic immunosuppressive therapy other than corticosteroids.

9. Active bacterial, viral, or fungal infection requiring systemic treatment at the time of study entry.

10. Human Immunodeficiency Virus (HIV) infection
11. Active hepatitis B or C as evidenced by detection of virus specific Deoxyribonucleic Acid (DNA) or Ribonucleic Acid (RNA).

12. History of stroke or intracranial hemorrhage within 6 months prior to enrollment

13. Chronic persistent atrial flutter or atrial fibrillation. Patients with intermittent atrial fibrillation may be enrolled if without episode for ≥ 6 months and without indication for anti-coagulation

14. Requirement for chronic anticoagulation with warfarin or with direct oral anticoagulants at the time of screening.

15. Chronic treatment (i.e. >7 days) with a strong CYP3A inhibitor which cannot be terminated prior to the first dose of ibrutinib. Examples include but are not restricted to: ritonavir, indinavir, nelfinavir, saquinavir, boceprevir, telaprevir, nefazodone)

16. Unstable angina pectoris, uncontrolled hypertension, uncontrolled asthma or other pulmonary disease

17. Other concomitant serious illness considered by the investigator to potentially compromise patient's safety in this trial or significant co-morbidities that would impede patients participation in the trial (examples: inability to travel to the site at prescribed intervals, inability to swallow oral medication)

18. Women who are pregnant, nursing, or who plan to become pregnant while in the trial

19. Known or suspected hypersensitivity to the study medication or excipients

20. Patients unable to comply with protocol

21. Concurrent participation in another therapeutic clinical trial

3.3.4 Removal of patients from therapy or assessments

3.3.4.1 Removal of individual patients

An individual patient may be withdrawn from BI 836826 trial treatment if:

- Disease progression as assessed by investigator
- Initiation of any other new anticancer therapy for CLL, in the absence of disease progression
- The patient withdraws consent for study treatment or study participation, without the need to justify the decision.
- The patient is not able to tolerate a second re-challenge for the same AE (see Section 4.1.4.5)
- The patient needs to take concomitant drugs that interfere with BI 836826, ibrutinib, or the trial results evaluation (see Section 4.2.1 and 4.2.2)
- The patient can no longer be treated with trial medication for other medical reasons (such as another severe intercurrent illness, pregnancy, or breastfeeding)

In the last two cases, consultation with the BI Clinical Monitor is recommended.
Given the patient's agreement, the patient will undergo the procedures for early treatment discontinuation and follow up as outlined in the Flow Chart and Section 6.2.3.
For all patients the reason for withdrawal (*e.g.* adverse events) must be recorded in the eCRF. These data will be included in the trial database and reported.

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.

If a patient should become pregnant during the trial, the combination treatment must immediately be interrupted. The patient will be followed up until delivery or termination of pregnancy (see Section 5.3.7). The data of the patient will be collected and reported in the Clinical Trial Report (CTR) until last patient last visit and any events occurring thereafter will be reported in BI drug safety database.

3.3.4.2 Discontinuation of the trial by the sponsor

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

1. Failure to meet expected enrolment goals overall or at a particular trial site
2. Emergence of any efficacy/safety information invalidating the earlier positive benefit-risk-assessment that could significantly affect the continuation of the trial
3. Violation of Good Clinical Practice (GCP), the Clinical Trial Protocol (CTP), or the contract disturbing the appropriate conduct of the trial

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

3.3.4.3 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 AEs that are unexpected considering the mode of action and that 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 AE.
- 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, enrollment to the trial will be stopped to allow for an in-depth analysis of the safety profile of the combination treatment. The risk-benefit profile will be re-assessed by the SRC. The outcome of the analysis and the recommendations will be shared with all involved regulatory health authorities prior to a possible re-start of enrollment.

4. TREATMENTS

4.1 TREATMENTS TO BE ADMINISTERED

4.1.1 Identity of BI Investigational Product(s), Combination Backbone Product(s)

Table 4.1.1: 1 Test product: BI 836826

Substance:	BI 836826
Pharmaceutical formulation:	Concentrate for solution for infusion
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Unit strength:	10 mg/mL (vials with 10 mL)
Posology	Rate controlled intravenous infusion Cycle 1: Day 1: administration of a 10 mg pre-dose Day 2: administration of 50% of the assigned dose Day 8: administration of 50% of the assigned dose Day 15: administration of first full dose (100% of the assigned dose) Cycles 2-4: administration of a full dose (100% of the assigned dose) on Days 1 and 15 of each 28-day cycle Cycles 5 - 12: administration of full dose (100% of the assigned dose) on Day 1 of each cycle Cycles 13-24: (for patients with CR, CRi and MRD-negative PR only): administration of full dose (100% of assigned dose) on Day 1 of each cycle
Route of administration:	Intravenous

Table 4.1.1: 2 Backbone product:

Ibrutinib Substance:	Ibrutinib
Pharmaceutical formulation:	White opaque capsules
Brand name:	Imbruvica
Source:	Pharmacyclics, Inc.; Janssen Biotech, Inc.
Unit strength:	140 mg capsule
Posology	420 mg once daily*
Route of administration:	Oral**

*As described in the current Package Insert (R15-5127).
**Capsule should be swallowed whole with water. Should not be opened, broken or chewed.

4.1.2 Method of assigning patients to treatment groups

There will be no randomization as this is a single-arm, open-label trial.
BI 836826 medication number will be assigned via the Interactive Response Technology (IRT) system to allow for tracking of used and available medication vials on site. To facilitate the use of the IRT, the Investigator will receive all necessary instructions.

Ibrutinib will not be provided by Boehringer-Ingelheim. Patients and their insurance will be responsible for securing supplies for ibrutinib. Patients entering the trial will receive daily dosing of ibrutinib.

4.1.3 Selection of doses in the trial

The starting dose of BI 836826 for this trial was selected on data from trial 1270.1, the first in human, dose escalation trial of BI 836826 in CLL. A dose of 400 mg was found to be safe in 1270.1. The first dose tier of BI 836826 to be tested in combination with ibrutinib will be BI 836826 100 mg. A dose of 100 mg includes a safety margin for the combination, and was found to be moderately clinically active.

Based on the Bayesian model in Section 7.1, the dose combination 100mg BI 836826 and 420mg ibrutinib has a prior probability of overdosing below 25%; it fulfills the overdose criterion and is therefore a suitable starting dose combination (see Section 7.1).

The dose is planned to be escalated in dose tiers recommended by the BLRM. A maximum escalation step of 100% will be allowed. The provisional dose levels are 100 mg, 200 mg, 400 mg, 600 mg, 800 mg, and 1400 mg of BI 836826, unless recommended differently by the BLRM/SRC. Intermediate or lower dose levels, depending on the number of DLTs observed

in the study may be investigated if agreed upon by the SRC. Intra-patient dose-escalation of BI 836826 will not be allowed in this trial.

4.1.4 Drug assignment and administration of doses for each patient

All patients enrolled into this study will be treated with a combination of ibrutinib (daily) and i.v. infusions of BI 836826.

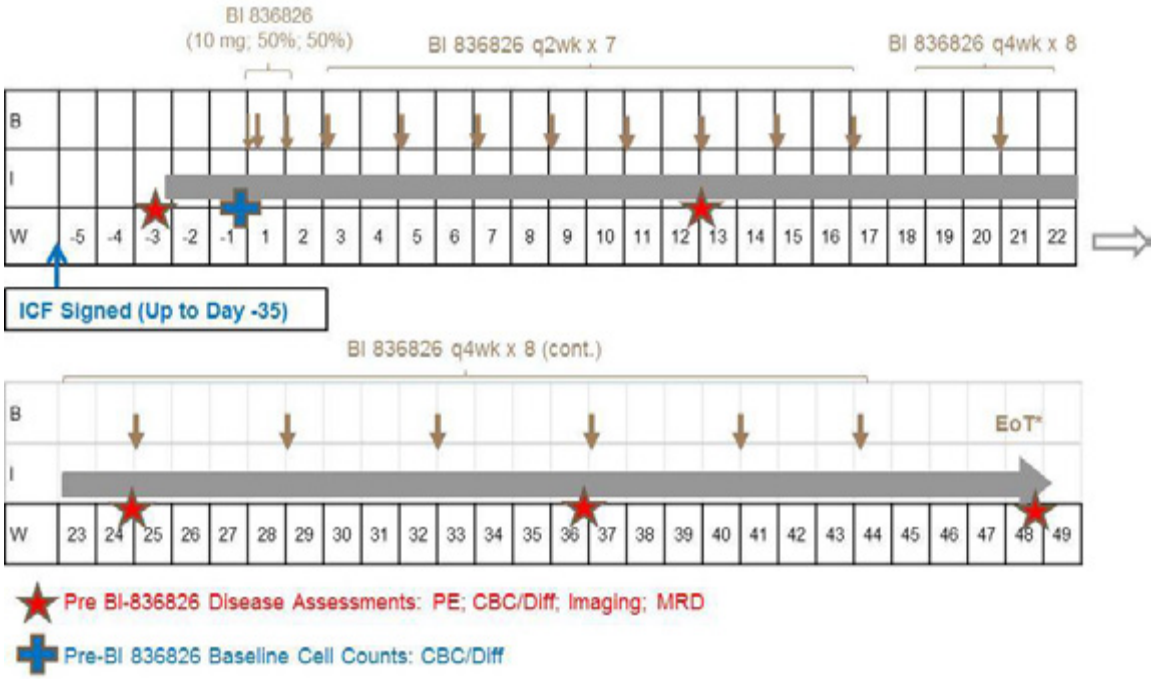
BI 836826 concentrate for solution for infusion is a clear to slightly opalescent, colorless to yellowish liquid. BI 836826 is provided as a concentrate for solution for infusion (10 mg/mL) that is sterile, filtered, and subsequently filled under aseptic conditions into 10 mL clear glass vials. Each vial is enclosed with a rubber stopper and sealed with an aluminum flip-off cap. Each vial contains 100 mg active ingredients (10 mg/mL); dilution is required prior to administration.

Detailed instructions for preparation and handling are included in the ISF.

To determine the dose regimen for the next cohort, the available toxicity information (including DLTs, AEs that are not DLTs, and AE information post-cycle 1), anti-tumor activity information (and –if available- PK/PD data) as well as the recommendations from the BLRM will be evaluated by the investigators and BI personnel (including the BI physician and statistician responsible for the trial) at the SRC meeting. The parties must reach a consensus on whether to declare MTD, escalate the dose any further, or whether to de-escalate and/or expand recruitment into particular cohorts. Dose escalation will continue until identification of the MTD estimate is encountered or until the trial is terminated for other reasons.

Prior to inclusion of a new patient during the cohort dose escalation phase, the Investigator has to confirm the actual dose tier of BI 836826 for the patient with the Sponsor's Clinical Monitor who oversees the cohort dose escalation steps.

The treatment schedule of BI 836826 and daily dosing of ibrutinib is summarized below:



Treatment details:

Screening:
Each patient will provide consent and enter the screening period to confirm eligibility. The screening period will be three weeks (Day -35 through Day -15) in duration and prior to the start of the run-in phase of ibrutinib administration. AEs will be collected from the time of consent; however they will not constitute part of the DLT assessment for combination therapy.

Run-in:
Each patient enrolled, completing the screening period and meeting eligibility will enter the run-in phase and start with ibrutinib monotherapy pre-treatment on Day -14 through Day - 1. While AEs from this period will be collected, they will not constitute part of the DLT evaluation period for combination therapy. The dose for ibrutinib will be 420mg daily, orally.

Cycle 1:
Patients completing the screening period and run-in phase will start the combination treatment. For prevention of IRRs and tumor lysis syndrome the first administration of BI 836826 will be a pre-dose of 10 mg/ml on Day 1. Subsequent two doses will be 50% of the target dose on Day 2 and on Day 8, followed by 100% of the target dose on Day 15 of the first cycle. Patients will continue to receive ibrutinib on days 1-28 of cycle 1. DLTs from the start of the first BI 836826 infusion through the MTD evaluation period (Cycle 1) as well as other AEs will be used to assess dose escalation steps and to determine the MTD.

Cycle 2-4:
Patients will receive 100% of assigned dose of BI 836826 on days 1 and 15 of each cycle. Patients will continue to receive ibrutinib on days 1-28 of each cycle (2-4). At the end of Cycle 3 (Imaging and Laboratory) and Cycle 4 (Laboratory) disease assessment will be performed. Patients without disease progression of CLL will be allowed to continue with BI 836826 and ibrutinib.

Cycle 5-12:
Patients will receive 100% of assigned dose of BI 836826 on Day 1 of each cycle. Patients will continue to receive ibrutinib on days 1-28 of each cycle. Disease assessment will be performed every three cycles or 12 weeks, and will be performed at the end of every third cycle, i.e. Day 21 through Day 28 of Cycle 6, 9, and 12. Treatment with BI 836826 will be terminated at the end of cycle 12 in all patients who achieve PR (MRD positive), PR-L, Stable Disease (SD) or PD in the response assessment at the end of cycle 12. Patients who achieve a CR (MRD positive or negative) or a PR (MRD negative), may continue treatment with BI 836826 as outlined below for additional 12 cycles. Treatment with ibrutinib monotherapy may be continued according to label at the discretion of the investigator or the patient's physician.

Cycle 13-24 (patients with CR and MRD-negative PR only):
Patients will receive 100% of assigned dose of BI836826 on Day 1 of each cycle. Patients will continue to receive ibrutinib on days 1-28 of each cycle. Disease assessment will be performed at the end of every fourth cycle, i.e. Day 21 through Day 28 of Cycle 16, 20 and 24. Treatment with BI 836826 will be terminated at the end of cycle 24 in all patients. Treatment with ibrutinib monotherapy may be continued according to label at the discretion of the investigator or the patient's physician.

4.1.4.1 BI 836826 infusion rates

Table 4.1.4.1: 1 provides a summary of planned and modified infusion rates. Pre-medication prior to each administration of BI 836826 is required Section 4.2.1.2.1

Table 4.1.4.1:1 Planned and modified infusion rates

Day of Treatment	Dose of BI 836826	Initial Rate of Infusion and Maximum Escalation Steps*	Maximum Allowed Infusion Duration	Maximum Allowed Infusion Rate
Cycle 1 Day 1	10 mg	2 mg/hr x 60 min Escalate by 1 mg/hr every 30 min as tolerated to maximum allowed rate**	24 hr	5 mg/hr
Cycle 1 Day 2	50% of target dose	≤ 50 mg/hr x 60 min Escalate by ≤ 50 mg/hr every 30 min as tolerated to maximum allowed rate**	24 hr	400 mg/hr
Cycle 1 Day 8	50% of target dose	≤ 50 mg/hr x 60 min Escalate by ≤ 50 mg/hr every 30 min as tolerated to maximum allowed rate**	24 hr	400 mg/hr
Cycle 1 Day 15	100% of target dose	≤ 50 mg/hr x 60 min Escalate by ≤ 50 mg/hr every 30 min as tolerated to maximum allowed rate**	24 hr	400 mg/hr
Cycle 2 Day 1 and subsequent Cycles	100% of target dose	≤ 50 mg/hr x 30 min, then ≤ 100 mg/hr x 30 min Escalate by ≤ 100 mg/hr as tolerated to maximum allowed rate**	24 hr	500 mg/hr

* Infusion rates may be adjusted and given extremely slowly over a longer period of time (not to exceed 24 hours) for patients with a White Blood Cell Count (WBC) ≥ 100 x 10^9/L at the time of infusion,
** slower start rate or smaller increments allowed at investigator's discretion

Cycle 1 Day 1: BI 836826 "pre-dose" of 10 mg:
BI 836826 administration will start with a "pre-dose" of 10 mg on Day 1 of the first cycle. Pre-medication according to Section 4.2.1.2.1 is mandatory. The initial infusion rate to mitigate the risk for severe infusion related reactions is 2 mg/h for the first 60 minutes. In the absence of infusion related reactions the rate can be escalated every 30 minutes by increments of 1 mg/h to a maximum rate of 5 mg/h.

In patients with a high risk for IRRs or TLS (e.g., a WBC ≥ 100 x 10^9/L at the start of infusion), or occurrence of an IRR during the infusion, the infusion may be given extremely slowly over a longer period of time, but not exceeding 24 hours.

Cycle 1 Day 2 and Cycle 1 Day 8: BI 836826 at 50% of target dose:
Pre-medication, according to Section 4.2.1.2.1, is mandatory. The recommended initial infusion rate to mitigate the risk for severe IRRs should not exceed 50 mg/h for the first 60 minutes. The rate can be escalated every 30 minutes by increments of 50 mg/h or less to a maximum rate of 400 mg/h in the absence of IRRs. A slower start rate or smaller increments are possible based on individual risk assessment. Reductions in the infusion rate may be applied as indicated to ensure tolerability. In patients with a high risk for IRRs or TLS (e.g., a white blood cell count (WBC) ≥ 100 x 10^9/L at the start of infusion), or occurrence of an IRR during the infusion, the infusion may be given extremely slowly over a longer period of time but not exceeding 24 hours.

Cycle 1 Day 15: BI 836826 at 100% of target dose:
Pre-medication, according to Section 4.2.1.2.1, is mandatory. The recommended initial infusion rate to mitigate the risk for severe IRRs should not exceed 50 mg/h for the first 60 minutes. The rate can be escalated every 30 minutes by increments of 50 mg/h or less to a maximum rate of 400 mg/h in the absence of IRRs. A slower start rate or smaller increments are possible based on individual risk assessment. Reductions in the infusion rate may be applied as indicated to ensure tolerability. In patients with a high risk for IRRs or TLS (e.g., a WBC ≥ 100 x 10^9/L at the start of infusion), or occurrence of an IRR during the infusion, the infusion may be given extremely slowly over a longer period of time but not exceeding 24 hours.

Cycle 2 Day 1 and subsequent cycles: BI 836826 at 100% of target dose:
In the absence of infusion related reactions during the administration of the previous full dose, the subsequent administration of BI 836826 is recommended to start at a rate of 50 mg/h or less for the first 30 minutes, followed by a rate of 100 mg/h or less for 30 minutes. Incremental steps thereafter may be larger depending on individual tolerability, but must not exceed 100 mg/h. A maximum rate of 500 mg/h is not to be exceeded. A slower start rate and smaller increments are possible based on individual risk. Reductions in the infusion rate may be applied as indicated to ensure tolerability. Pre-medication should be considered according to Section 4.2.1.2.1.

4.1.4.2 Management of infusion related reactions

IRRs are events that are directly related to antibody–antigen interactions and have been also characterized as cytokine-release syndromes that result from the interaction of antibody with antigen on circulating hematopoietic cells [R14-4170]. Symptoms are often difficult to distinguish from anaphylactoid or hypersensitivity reactions. IRRs will be captured as an AE on the dedicated IRR eCRF page together with the clinically most important symptoms. Cytokine-release syndrome should be reported under the term IRR, while a true allergic IgE mediated hypersensitivity reaction should be reported on the regular AE page.

Hospitalization and overnight surveillance should be considered by the investigator for patients at high risk for TLS in Cycle 1 on Day 2 following the first infusion of BI 836826 at

50% of the assigned dose. Surveillance of the patient during and until at least 2 hours after the end of each BI 836826 infusion in Cycle 1 is required. Mandatory surveillance can be reduced to at least 1 hour in Cycle 2 and subsequent Cycles if no AE which would necessitate longer observation as per investigator's judgement occurs during the infusion or the 1 hour surveillance period. Surveillance should be prolonged as clinically indicated to monitor or treat AEs.

During the infusion and surveillance period, appropriate monitoring of vital signs is recommended, and access to emergency care should be available.

In case an IRR is observed, appropriate measures depending on the type and severity of the reaction should be taken by the investigator according to best medical judgment and local guidelines. Supportive therapy for symptoms of IRRs may be administered at the investigator's discretion as indicated. Additional glucocorticoids should be considered in particular in patients with Grade 3 or 4 reactions or potentially life threatening symptoms, *e.g.* bronchospasm.

If symptoms of an IRR occur while BI 836826 is administered, the following instructions and tabular summary of procedures for rate changes and interruptions of BI 836826 must be followed:

Table 4.1.4.2: 1 BI 836826 management of infusion-related reactions

NCI CTCAE Grade of IRR	**Action**	**Continuing BI 836826***	
Grade 1	Reduce infusion rate to 50% of the rate at which symptoms occurred; infusion may be interrupted at investigator's discretion	After resolution of symptoms	Increase infusion rate to the rate at which the reaction occurred
Grade 2	Interrupt infusion	After resolution of symptoms	Resume infusion at a slower rate than that at which the reaction occurred
Grade 3	Interrupt infusion	After resolution of symptoms	Resume infusion at ≤ 50% of the rate at which the reaction occurred x 30 minutes
Grade 4	Stop infusion	Do not re-expose	

- *Once subject is stable after reintroduction of initial infusion rate, proceed per Section 4.1.4.1, Dosage and Administration of BI 836826

- In the case of an infusion-related reaction of CTCAE Grade 1, the infusion rate of BI 836826 should be reduced to 50% of the previous rate, but may also be interrupted. Upon resolution of symptoms, the infusion may be resumed at an infusion rate not higher

than the rate at which the IRR occurred, and escalated at the investigator's discretion within the limits described above.

- In the case of an infusion-related reaction of CTCAE Grade 2, the infusion of BI 836826 should be interrupted. Supportive treatment may be administered as indicated. Upon resolution of symptoms, the infusion may be resumed at 50% of the previous infusion rate and infusion rate escalated at the investigator's discretion within the limits described above.

- In the case of an infusion-related reaction of CTCAE Grade 3, the infusion with BI 836826 has to be stopped immediately. Supportive therapy is typically indicated, glucocorticoids should be considered for management. Once all symptoms have resolved, administration of BI 836826 may be resumed for at least 30 minutes at a rate which should not exceed 50% of the rate at which the reaction occurred. Re-increase of the infusion rate as tolerated by the subject is possible within the limits described above.

- In the case of an IRR reaction of CTCAE Grade 4, the infusion has to be stopped immediately. Symptoms should be aggressively treated, glucocorticoids should be considered for management. Re-exposure after the event is not permitted.

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

4.1.4.3 Ibrutinib dosing

Dosing of ibrutinib will be guided by the package insert (R15-5127). The prescribed dose of 420 mg of ibrutinib will be administered orally daily. Capsules should be taken orally with a glass of water. The capsules should not be broken, opened or chewed. Patients should be instructed not to drink grapefruit juice, eat grapefruit, or eat Seville oranges while taking ibrutinib.

If a dose of ibrutinib is not taken at the scheduled time, it can be taken as soon as possible on the same day with a return to the normal schedule the following day. Extra capsules of ibrutinib should not be taken to make up for the missed dose.

On days of BI 836826 dosing, ibrutinib will be administered in the clinic before the start of the infusion. Prior to these visits, patients should be reminded to record the time of their dose the day prior to their scheduled visit and not to take their morning dose of ibrutinib before coming into the clinic. Patients should also be reminded to bring their supply of ibrutinib to the clinic for dosing. Ibrutinib administration information, including the exact time of dose, administered in the clinic or hospital is to be recorded.

4.1.4.4 Criteria for administration of BI 836826 at 100% of the assigned dose (Cycle 1 Day 15 and Following)

Prior to each administration of full dose of BI 836826 (i.e. Cycle 1 Day 15 and subsequent administrations), AEs and CBC with differential will be assessed. To continue treatment with a further infusion of BI 836826, all of the following criteria must be met:

- Neutrophils ≥ 1000 /µL (1.0×10^9/L)
- Platelets ≥ 25.000 /µL (25×10^9/L)
- Acceptable tolerability and recovery from AEs (see Section 4.1.4.5)

In case one of these criteria is not fulfilled, blood counts and/or the AE should be re-evaluated at in appropriate intervals and additional laboratory data should captured in the eCRF.

Treatment with BI 836826 may be delayed to enable resolution of AEs, concurrent diseases, recovery from surgical procedures, or other individual reasons. Delays of the next infusion for > 4 weeks for other reasons should be discussed and agreed with the Sponsor.

4.1.4.5 Recommendations for dose modification in response to AEs

AEs should be assessed for relatedness as outlined in Section 5.3.6. In case an AE is considered related to ibrutinib, recommendations for dose modifications for ibrutinib should be considered. In case an AE is considered related to BI 836826, recommendations for dose modifications for BI 836826 should be followed. In case an AE is considered related to both ibrutinib and BI 836826, it is at the discretion of the investigator whether to modify the dose for both drugs at the same time, or only for one drug.

Dose modifications for adverse events related to ibrutinib:

Ibrutinib will be used within the approved label indication as per clinical routine. The following recommendations as per label should be considered by the investigator when administering ibrutinib:
'Interrupt ibrutinib for

- any Grade 3 or greater non-hematological,
- Grade 3 or greater neutropenia with infection or fever, or
- Grade 4 hematological toxicities.

Once the symptoms of the toxicity have resolved to Grade 1 or baseline (recovery), ibrutinib may be reinitiated at the starting dose. If the toxicity reoccurs, reduce dose by one capsule (140 mg per day). A second reduction of dose by 140 mg may be considered as needed. If these toxicities persist or recur following two dose reductions, discontinue ibrutinib.'

Dose modifications for adverse events related to BI 836826

Worst NCI CTCAE Grade after previous dose	**BI 836826**
Neutrophil values at nadir after previous dose	
< LLN and ≥1 x 10^9/L	Maintain current dose level and schedule
< 1 x 10^9/L and ≥ 0.5 x 10^9/L or <0.5 x 10^9/L for ≤ 7 days	Monitor neutrophils until recovery. Delay BI 836826 until Grade ≤2. Thereafter resume at full dose.
<0.5 x 10^9/L for >7 days	Monitor neutrophils until recovery. Delay BI 836826 until Grade ≤2. Thereafter may resume at full dose. Consider G-CSF support. If neutropenia Grade 4 for > 7 days recurs despite G-CSF support in subsequent cycle, the dose of BI 836826 should be reduced to 50%.
Thrombocytopenia	
PLT > 10 000/µL	Maintain current dose level and schedule
PLT ≤ 10 000/µL at two separate measurements (at least 24 hours apart)	Monitor thrombocytes until recovery to Grade 3. Consider platelet transfusion. Delay BI 836826 until Grade ≤3 (recovery). Upon recovery, BI 836826 may be resumed at full dose. If a level of PLT ≤ 10 000/µL, at two separate measurements at least 24 hours apart, recurs in the subsequent cycle, dose of BI 836826 should be reduced by 50%.
Hepatic Adverse Events (elevations in ALT, AST)	
Grade ≤1 (ALT/AST ≤ 3xULN)	Maintain current dose level and schedule
Grade 2 (ALT/AST >3 and ≤5 x ULN)	Delay BI 836826 until Grade ≤1. Thereafter resume at full dose.
Grade 3 or 4 (ALT/AST >5 and ≤20 x ULN)	Withhold BI 836826. Monitor ALT/AST at least 1x per week until Grade ≤1. Thereafter, may resume at full dose. If ALT/AST elevation Grade ≥3 recurs with BI 836826 at full dose, reduce BI 836826 by 50%. Reescalation of BI 836826 upon resolution of symptoms to 100% possible at

Worst NCI CTCAE Grade after previous dose	**BI 836826**
	the investigator's discretion in later infusions.
Hepatic Adverse Events (elevations in bilirubin)	
Grade ≤1 (bilirubin ≤1.5 x ULN)	Maintain current dose level and schedule
Grade 2 (bilirubin >1.5 and ≤3.0 x ULN)	Delay BI 836826 until Grade ≤1. Thereafter resume at full dose.
Grade 3 or 4 (bilirubin >1.5 and ≤3.0 x ULN)	Withhold BI 836826. Monitor bilirubin at least 1x per week until Grade ≤1. Thereafter, may resume at full dose. If bilirubin elevation Grade ≥3 recurs with BI 836826 at full dose, reduce BI 836826 by 50%. Reescalation of BI 836826 upon resolution of symptoms to 100% possible at the investigator's discretion in later infusions.
Other Non-haematological Adverse Events	
Grade ≤2	Maintain current dose level and schedule
Grade ≥3	Withhold study drug until Grade ≤1. Study drug may be resumed at initial or lower dose level or discontinued at investigator's discretion.

A dose reduction of BI 836826 may be performed twice as outlined in the next table. In case an AE recurs or persists following two dose reductions, BI 836826 should be discontinued.

Occurrence of a BI 836826 related AE included in previous table	BI 836826 Dose Modification at subsequent Infusion
First	Restart at assigned dose
Second	Reduce BI 836826 by 50% at next infusion (dose level -1)
Third	Reduce dose level -1 by 50%, i.e. reduce initially assigned dose of BI 836826 by 75% at next infusion (dose level-2)
Fourth	Discontinue BI 836826

4.1.5 Blinding and procedures for unblinding

4.1.5.1 Blinding

Not applicable as this is an open-label single-arm trial.

4.1.5.2 Unblinding and breaking the code

Not applicable.

4.1.6 Packaging, labelling, and re-supply

For details of packaging and the description of the label, refer to the ISF. Re-supply of BI 836826 will be managed by an IRT system. To facilitate the use of IRT, the investigator will receive an IRT manual including all necessary instructions.

4.1.7 Storage conditions

BI 836826 drug supplies will be kept in their original packaging and in a secure limited access storage area according to the recommended storage conditions on the medication label. A temperature log must be maintained for documentation.

If the storage conditions are found to be outside the specified range, the CML (as provided in the list of contacts) and the Interactive Voice Response System/ Interactive Web-based Response System (IVRS/IWRS) must be contacted immediately.

For more details on BI 836826, please refer to the IB (c01715907-08) and to the ISF.

Ibrutinib will be stored under the conditions specified in the package insert. Excursions are permitted as described in the package insert.

4.1.8 Drug accountability

The Investigator and/or pharmacist and/or investigational drug storage manager will receive the investigational drug BI 836826 delivered by the Sponsor when the following requirements are fulfilled:

- Approval of the trial protocol by the Institutional Review Board (IRB)/ethics committee,
- Availability of a signed and dated clinical trial contract between the Sponsor and the head of the investigational site,
- Approval/notification of the regulatory authority, (e.g. Competent Authority),
- Availability of the curriculum vitae of the principal Investigator,
- Availability of a signed and dated CTP
- Availability of the proof of a medical license for the principal Investigator
- Availability of Form 1572

The Investigator and/or pharmacist and/or investigational drug storage manager must maintain records of the BI 836826 product's delivery to the trial site, the inventory at the site, the use by each patient, and the return to the Sponsor or alternative disposal of unused products.

These records will include dates, quantities, batch / serial numbers, expiry ('use- by') dates, and the unique code numbers assigned to the investigational product and trial patients. The Investigator / pharmacist / investigational drug storage manager will maintain records that

document adequately that the patients were provided the doses specified by the CTP and reconcile all investigational products received from the Sponsor. At the time of return to the Sponsor and/or appointed CRO, the Investigator / pharmacist / investigational drug storage manager must verify that all unused or partially used drug supplies have been returned by the clinical trial patient and that no remaining supplies are in the Investigator's possession.

4.1.8.1 Ibrutinib sourcing and accountability

Ibrutinib (Imbruvica) will not be supplied by Boehringer-Ingelheim. Sourcing of ibrutinib will be the responsibility of the patient and their insurance. Ibrutinib is the standard of care for patients with relapsed/refractory CLL who have received at least one prior therapy and will be prescribed by the investigator or the patient's physician. Site staff should request that patients bring their backbone medication (i.e., ibrutinib) supply to clinic visits to record quantities of capsules and to monitor dosing compliance. Unused drug should not be returned to Boehringer Ingelheim.

4.2 CONCOMITANT THERAPY, RESTRICTIONS, AND RESCUE TREATMENT

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

4.2.1.1 Rescue medication

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

Rescue medication or antidote to reverse the action of ibrutinib is not available or referenced in the package insert (R15-5127). Side effects associated with ibrutinib have to be treated as described by the package insert and at the discretion of the Investigator.

4.2.1.2 Concomitant medication

All concomitant therapies to provide adequate care may be given as clinically necessary, unless given as anti-leukemia therapy. All concomitant treatments should be recorded in the eCRF except for vitamins or nutrient supplements. Trade name, indication and dates of administration of concomitant therapies will be documented. For parenteral nutrition during the trial, the components need not to be specified in detail. It should just be indicated as 'parenteral nutrition'. If a patient needs general anaesthesia, it will be sufficient to indicate 'general anaesthesia' without specifying the details. For glucocorticoids and growth factors, the dose should be captured in addition in the eCRF.
Concomitant therapy should be recorded in the eCRF during the screening and on-treatment period, starting at the date of signature of informed consent, and ending at the end of the Residual Effect Period (REP), 30 days after the last infusion of BI 836826 (see Section 5.3.7).

If a new anti-leukaemia treatment is started, it will be documented in the eCRF on a separate page of subsequent therapy, different from the concomitant therapies pages.

4.2.1.2.1 Pre-Medication prior to BI 836826 infusion

Pre-medication is mandatory 30-120 minutes prior to the administration of BI 836826 to mitigate the risk for IRRs. In case a contra-indication for one of the drug exists, the drug may be replaced or omitted. If BI 836826 has been well tolerated without signs of IRRs during cycle 2, the glucocorticoid dose may be reduced in Cycle 3 while the other drugs are maintained. The first step in cycle 3 may be a reduction from 100 mg to 50 mg prednisolone or equivalent. If the cycle 3 doses are tolerated without IRR, the glucocorticoid may be reduced to 25 mg prednisolone or equivalent prior to a subsequent administration in cycle 4. If BI 836826 is tolerated without IRR after pre-medication with prednisolone 25 mg or equivalent, acetaminophen and antihistamine in cycle 4, the investigator may individually decide whether to administer pre-medication in cycle 5 and subsequent treatment cycles and which of the recommended drugs to use.

All pre-medications with doses should be source documented.

If IRRs are still seen at later infusions, pre-medication triplet should continue to be used for all administrations.

Table 4.2.1.2.1:1 Premedication table

Cycle	**Patients Requiring Premedication**	**Premedication**	**Completion Prior to BI 836826**
1-2	all patients	Analgesic/Antipyretic p.o. or i.v.[1] Antihistamine p.o. or i.v.[2] Glucocorticoid i.v., equivalent to prednisolone 100 mg	60-120 minutes
3	all patients with IRR in the previous infusion and/or with ALC ≥ 25000/µl	Analgesic/Antipyretic p.o. or i.v.[1] Antihistamine p.o. or i.v.[2] Glucocorticoid i.v., equivalent to prednisolone 100 mg	60-120 minutes
3	patients without IRR in previous infusion and ALC < 25000/µl	Premedication Level -1: Analgesic/Antipyretic p.o. or i.v.[1] Antihistamine p.o. or i.v.[2] Glucocorticoid i.v., equivalent to prednisolone 50 mg	30-120 minutes
4 and subsequent Cycles	patients with ALC < 25000/µl and without IRR and premedication at level -1 at previous infusion	Premedication Level -2: Analgesic/Antipyretic p.o. or i.v.[1] Antihistamine p.o. or i.v.[2] Glucocorticoid i.v., equivalent to prednisolone 25 mg	30-120 minutes
5 and subsequent Cycles	patients with ALC < 25000/µl and without IRR and premedication at level -2 at previous infusion	Premedication at the discretion of the investigator	

1 equivalent to Acetaminophen/Paracetamol; [2]1000 mg equivalent to diphenhydramine 50 mg i.v.

4.2.1.2.2 Tumor Lysis Syndrome (TLS) prophylaxis and monitoring

Patients at risk for TLS, e.g. with a high tumor burden or preexisting renal dysfunction, should receive prophylaxis for TLS prior to the initiation of treatment. These subjects must be well hydrated. It is desirable to maintain a fluid intake of approximately 2-3 liters per day for 1-2 days before the first 50% dose of BI 836826. Treatment with allopurinol (≥300 mg p.o./day) or a suitable alternative (e.g., rasburicase) starting ≥ 24 hours prior to the first infusion should be considered unless contraindications exist. Repeated prophylaxis with allopurinol and adequate hydration should be continued prior to each subsequent infusion, if deemed appropriate by the investigator. For all patients, electrolytes, fluid balance and renal function should be monitored and corrected. Supportive care should be administered, including dialysis, if indicated.

TLS will be classified and recorded according to CTCAE: Grade 3 (present), Grade 4 (life threatening consequences; urgent intervention indicated) and Grade 5 (death).

Clinical tumor lysis syndrome: is considered present if laboratory TLS is diagnosed and one or more of the following criteria is met:

- increased serum creatinine (≥1.5 times upper limit of normal)
- cardiac arrhythmia
- seizure

4.2.1.2.3 Antibiotics and antivirals

Prophylactic antibiotics and antivirals are allowed. For patients considered to have an increased risk for infections, prophylactic therapy is strongly recommended unless medically contraindicated. For restrictions on use of CYP 3A inhibitors, see Section 4.2.2.1

Prophylactic antiviral therapy, e.g. acyclovir 400 mg three times a day orally, should be considered for patients at risk for a herpes infection or reactivation, e.g. with a history of recurrent herpes virus infections, herpes infection during previous anti-tumour therapy, neutropenia and low CD4+ cell counts (< 200 cells/µl). For restrictions on use of CYP 3A inhibitors, see Section 4.2.2.1

Prophylaxis against Pneumocystis jiroveci, e.g. oral trimethoprim/sulfamethoxazole 800 mg/160 mg every other day, should be considered for patients at increased risk, e.g. patients with low CD4+ cell counts (< 200 cells/µl). For restrictions on use of CYP 3A inhibitors, see Section 4.2.2.1

Cytomegalovirus reactivation during treatment should be treated according to local standards or available guidelines [R10-4431]. Treatment with BI 836826 must be interrupted until CMV DNA is within limits prior to reactivation.
Infections should be treated according to local guidelines/standard. For restrictions on use of CYP 3A inhibitors, see Section 4.2.2.1.

4.2.1.2.4 Growth factors

The use of growth factors such as granulocyte colony stimulating factor (G-CSF) will be permitted during therapy and should be recorded in the eCRF. However, use of G-CSF is not allowed within 3 days prior to laboratory at screening to reach the inclusion criterion for the neutrophils in patients with pre-existing neutropenia.

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

Prior antineoplastic therapy for CLL must have been discontinued as specified in inclusion criterion 5, and the patient must have recovered from all clinically relevant reversible toxicities.

No concomitant anti-neoplastic therapy during combination therapy of BI 836826 and ibrutinib is allowed.

Steroids:
Short term glucocorticoid medications may be used as clinically indicated to treat IRRs or autoimmune phenomena, 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.

CYP3A Inhibitors:
Due to possible DDIs concomitant use of ibrutinib and CYP3A inhibitors or inducers should be avoided.

Short-term use (i.e. treatment for 7 days or less) of strong CYP3A inhibitors (e.g., antifungals and antibiotics) is permitted while ibrutinib therapy is temporarily discontinued. If use of a strong CYP3A inhibitor is required for an extended period, i.e. more than 7 days, the patient must be discontinued from treatment and trial.

If a moderate CYP3A inhibitor must be used (e.g., fluconazole, darunavir, erythromycin, diltiazem, atazanavir, aprepitant, amprenavir, fosamprevir, crizotinib, imatinib, verapamil, and ciprofloxacin), ibrutinib dose has to be temporarily reduced to 140 mg until the CYP3A inhibitor is no longer needed.

Patients taking concomitant strong or moderate CYP3A inhibitors should be monitored more closely for signs of ibrutinib toxicity.

Anticoagulants and antiplatelet therapy:
Oral anti-coagulants are prohibited throughout the study. If patients require anticoagulation- the use of unfractionated heparin or low molecular weight heparin is recommended for the duration of the treatment with ibrutinib. For patients with a platelet count below 50 x 10^9/L, decisions on treatment and dosage of anticoagulants and/or antiplatelet therapy should be made on a case by case basis with the utmost caution (P13-02472). In case the platelet count

declines below 50 x 10^9/L, treatment with acetylsalicylic acid should be paused until the platelet count recovers to values > 50 x 10^9/L.

4.2.2.2 Restrictions on diet and lifestyle

No restrictions apply with regard to diet or lifestyle.

4.2.2.3 Restrictions regarding women of childbearing potential

Women of childbearing potential must be ready and able to use highly effective methods of birth control per ICH M3(R2) that result in a low failure rate of less than 1% per year when used consistently and correctly, and this during treatment within the trial and for at least one year after last dose of BI 836826 and 1 month after the last dose of ibrutinib (see Section 3.3.2 and explanation given in the informed consent information form for more information on highly effective methods of birth control).
Male patients with partners of childbearing potential need to use condoms and ensure their partner is using an additional highly effective method of birth control, during the trial and until at least one year after the last dose of BI 836826 and 3 months after the last dose of ibrutinib.

5. VARIABLES AND THEIR ASSESSMENT

5.1 TRIAL ENDPOINTS

Primary endpoints:

- Recommended phase 2 dose of BI 836826 in combination with ibrutinib
- Number of patients with DLTs during the first treatment cycle

Secondary endpoint:

- MTD

5.1.1 Primary endpoint(s)

One primary endpoint is to determine the RP2D of BI 836826 in combination with ibrutinib. If a MTD can be determined based on the criteria as described in Section 7, the RP2D will be either the MTD or a lower dose. The RP2D will be determined based on safety and efficacy criteria. Safety criteria include, but are not limited to the number of DLTs during the first treatment cycle, other AE and laboratory abnormalities may be considered in addition. Efficacy criteria include, but are not limited to the effect of BI 836826 on ALC, lymph node size as assessed by SPD, improvement of decreased blood cell counts related to CLL at baseline, overall response. Biomarkers may be considered in addition.

The second primary endpoint is the number of patients with DLT during the first treatment cycle. The number of evaluable patients per dose level with DLTs will be used to update the Bayesian model and to eventually determine the MTD.

5.1.2 Secondary endpoint(s)

The Secondary endpoint of this trial is the MTD.

The MTD may be considered reached if the probability that the true DLT rate is in the target interval [0.16, 0.33) is sufficiently large. For details on determination of MTD, please refer to Section 7.1. For the definition of DLT, see Section 5.3.6.2.

5.2 ASSESSMENT OF EFFICACY

5.2.1 Overall response assessment

Response will be assessed by the investigator according to modified IWCLL guidelines [R10-4429] (See Appendix 10.2) at all disease assessment timepoints specified in the flowchart. All relevant clinical and radiographic information required to make each assessment must be made available for source verification.

Imaging:
All relevant lymph node areas should be documented with either contrast enhanced Computerized Tomography (CT) (preferred) or contrast enhanced MRI at the time points indicated in the Flow Chart.

The same method of assessment and the same technique (*e.g.*, scan type, patient position, dose of contrast, injection/scan interval) should be used to characterize each identified and reported lesion at baseline and during study treatment and follow up. If contraindication for contrast agents exists, non-contrast enhanced CT or MRI scans may be performed.

Disease/response status will be assessed with imaging (CT/MRI) at screening prior to the first dose of ibrutinib, and at the end of Cycles 3, 6, 9 and 12. In case patients qualify for prolonged treatment, CT/MRIs will be performed in addition at the end of cycles 16, 20 and 24. A CT/MRI scan will be performed at the EOT visit if it was not performed at a scheduled visit within 29 days prior to EOT (R10-4429). At the time of clinically suspected disease progression, a CT/MRI should be obtained; a confirmatory scan is not required in the case of PD.

The disease/response assessment will be based on Complete Blood Count (CBC) and imaging (CT or MRI). MRD assessments will coincide with the schedule of imaging studies. Physical examination of lymph nodes will be used to exclude PD prior to starting the next treatment cycle at visits where no imaging study is scheduled. Bone marrow biopsy results will be used to support the evaluation of CR, CRi and PR.

At all disease/response assessment timepoints, response to treatment (CR/CRi/PR/PR-L/SD/PD) should be determined based on the modified IWCLL criteria in Appendix 10. 2.

The BOR is the best response recorded from the start of treatment until disease progression or initiation of subsequent therapy. Post-treatment assessments will be considered in the determination of best overall response as long as a patient does not initiate a new anti-CLL therapy.

5.2.2 CBC and differential

A CBC and differential should be obtained at each disease/response assessment timepoint in the same laboratory at the investigational site. The sample has to be obtained prior to administration of pre-medication and prior to the start of BI 836826, if an infusion is administered on the same day. Absolute lymphocyte count, neutrophil count, hemoglobin and platelet count have to be captured in the eCRF and will be considered for the disease/response assessment, (time points specified in the Flow Chart).

5.2.3 Bone marrow aspirate and biopsy

Bone marrow aspirate and biopsy for response assessment is mandatory according to IWCLL guidelines [R10-4429] in patients who meet all other IWCLL response criteria for CR. The bone marrow should be analysed morphologically and by flow cytometry and/or immunohistochemistry to check for CLL infiltration, or to evaluate a possible cause for persistent cytopenia.

Each time when a BM assessment is performed, a CBC with differential should be available, from the same day as the bone marrow biopsy.

A screening BM assessment is to be performed. Historical data from a BM is acceptable, if the BM assessment has been performed within 4 weeks of consent. A BM assessment will also be performed at EOT.

5.2.4 Physical examination

At day 1 of each treatment cycle, a physical examination will be performed to assess disease progression. In case Progressive Disease (PD) is suspected based on physical examination, imaging should be performed.

ECOG Performance Status:
The ECOG performance status is a scale used to assess how a patient's disease is progressing and how the disease affects daily living abilities. Performance status is graded using the following scale from 0 to 5:

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

5.2.5 Constitutional symptoms

All patients will be evaluated for constitutional symptoms at the same time points when a physical examination is indicated in the Flow Chart. Analysis of constitutional symptoms will be based on the following parameters which have to be reported in the eCRF:

- Unintentional weight loss (10% or more within the previous 6 months)
- Significant fatigue (ECOG PS 2 or worse; inability to work or perform usual activities)
- Fevers higher than 38.0°C (for 2 or more weeks without other evidence for infection)
- Night sweats (for more than 1 month without evidence of infection)

5.2.6 Minimal Residual Disease (MRD)

MRD detection will follow a flow cytometry protocol in a central laboratory according to established standards as e.g. published by the European Research Initiative on CLL (ERIC) [R14-4986]. Modifications according to updated guidance are possible.

For MRD assessment, approximately 10 mL of peripheral blood will be required from each patient at each of the time points specified in the Flow Chart, i.e. at screening, before Day 1 of Cycle 1 (C1D1), and at the end of Cycle 3, 6, 9 and 12. For those patients continuing beyond Cycle 12, assessments have to be performed at the end of Cycle 16, 20, 24, at the EOT visit, and at the first follow-up visit.

MRD negativity is defined as less than 1 leukemic cell per 10000 leukocytes detected in an multi-parameter flow cytometry with adequate sensitivity. In case peripheral blood is MRD negative, approximately 4 mL of bone marrow aspirate will be taken from the patient in addition to peripheral blood at the next time point when a blood MRD assessment is scheduled in order to confirm MRD negativity in bone marrow.

At any time when a BM is performed to confirm a clinical CR or CRi, a blood and bone marrow sample should be sent for MRD.

At all timepoints when MRD sample is obtained, a CBC with differential will be performed at the central laboratory. This CBC/differential from the central laboratory should be used for disease/response assessment whenever possible.

Detailed instructions for sampling, handling, storage, and shipment of the MRD samples will be provided in the laboratory manual included in the ISF. Date of sampling will be recorded in the eCRF.

5.3 ASSESSMENT OF SAFETY

Safety will be assessed by:

- Overall incidence and severity of AEs, as well as seriousness and relatedness
- AE leading to treatment discontinuation
- AE leading to death
- AE of special interest
- Changes in safety laboratory parameters
- Changes in vital signs, physical examination, ECG

Changes in laboratory parameters and AEs will be graded according to US NCI CTCAE version 4.0 [R10-4848]. In addition, hematological toxicity based on laboratory values will be assessed using the criteria as described in IWCLL guidelines (R10-4429).

5.3.1 Physical examination

A physical examination including height (only at screening), weight and ECOG performance score (see Section 5.2.4) as well as the tumor size determination (see Section 10.2) will be performed at screening and at the time points specified in the Flow Chart. During the physical examination, the patient should be assessed for possible AEs.

5.3.2 Vital signs

Vital signs (blood pressure, pulse rate and body temperature) will be recorded at every visit during screening, treatment and follow-up, before proceeding with any other protocol specific procedure and after at least 5 minutes of rest. More frequent measurements of vital signs must happen on the days of study drug administration, at the investigator's discretion, or to detect possible IRRs which have then to be reported as AE. In case of IRR, the investigator should decide whether to intensify or prolong the monitoring of vital signs of the patient and to adapt patient's surveillance during subsequent applications.

5.3.3 Safety laboratory parameters

5.3.3.1 General safety laboratory parameters

Blood and urine samples have to be collected at the time points specified in the Flow Chart. However, more frequent samplings may be done to perform additional safety laboratory

examinations whenever the investigator deems it necessary. Local laboratories of the sites will be used for safety laboratory assessments. Sample and handling will be performed in accordance with local site procedures.

Hematology:	Hemoglobin, red blood count (RBC), white blood count (WBC) with differential: neutrophils, basophils, lymphocytes, monocytes, eosinophils - expressed preferably in absolute values percentages accepted (including Gumprecht shadow (Smudge Cells) and Large Unstained Cells (LUC)) and platelets
Biochemistry:	Sodium, potassium, calcium, inorganic phosphate, creatinine, AST, ALT, Alkaline Phosphatase (AP), Lactate Dehydrogenase (LDH), Blood Urea Nitrogen (BUN), uric acid, total bilirubin. If total bilirubin is elevated, direct bilirubin should be provided. If direct bilirubin is elevated, the following tests to assess haemolysis should be obtained in addition: direct antiglobulin test, reticulocytes, haptoglobin.
Coagulation:	Activated Partial Thromboplastin Time (aPTT) in seconds, Prothrombin Time (PT) in seconds or International Normalized Ratio (INR) have to be measured at screening, at visit 1 of every other cycle and at the EOT visit
Urine:	Urine pH, glucose, erythrocytes, leukocytes, protein, nitrite will be analysed by dipstick. In case of suspicion of a clinically relevant proteinuria, *i.e.* at least 2 positive results after prior negative tests, protein should be quantified in 24 hour urine
Pregnancy test:	A pregnancy test in serum or urine needs to be obtained at the time points indicated in the Flow Chart in women of childbearing potential

5.3.3.2 Serum immunoglobulin levels

Serum immunoglobulin levels (IgA, IgG, Immunoglobulin M (IgM)) have to be analysed quantitatively at screening, at visit 1 of each other cycle (Cycle 2, 4, 6, etc…) and at the EOT visit.

5.3.3.3 Screening for laboratory evidence of Tumor Lysis Syndrome

To allow for early treatment in case TLS develops, monitoring is recommended.

After the first 50% dose of BI 836826 in Cycle1 on Day 2, the following laboratory parameters should be obtained in appropriate intervals, but at least twice within the first 24 hours after the end of infusion:

- uric acid
- potassium
- phosphorus
- calcium

- LDH
- creatinine

In case of laboratory values pointing towards laboratory signs of TLS, hospitalization, appropriate monitoring and treatment should be initiated (see also Section 4.2.1.2.2).

5.3.3.4 Virology

5.3.3.4.1 Screening for hepatitis B, hepatitis C and HIV

A local laboratory will be used.

Patients with active Hepatitis B Virus (HBV), Hepatitis C Virus (HCV) or laboratory evidence of a chronic infection have to be excluded from the trial. The same applies to patients with HIV infection or detection of a HIV infection at screening.

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), HBV DNA and HCV RNA by quantitative assays. HIV Antibody (anti-HIV).

Patients can be treated with BI 836826 if:
- HBV DNA negative
- HCV RNA negative
- HIV antibody negative

Patients who are HBc antibody positive at screening will be monitored for potential HBV reactivation by quantitative HBV DNA at visit 1 of every even course and at the EOT visit. If there is evidence for HBV reactivation, immediately discontinue BI 836826 and start appropriate treatment for HBV.

5.3.3.4.2 CMV monitoring

Monitoring of CMV has to be performed at the time points indicated in the Flow Chart at a local laboratory by quantitative Polymerase Chain Reaction (PCR) assays to detect CMV DNA. The same method and cutoff should be used for the same patients, and preferably for all patients treated at the same investigational site.

Results have to be reported in the eCRF.

5.3.4 Electrocardiogram

A 12-lead resting ECG will be performed in all patients according to the schedule in the Flow Chart. The ECG will be assessed locally for pathological results to be recorded as an AE if deemed clinically significant by the Investigator, or qualified individual delegated by the PI. Additional examinations should be done whenever the Investigator deems necessary. ECGs will be stored locally at the clinical sites and not transferred to a central lab.

5.3.5 Other safety parameters

Not Applicable.

5.3.6 Assessment of adverse events

5.3.6.1 Definitions of AEs

Adverse Event:
An AE is defined as any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

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

Serious Adverse Event (SAE):
A SAE is defined as any AE which:

- results in death,
- is life-threatening,
- requires inpatient hospitalisation or prolongation of existing hospitalisation,
- results in persistent or significant disability or incapacity,
- is a congenital anomaly/birth defect,
  or
- is to be deemed serious for any other reason if it is an important medical event when based upon appropriate medical judgment which may jeopardize the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions.

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

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

The latest list of “Always Serious AEs” can be found in the Remote Data Capture (RDC) A copy of the latest list of “Always Serious AEs” will be provided to you upon request. These events should always be reported as SAEs.

Every new occurrence of cancer of new histology must be classified as serious event regardless of the time since the discontinuation of the trial medication and must be reported as described in 5.3.7, subsections “AE collection” and “AE reporting to sponsor and timelines

Adverse events of special interest:
The term AESI relates to any specific AE that has been identified at the project level as being of particular concern for prospective safety monitoring and safety assessment within this trial, e.g. the potential for AEs based on knowledge from other compounds in the same class. AESI need to be reported to the Sponsor's Pharmacovigilance Department within the same timeframe that applies to SAE, see Section 5.3.7.

The following events are considered as AESIs:
1. Hepatic injury
2. Late onset infections
3. Any AE qualifying for a DLT

Hepatic injury:
Although rare, drug-induced liver injury is under constant surveillance by sponsors and regulators and is considered an AESI. 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 are important for patient safety.

In patients with normal transaminases and bilirubin at baseline, a hepatic injury is defined by any of the following alterations of hepatic laboratory parameters:
- an elevation of AST and/or ALT ≥ 3 fold Upper Limit of Normal (ULN) combined with an elevation of total bilirubin ≥ 2 fold ULN measured in the same blood sample, and/or
- marked peak aminotransferase (ALT, and/or AST) elevations ≥10 fold ULN.

In patients with elevated transaminases and/or bilirubin at baseline in line with in- and exclusion criteria of this protocol, a hepatic injury is defined by the following alterations of hepatic laboratory parameters:
- 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 sample, and/or
- marked peak aminotransferase (ALT, and/or AST) elevations ≥10 fold ULN.

These lab findings constitute a hepatic injury alert and the patients showing these lab abnormalities need to be followed up according to the "Drug Induced Liver Injury (DILI) checklist" provided via the RDC-system and within the ISF.

Work-up as outlined in the "DILI-checklist" will serve to confirm the initial abnormality, obtain a comprehensive history and medical assessment, assess the severity of liver injury, evaluate data for potential alternative causes and decide on management of trial drug. Follow up of the potential DILI case should be initiated within 48 hours of the initial laboratory alert, or as soon as possible if timelines cannot be met. When performing all of the required examinations, the investigator may use clinical judgement, based on the patient's disease, comorbidities, clinical situation, past viral infections and risk for reactivation, exposure, prior therapy for malignant disease, co-medications and other factors as applicable. The sequence of tests in the DILI checklist may be used as guidance. The findings from the hepatic imaging (including comparison to prior imaging if available) must be made available as soon as

possible as part of the AE reporting process and/or on the respective CRF pages. In the event the etiology of the abnormal liver test results is not identified based on the imaging (e.g. biliary tract, pancreatic or intrahepatic pathology), the "DILI checklist" must be completed. Virus reactivation should be assessed by viral load and PCR testing where possible. Diagnostics for auto-immune hepatitis, Wilson's disease and hemochromatosis can be completed at the end of all assessments, as these examinations will not change within a short time period but can be considered proof of a long persisting chronic condition. In case a laboratory parameter of the DILI checklist cannot be performed, the investigator should provide a comment including a brief assessment of the relevance of this parameter for the overall evaluation of DILI.

In case of clinical symptoms of hepatic injury (icterus, unexplained encephalopathy, unexplained coagulopathy, right upper quadrant abdominal pain, etc.) without lab results (ALT, AST, total bilirubin) available, the investigator should make sure these parameters are analysed, if necessary in an unscheduled blood test. Should the results meet the criteria of hepatic injury alert, the procedures described in the DILI checklist should be followed.

If the investigator determines any AESI is related to study drug, the administration of the study drug must be managed according to Section 4.1.4 of the protocol.

Late onset infections with onset date during the extended follow-up period and considered clinically relevant and/or BI 836826 related by the investigator are also AESIs.

Any AE qualifying for a DLT:

No other AESIs have been defined for this trial.

Severity of AEs:

The severity of AEs should be classified and recorded in the (e)CRF according to the CTCAE v 4.0.

Causal relationship of AEs:
Medical judgment should be used to determine the relationship considering all relevant factors, including pattern of reaction, temporal relationship, de-challenge or re-challenge, confounding factors such as concomitant medication, concomitant diseases and relevant history.

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

The causal relationship must be provided by the Investigator for the trial medication BI 836826 investigational drug and for the backbone therapy, ibrutinib.
The reason for the decision on causal relationship needs to be provided on the SAE form (if applicable).

5.3.6.2 Dose limiting toxicities

All drug related AEs, including SAEs and deaths, will be carefully evaluated by investigators for DLT. Dose escalation decisions will be based on DLTs observed in Cycle 1. Dose Limiting Toxicity is defined as follows:

- Any non-hematologic AE of Grade ≥ 3 related to BI 836826 and/or ibrutinib will be considered DLT, except:
  - Infusion-related reaction, any Grade
  - Grade 3 AST- and/or ALT elevation without concomitant bilirubin elevation or any other asymptomatic Grade 3 laboratory abnormality with spontaneous recovery within 1 week

- The following hematologic AEs related to BI 836826 and/or ibrutinib will be considered DLT:
  - Grade 4 neutropenia with concomitant infection
  - Grade 4 febrile neutropenia, and Grade 3 febrile neutropenia not resolving within 72 hours with appropriate treatment (antibiotics, antivirals, antifungals, growth factor support)
  - Grade 4 thrombocytopenia with clinically significant bleeding
  - Grade 4 anemia
  - Any Grade 5 hematologic AE

Patients will be evaluable for MTD in Cycle 1 if:
- a DLT occurs at any time, or
- a minimum exposure to BI 836826 and ibrutinib has been achieved. The minimum exposure is defined as ≥80% of the planned ibrutinib doses (since Day 1 of Cycle 1) and all planned administrations of BI 836826 in Cycle 1. If the administration in Cycle 1 on Day 15 is delayed, the DLT evaluation will be prolonged to cover 14 days after the D15 administration.

All patients who have started trial treatment, but do not meet at least one of the above criteria at the end of Cycle 1 will be evaluated for safety, but replaced for MTD evaluation.

5.3.7 Adverse event collection and reporting

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

- From signing the informed consent onwards through REP, until individual patient's end of trial:
  all AEs (non-serious and serious), and all AESIs.
- After the individual patient's end of trial: the investigator does not need to actively monitor the patient for new AEs but should only report relevant SAEs and relevant AESIs of which the investigator may become aware of.

The REP is defined as 30 days after the last application of BI 836826. All AEs which occurred through the treatment phase and throughout the REP will be considered as on treatment please see Section 7.3.4.

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

Information required:
For each AE, the Investigator should provide the information requested on the appropriate (e)CRF pages and the BI SAE form (if applicable)

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

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

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

All (S)AEs, including those persisting after trial completion must be followed up until they have resolved, have been sufficiently characterized, or no further information can be obtained.
Pregnancy:
In the rare case that a female patient participating in this clinical trial becomes pregnant after having taken trial medication, the Investigator must report immediately (within 24 hours) the Drug Exposure During Pregnancy (DEDP) to the Sponsor's unique entry point (country-specific contact details will be provided in the ISF). The Investigator must also report pregnancies that occurred in a female partner of a male subject. The Pregnancy Monitoring Form for Clinical Trials (Part A) should be used.

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

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

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

Exemptions to SAE Reporting:

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

Examples of exempted events of PD are:

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

However, when there is evidence suggesting a causal relationship between the study drug and the progression of the underlying malignancy, the event must be reported as an (S)AE on the SAE form and on the (e)CRF.

5.6 OTHER ASSESSMENTS

Not applicable.

5.7 APPROPRIATENESS OF MEASUREMENTS

The endpoints chosen for this study are generally recognized methods of assessing efficacy and safety in CLL studies and are in line with the recommendation from International Workshop for Chronic Lymphocytic Leukemia National Cancer Institute-Working Group published in 2008 (R10-4429).

Adverse events will be graded according to the NCI CTC AE criteria version 4.0 (R10-4848), which is commonly used in the assessment of AEs in cancer patients.

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

The screening period is a maximum of 21 days prior to the start of the Run-In Phase. Patients who meet all trial eligibility criteria will continue into the Run-in phase and begin two weeks (+/- 2 days) of ibrutinib monotherapy dosing prior to the first infusion of BI 836826. Treatment with BI 836826 will be administered in cycles of 28 days duration. The dose of BI 836826 will be tapered up to the target dose during Cycle 1 to mitigate the risk for IRRs and TLS. Treatment with BI 836826 starts with the first administration of 10 mg ('pre-dose') on Cycle 1 Day 1 (see Section 3.1), followed by 50% of the target dose of BI 836826 on Cycle 1 Day 2 and Cycle 1 Day 8. The first full dose of BI 836826 (100% of the target dose) will be administered on Cycle 1 Day 15.

In Cycles 2 to 4, patients will receive 100% of the target dose of BI 836826 on Day 1 and Day 15 of each cycle. In Cycles 5 to 12, BI 836826 will be administered at 100% of the target dose on Day 1 only. A response evaluation, including imaging (if clinically indicated), will be performed at the end of Cycle 3, 6, 9 (Day 21-28) and 12 (Day 21-30). Only those patients with CR, CRi, or MRD negative PR in the response assessment at the end of Cycle 12 will be allowed to continue with additional 12 Cycles of combination treatment or until relapse, undue toxicity, withdrawal of consent or until the end of the maximum treatment duration of BI 836826 at the end of 24 Cycles, whichever comes first. In patients who continue treatment beyond 12 cycles and proceed to Cycles 13-24, a response evaluation including imaging (if clinically indicated) will be performed at the end of Cycles 16, 20, and 24.

Once a patient stops the BI 836826 treatment, he/she will undergo an End of Treatment (EOT) visit.

In case the patient completes Cycle 12 or Cycle 24 and terminates treatment with BI 836826 according to protocol in the absence of PD, the assessments indicated for the EOT and End of REP (EoR) visit in the flowchart may be performed once at the time specified for the EoR visit.

In case a patient experiences PD, an EOT visit including imaging should be performed as soon as possible after discontinuation of BI 836826 and prior to initiation of subsequent therapy. An EoR visit should be performed 30 days (+ 7 days) after EOT.

In case BI 836826 is discontinued permanently for reasons other than PD, at any other timepoint than end of cycle 12 or end of cycle 24, e.g. due to AEs, the patient should complete an EOT visit as soon as possible after discontinuation of BI 836826 or when the decision to discontinue BI 836826 is taken.

If the EOT is performed less than 30 days after the last dose of BI 836826, an additional EoR visit has to be scheduled after 30(+ 7 days), if the EOT visit is ≥30 days after the last dose of BI 836826, the EOT and EoR may be performed on the same date.

The "last-patient-last-visit-primary-endpoint" is defined in Section 8.6.

All patients should adhere to the visit schedule as specified in the Flow Chart. However, in case a patient misses a visit and the patient reports to the investigator between the missed and the next scheduled visit, the procedures that were planned at the missed visit should be done and the actual date and the reason for the delay should be documented in the eCRF. In the case a Day 1 treatment of BI 836826 is delayed, all subsequent visits of a cycle will be recalculated based on the actual date of Visit 1 of the delayed cycle.
Some flexibility is allowed in scheduling the visits according to the time window specified in the Flow Chart.

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

In case ibrutinib is to be discontinued permanently for other reasons than PD, patients may be kept on BI 836826 and follow the treatment visit schedule as outlined in the Flow chart.

Treatment may be delayed to enable resolution of AEs, concurrent diseases or recovery from surgical procedures, or other individual reasons. Day 15 in Cycles 1-4 may be delayed by 1 week, in case a longer delay would be required, this dose should be omitted. Day 1 in Cycles 2-24 may be delayed by up to 4 weeks. In case longer delays would be required, this should be discussed and agreed between the investigator and the sponsor's Clinical Monitor.
Ibrutinib dose modifications will be at the discretion of the Investigator. Changes in ibrutinib dosing will be recorded in the eCRF.

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

The investigations as outlined in the Flow Chart will be performed at the respective visits. All assessments should be performed prior to BI 836826 administration on dosing days, unless otherwise specified.

6.2.1 Screening and run-in period(s)

Screening Period:
The examinations required for the screening visit may be conducted within a time interval of 21 days prior to the start of ibrutinib and up to 35 days from the first drug administration of BI 836826 on Cycle 1 Day 1. Pre-ibrutinib disease assessments should be performed close to the start of ibrutinib (within 7 days). Patients who have consented should secure sourcing and be on a stable and continuous dosing of ibrutinib prior to Cycle 1 Day 1.

The site should call IRT after informed consent is obtained to register the patient as enrolled. The patient will be officially entered via IRT after all the eligibility criteria are met.

If for administrative or medical reasons, the patient does not start with study medication after the defined screening period, it is allowed to re-screen a patient within 7 days. In case a patient is re-screened, he/she will keep the same patient number and an unscheduled additional screening visit will be created with the examinations that were re-performed for screening.

Biomarkers tests, imaging and virology testing may not need to be repeated if performed within the permitted window, relative to Cycle 1 Day 1. Other tests (i.e. safety labs) must be performed if older than 48 hours.

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

Demographics and Oncological History:
Demographics (sex, birth date, race and ethnicity) will be collected during the screening visit. A detailed cancer history will be obtained. The date of first diagnosis of CLL (month and year may be sufficient) will be recorded in the eCRF. The current stage according to the Rai classification (See Section 10.1) should be recorded [R10-4429]. Previously administered chemo-and immunotherapy will be documented, including start and end dates (year and month may be sufficient), the treatment regimen/protocol with the number of courses (chemo-, immunotherapy), the best response obtained (CR, Cri, PR, PR-L, SD, PD, unknown). If the patient has received an autologous Stem Cell Transplant (SCT) or an allogeneic stem cell transplant, procedural details, including the treatment regimen prior to transplantation should be collected. Documentation of previous radiotherapy should include the total radiation dose and radiation field(s). Previous surgeries within the past 5 years should be recorded. In addition, any previous surgery, which may, according to the investigator affect tumor assessment in this trial, e.g. splenectomy or removal of lymph nodes, should be documented in the eCRF.

Re-screening:
Sites will be allowed to re-screen patients. If more than 3 weeks have elapsed prior to re-screening, all screening procedures must be repeated. In case a patient is re-screened, the patient will keep the same assigned patient number.

Below are the specific requirements during the screening period. For a global overview of tests to be performed, please refer to the Flow Chart.

Run-In Phase:
Patients who complete the screening phase and are still eligible will enter the run-in phase. The run-in phase will begin with the first dose of ibrutinib and continue for two weeks of dosing (+/- 2 days) until Cycle 1 Day 1. Patients who are unable to receive ≥ 80% of ibrutinib doses (12 doses) during the run-in phase will be ineligible to continue on trial and would be considered "screen failures". These patients do not need to continue on trial nor complete an EOT Visit or follow-up. They will need to be replaced. To confirm compliance with daily dosing of ibrutinib during the run-in phase and Cycle 1, patients entered in the trial will be required to maintain and complete a dosing diary. At the end of the run-in phase and prior to the first infusion of BI 836826 on day 1, patients must meet the laboratory requirements listed in Section 4.1.4 .

6.2.2 Treatment period(s)

The first BI 836826 dose should within 35 days after the first screening procedure has been performed and within 14 days after the start of ibrutinib, on Day 1 of the first cycle, as a pre-dose infusion of 10 mg, starting with the first half dose the next day, on Day 2 of first cycle and the second half dose on Day 8. A treatment cycle is defined as 28 days.

Patients may continue with BI 836826 treatment beyond 12 cycles if they achieve a CR (MRD negative or positive) or a PR (MRD negative) at the Cycle 12 disease assessment time point. Treatment beyond Cycle 12 may continue until relapse, undue toxicity, withdrawal of consent or until a maximum of 24 treatment cycles with BI 836826.

Site staff to contact IRT at each dosing visit to obtain medication number(s) of vial(s) to be used.

All peripheral blood and bone marrow samples will be handled according to the laboratory manual instructions in ISF and lab manual.

For a global overview of tests to be performed, please refer to the Flow Chart.

6.2.2.1 End of treatment visit

The EOT visit will be performed after permanent discontinuation of BI 836826 (for any reason) and as soon as possible, but no later than 7 days after the last administration of BI 836826. Site staff to contact IRT to register the patient as discontinued. Ibrutinib dosing may continue throughout the EOT period and beyond based on the discretion of the Investigator or patient's physician.

If the decision is to discontinue a patient from combination treatment on a scheduled protocol visit and the last dose of BI 836826 has been less than 7 days, the visit can be used as the EOT and tests do not need to be repeated.

6.2.3 Residual Effect Period (REP) and trial completion

6.2.3.1 Residual Effect Period (REP)

The REP is defined in Section 5.3.7. The EoR visit should not be performed earlier than 30 days after permanent discontinuation of the trial medication. The EoR visit should be performed at the end of the REP (+ 7 days). Patients who discontinue the trial due to PD will be considered off trial at the completion of the EoR visit. There will be an additional contact with regard to the End of Trial status as soon as the end of the whole trial is reached (see Section 8.6).

The information collected at this visit should include all new AEs and associated concomitant medications and anti-cancer treatments that occurred after EOT and a follow-up of AEs ongoing at EOT.

6.2.3.2 Trial completion for an individual patient:

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

- Completion of planned treatment period
- Withdrawal of Consent
- Death

At the earliest of the above criteria, the Patient Completion (PC) information should be entered in the CRF. There will be an additional contact with regard to the End of Trial status as soon as the end of the whole trial is reached (see Section 8.6).

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 STATISTICAL DESIGN – MODEL

This trial will be performed as an open-label single-arm study. The primary objective of the trial is to determine the RP2D of BI 836826 in combination with ibrutinib. The RP2D will be either the MTD or a lower dose. To determine the MTD, patients are entered sequentially into escalating dose cohorts. The dose-finding will be guided by a Bayesian 5-parameter logistic regression model with overdose control (R13-4806), (R13-4803). This design is based on practical experience and is a preferable algorithmic method due to its superior ability to identify the dose with a desired toxicity rate and its allocation of a greater proportion of patients to doses at, or close to, that dose (R13-4802, R13-4804, R13-4805).

In the following, DLT denotes a dose-limiting toxicity occurring during the first cycle. The 5-parameter logistic regression model is defined as follows. Let $\pi_{1,d1}$ be the probability of having a DLT when giving dose d_1 of BI 836826, and $\pi_{2,d2}$ the probability of having a DLT when giving dose d_2 of ibrutinib, respectively. A logistic regression is used to model the dose-toxicity relationship for each of these drugs individually:

$$\underline{\text{BI 836826:}} \quad \text{logit}(\pi_{1,d1}) = \log(\alpha_1) + \beta_1 \log(d_1/d_1^*)$$
$$\underline{\text{Ibrutinib:}} \quad \text{logit}(\pi_{2,d2}) = \log(\alpha_2) + \beta_2 \log(d_2/d_2^*)$$

Here, the doses $d_1^* = 200$mg and $d_2^* = 420$mg BBB represent the reference doses for BI 836826 and ibrutinib, respectively.
Under independence, the probability of a DLT when giving the combination dose d_1, d_2 is obtained as

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

with corresponding odds

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

In order to account for a potential positive (higher toxicity than expected under independence) or negative (lower toxicity than expected under independence) interaction between BI 836826 and ibrutinib, a dose-dependent interaction term $-\infty<\eta<\infty$ is introduced in the model:

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

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

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

where $r_{d1,d2}$ denotes the number of DLTs observed in $n_{d1,d2}$ patients at dose combination d_1, d_2. Since a Bayesian approach is applied, prior distributions *f* for each of the parameter vectors $\theta_1=(\log(\alpha_1),\log(\beta_1))$, $\theta_2=(\log(\alpha_2),\log(\beta_2))$ and for the interaction term η need to be specified.

The prior distributions for θ_k will be specified as a mixture of two bivariate normal distributions,

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

with

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

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

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

Mixture prior distributions have the advantage that they allow for specification of different logistic dose-toxicity curves, therefore making the prior more robust. A weakly-informative normal prior distribution will be used for η.

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

The BLRM-recommended dose for the next cohort is the level at which the probability for the target toxicity interval is maximal out of the dose candidates satisfying the escalation overdose control criterion EWOC. Per EWOC it should be unlikely (<25% posterior probability) that the DLT rate at the dose combination will exceed 0.33. The overdose control criterion requires the probability of overdosing to be below 0.25.However, the maximum allowable dose increment for the subsequent cohort will be no more than 100% for each drug

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

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

Prior derivation:
To determine the prior distributions for $(\log(\alpha_1), \log(\beta_1))$ and $(\log(\alpha_2), \log(\beta_2))$, a meta-analytic predictive (MAP) approach will be used. Toxicity information on BI 836826 from the 1270.1 Phase I study and from two published studies of ibrutinib will be incorporated. Exact details on the derivation of the prior distributions and on the evaluation of the model using hypothetical data scenarios and operating characteristics are provided in the statistical appendix; a brief description is given here.
The historical data for BI 836826 can be found in Table 7.1:1. For ibrutinib, the historical data can be found in Table 7.1:2.

Table 7.1:1 Historical data for BI 836826

Study	Dose(mg)	N of DLTs during first cycle / N of patients
1270.1		
	1	0/3
	3	0/3
	9	0/6
	25	0/6
	50	0/3
	100	0/3
	200	1/6
	400	0/3
	800	1/2

Table 7.1:2 Historical data for ibrutinib

Study	Dose(mg)	N of DLTs / N of patients
Byrd et al*		
	420	2 / 51
	840	4 / 34
Advani et al**		
	87.5	0 / 7
	175	1 / 9
	350	0 / 6
	560	0 / 9
	581	1 / 18
	875	0 / 7

* No DLTs were reported for this study. The number of DLTs was therefore approximated by the number of AEs leading to discontinuation.
** Dosing based on mg/kg was used. The corresponding fixed dose was calculated as the dose corresponding to a weight of 70kg.

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

1. $\log(\alpha_1)$, $\log(\beta_1)$:
    a. The meta-analytic-predictive prior was derived using the information in Table 7.1:1, allowing for moderate to substantial between-trial heterogeneity. This mixture component was assigned 90% mixture weight.
    b. A second, weakly-informative component was added with 10% mixture weight.
2. $\log(\alpha_2)$, $\log(\beta_2)$:
    a. The meta-analytic-predictive prior was derived using the information in Table 7.1:2, allowing for large to very-large between-trial heterogeneity. This mixture component was assigned 90% mixture weight.
    b. A second, weakly-informative component was added with 10% mixture weight.
3. η: based on the a priori assumption of no interaction between the two compounds, a normal distribution with mean 0 and standard deviation 0.56 was chosen. A the starting dose combination, the corresponding 95% prior interval covers an up to 1.4 fold increase (or decrease) in the odds of DLT over no interaction.

The prior distributions are given in Table 7.1:3. The corresponding prior probabilities of a DLT at different doses and the corresponding probability of under-dosing, targeted dosing and overdosing are shown in Table 7.1:4. As can be seen from Table 7.1:4, the dose combination 100mg BI 836826 and 420mg ibrutinib has prior probability of overdosing below 25%; it fulfills the overdose criterion and is therefore a suitable starting dose combination.

Table 7.1:3 Prior distributions

Parameter	means, standard deviations, correlation	mixture weight
$\log(\alpha_1)$, $\log(\beta_1)$: component 1	(-2.282, 0.062, 1.065, 0.699, -0.105)	0.9
$\log(\alpha_1)$, $\log(\beta_1)$: component 2	(-2.282, 0.062, 2, 1, 0)	0.1
$\log(\alpha_2)$, $\log(\beta_2)$: component 1	(-2.819, -0.522, 1.303, 0.926, -0.047)	0.9
$\log(\alpha_2)$, $\log(\beta_2)$: component 2	(-2.819, -0.522, 2, 1, 0)	0.1
η	0, 0.56	N/A

Table 7.1:4 Prior probabilities of DLT

Dose BI 836826	Dose ibrutinib	Probability of true DLT rate in					Quantiles		
		[0,0.16]	**[0.16,0.33]**	**[0.33,1]**	**Mean**	**StD**	**2.5%**	**50%**	**97.5%**
50mg	**420mg**	0.695	0.209	0.096	0.144	0.140	0.011	0.099	0.545
100mg	**420mg**	0.607	0.262	0.131	0.171	0.150	0.016	0.125	0.592
200mg	**420mg**	0.448	0.312	0.241	0.233	0.181	0.025	0.181	0.707
300mg	**420mg**	0.347	0.279	0.373	0.302	0.226	0.025	0.243	0.843
400mg	**420mg**	0.305	0.232	0.463	0.361	0.268	0.021	0.298	0.931

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

For the analysis of all primary, secondary and further endpoints, all treated patients (i.e. treated with at least one dose of trial medication) will be included in the analysis.

For the determination of MTD only MTD evaluable patients will be considered.
Cohorts of patients treated with BI 836826 in combination with ibrutinib will be evaluated continuously based on the totality of the safety data available in order to determine the RP2D and MTD.

The primary analysis of all primary, secondary and further endpoints will be conducted when "last-patient-last-visit-primary-endpoint" has been reached (see Section 8.6).

7.3.1 Primary endpoint analyses

RP2D and number of patients with DLTs in first cycle, measured from first administration of BI 836826 until the end of the first cycle. The number of patients with DLTs at each dose level will be presented (all cycles and cycle 1 separately).

7.3.2 Secondary endpoint analyses

The secondary endpoint MTD will be analysed via the number of patients with DLTs during the first treatment cycle.

7.3.4 Safety analyses

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary. Standard BI summary tables and listings will be produced. All AEs with an onset between start of treatment with BI 836826 and end of the REP, a period of 30 days after the last dose of BI 836826, will be assigned to the treatment period for evaluation. All treated patients will be included in the safety analysis. In general, safety analyses will be descriptive in nature and will be based on BI standards. No hypothesis testing is planned.

Statistical analysis and reporting of AEs will concentrate on treatment-emergent AEs. To this end, all AEs occurring between start of treatment with BI 836826 and end of the REP will be considered 'treatment-emergent'. The REP is defined as last administration of BI 836826 plus 30 days. Adverse events that start before first intake of BI 836826 and deteriorate under treatment will also be considered as 'treatment-emergent'. Adverse events occurring during screening and/or run-in period with ibrutinib as well as during post-treatment will be listed separately.

Analyses of AEs of all treatment cycles will be carried out under the initial treatment.

Adverse events will be graded according to CTCAE Version 4 and reported according to BI standards.
Serious Adverse Events, drug-related AEs and AESI will be tabulated. In addition, events leading to treatment discontinuation will be examined.
Frequency, severity, and causal relationship of AEs will be tabulated by system organ class and preferred term after coding according to the current version of the MedDRA.

Descriptive statistics will be used to describe changes in laboratory tests over time. In addition, all abnormalities of potential clinical significance will be reported. In general, potential clinical significance is defined as at least CTC Grade 2 and an increase in CTC

classification from baseline. Hematologic toxicity based on laboratory values will be not only described using CTCAE grading but also using the criteria described in the 'Guidelines for the diagnosis and Treatment of CLL (R10-4429).

Vital signs, physical examinations, or other safety-relevant data observed at screening, baseline, during the course of the trial and at the end-of-trial evaluation will be assessed with regard to possible changes compared to findings before start of treatment.

7.4 INTERIM ANALYSES

No formal interim analysis is planned for this trial. Interim safety evaluations will be performed as considered necessary. Safety evaluations will be performed after each dose cohort by the SRC (for SRC details refer to Section 3.1). SRC meeting minutes and outputs provided for these SRC meetings will be documented and archived in the clinical trial master file.

7.5 HANDLING OF MISSING DATA

In general, missing data will not be imputed. Every effort will be undertaken to obtain the date of progression or response for patients known to have progressed or experienced a response and to obtain complete information on all AEs. Consequently no missing data will be imputed unless otherwise specified.

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

7.6 RANDOMIZATION

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

7.7 DETERMINATION OF SAMPLE SIZE

Approximately 20 patients will be expected for this trial. The exact number of patients within a cohort of the trial will be based on the recommendation of the SRC and the criteria specified (see Section 7.1). Based on the simulation study to evaluate operating characteristics of the BLRM (see Section 10.7), 20 patients should be a good estimate for patients to be treated in the dose escalation part for the model to have reasonable operating characteristics relating to its MTD recommendation.

8. INFORMED CONSENT, DATA PROTECTION, TRIAL RECORDS

The trial will be carried out in compliance with the protocol, the ethical principles laid down in the Declaration of Helsinki, in accordance with the ICH Harmonized Tripartite Guideline for GCP and relevant BI SOPs*.

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

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

The rights of the Investigator and of the Sponsor with regard to publication of the results of this trial are described in the Investigator contract.

The certificate of insurance cover is made available to the Investigator and the patients, and is stored in the ISF.

8.1 TRIAL APPROVAL, PATIENT INFORMATION, AND INFORMED CONSENT

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

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

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

8.2 DATA QUALITY ASSURANCE

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

8.3 RECORDS

Case Report Forms/ (e)CRF for individual patients will be provided by the Sponsor. For drug accountability, refer to Section 4.1.8.

8.3.1 Source documents

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

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

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

8.3.2 Direct access to source data and documents

The Investigator/institution will permit trial-related monitoring, audits, IRB/IEC review and regulatory inspection, providing direct access to all related source data/documents.
CRF/eCRF and all source documents, including progress notes and copies of laboratory and medical test results must be available at all times for review by the Sponsor's clinical trial monitor, auditor and inspection by health authorities (e.g. FDA). The (CRA) /on site monitor

and auditor may review all CRF/eCRF, and written informed consents. The accuracy of the data will be verified by reviewing the documents described in Section 8.3.1.

8.4 LISTEDNESS AND EXPEDITED REPORTING OF ADVERSE EVENTS

8.4.1 Listedness

To fulfil the regulatory requirements for expedited safety reporting, the Sponsor evaluates whether a particular AE 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 (IB).

For ibrutinib this is the US-PI, or another regulatory label document;

The current versions of these reference documents are provided in the ISF.

8.4.2 Expedited reporting of adverse events

BI is responsible to fulfill their legal and regulatory reporting obligation in accordance with regulatory requirements. Exemptions from expedited reporting are described in Section 5.3.7, if applicable..

8.5 STATEMENT OF CONFIDENTIALITY

Individual patient medical information obtained as a result of this trial is considered confidential and disclosure to third parties is prohibited with the exceptions noted below. Patient confidentiality will be ensured by using patient identification code numbers. Treatment data may be given to the patient's personal physician or to other appropriate medical personnel responsible for the patient's welfare. Data generated as a result of the trial need to be available for inspection on request by the participating physicians, the Sponsor's representatives, by the IRB/IEC and the regulatory authorities.

8.6 END OF TRIAL

The end of the trial is defined as:

- The trial is completed once the RP2D for the combination of BI 836826 with ibrutinib has been defined by the SRC (see Section 3.1)

Last patient last visit (primary endpoint)
The "last-patient-last-visit-primary-endpoint" will be reached once:

- all patients have completed the REP

At this time, the CTR will be written. In case, the end of the whole trial is not reached at the time the report of the trial is being performed revised main results will be reported in a revision to the report after the end of the whole trial. There will be an additional patient contact with regard to the End of Trial status as soon as the end of the whole trial is reached.

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10. APPENDICES

10.1 RAI CLASSIFICATION

Rai staging system as reported in the IWCLL guideline (R10-4429):

This system divides CLL into 5 stages:

- **Rai stage 0 (Low Risk):** Lymphocytosis in blood or bone marrow
- **Rai stage I (Intermediate Risk):** Lymphocytosis and enlarged lymph nodes.
- **Rai stage II (Intermediate Risk):** Lymphocytosis and enlarged liver or spleen with or without lymphadenopathy
- **Rai stage III (High Risk):** Lymphocytosis and anemia (Hgb <11 g/dl) with or without enlarged liver, spleen or lymph nodes
- **Rai Stage IV (High Risk):** Lymphocytosis and thrombocytopenia (platelet count <100,000/µl) with or without anemia or enlarged liver, spleen or lymph nodes

10.2 CRITERIA FOR RESPONSE DETERMINATION

The determination of CLL response and progression will be based on IWCLL criteria (R10-4429), including recently published clarifications and modifications (R15-4922, R15-4923, R15-4921) and clarifications as outlined below. In case a CR or a PD is suspected for the first time based on clinical examinations, imaging should be performed for complete response assessment.

At all protocol defined response evaluation time points, i.e. at the end of Cycle 3, Cycle 6, Cycle 9 and Cycle12, as well as EOT, a response assessment will be performed based on CBC with differential and imaging assessment of CLL manifestations. In case a CR or a PD are suspected based on physical examination and laboratory data at any other timepoint, imaging should be obtained to confirm CR or PD. An exception is possible if unequivocal diagnosis of PD is based on criteria other than lymph node, liver or spleen size.

The ALC, neutrophil count the platelet count and hemoglobin will be used for the response assessment and all efforts should be made to obtain all parameters for response assessment on the same day. If the CBC/Differential is missing on the date of imaging, the values from a previous date as close to the imaging as possible may be used, provided that this date is 8 days or more after the last administration of BI 836826. In case ANC, PLT or hemoglobin is considered influenced by supportive therapy, e.g. growth factors, transfusions, a CR, CRi, PR, PR-L should not be based on these laboratory values. Reevaluation of blood counts should be performed as close as possible to the imaging to evaluate response. Findings on physical examination with potential impact on response assessment should be confirmed by imaging. A CBC with Differential will be performed at a central laboratory at all timepoints where MRD is assessed, and absolute lymphocyte count, absolute neutrophil count, platelet count and hemoglobin from the central laboratory should be used for disease/response assessment when available.

On imaging studies, the CLL manifestations will be classified as target lesions and non-target lesions.

Target lesions:
At baseline, up to 6 pathologically enlarged lymph nodes or lymph node masses should be selected as target lesions which will be used at each subsequent imaging for quantitative lymph node assessments during the study. Ideally, the target lesions should represent nodal disease burden due to CLL, if possible be located in disparate regions of the body, and should be reproducibly measurable in 2 perpendicular dimensions on repeated measurements. Whenever possible, mediastinal and retroperitoneal areas of disease should be considered as target lesion.

Target lesions will be measured and recorded at baseline and at all subsequent imaging time points. Bi-dimensional measurements of the Largest Diameter (LD) and the corresponding Perpendicular Diameter (PLD) will be recorded for each target lesion. The product of the LD and PLD will be calculated for each target Single Lesion Product (SLP) and the sum of the product of diameters (SPD) for all target lesions will be calculated and recorded. The baseline SPD will be used as reference for assessment of best response during treatment. The nadir LD of individual target lesions and the nadir SPD of all target lesions will be used as reference for PD.

To be considered pathologically enlarged and measurable at baseline, a lymph node must be at least 1,5 cm in short axis and measurable in two perpendicular dimensions. Smaller lymph nodes should be classified as non-target lesions if considered pathological.

At post baseline imaging time points, the LD for individual lesions and the SPD of all target lesions will be considered. Once selected, all target lesions should be measured as accurate as possible. Once a lymph node shrinks to a LD <1.5 cm, the node is considered of normal size.

Any new node considered a manifestation of CLL that measures ≥1.5 cm in short axis will be considered PD.

A lymph node mass may be selected as a target lesion if it is measurable at baseline. In case a lymph node mass splits into separate nodes, all separate nodes should be assessed according to the rules for single lesions and will be used in calculating the SPD. Progression of the lesion will be based on the SPD of split lesions.

Liver and spleen size:
Liver and spleen size will be measured as the Longest Cranio-Caudal Diameter (LCCD) on CT/MRI scan. The baseline and nadir values for the LCCD of liver and spleen will be used as a reference to assess tumor response. The LCCD may be directly measured on appropriate coronal or sagittal planes, or will be calculated as the product of the number of axial sections on which the organ is visualized (between the most superior and the most inferior margin) and the thickness of the sections.
The spleen will be considered enlarged if the LCCD is >12 cm (R15-0874). A LCCD decrease ≥50% (minimum 2 cm) compared to baseline, if the spleen was enlarged at baseline, or a decrease to ≤ 12 cm is required for a spleen response. An increase in spleen LCCD by

≥50% from nadir (minimum increase of 2 cm and minimum total size of 14 cm) is required for diagnosis of splenic progression.

The liver if will be considered enlarged if it is >18 cm in LCCD (R15-0873). A LCCD decrease ≥50% (minimum 2 cm) compared to baseline, if the liver was enlarged at baseline, or a decrease to ≤18 cm is required for a liver response. Conversely, an increase in liver enlargement by ≥50% from nadir (minimum increase of 2 cm, and minimum total size of 20 cm) is required for diagnosis of liver progression.

Non-target lesions:
Any other measurable and pathological nodal lesions not selected as target lesion may be considered a non-target lesion. In addition, non-measurable evidence of CLL may be considered non-target lesion, e.g. nodal lesions too small to qualify as target lesion, extranodal lesions, bone lesions, ascites, pleural or pericardial effusions, non-measurable nodal masses.

Even if measurable, non-target lesions will not be quantitatively assessed. The persistence, unequivocal progression or complete disappearance/absence of non-target lesions should be recorded at baseline and at the subsequent imaging time points. If present at baseline, up to 6 non-target lesions should be recorded. The non-target lesions selected at baseline will be used as a general reference to further characterize regression or progression of CLL during response assessments.

Responses will be based on imaging and laboratory data, bone marrow examination needs to be added to complete response assessment for CR, and PR in some cases. Responses will be categorized as CR, CRi, PR, PR-L, SD or PD by the investigator. All data used for the assessment should be reflected in the eCRF.

Definitions of response and progression:

Complete Response (CR)
CR requires all of the following criteria to be met:

- Absolute lymphocyte count below 4 x 10^9/L.
- Regression of all target nodes/masses, i.e. all target lesions have a LD < 1.5 cm
- Disappearance/absence of all non-nodal non-target lesions, regression of all nodal nontarget lesions to normal sized lymph nodes
- Normal liver size (≤18 cm), based on CT imaging or non-palpable by Physical Exam
- Normal spleen size (≤12 cm), based on CT imaging or non-palpable by Physical Exam
- No evidence of new disease.
- Morphologically negative bone marrow, defined as normocellular marrow in relation to patient age, less than 30% of nucleated cells being lymphoid cells and no lymphoid nodules.
- Platelet count more than 100 x 10^9/L (without exogenous growth factors or transfusion).
- Hemoglobin more than 110 g/L (without exogenous growth factors or transfusions)

- Absolute Neutrophil Count more than 1.5 x 10^9/L (without exogenous growth factors).

Patients who fulfil all criteria for a CR (including a bone marrow examinations) but who have a persistent anaemia, thrombocytopenia, neutropenia or a hypocellular bone marrow related to prior or ongoing CLL therapy, but unrelated to CLL should be classified as CRi.

Partial Response (PR)
To define a PR, all of the following criteria must be met:

- No evidence of new disease
- At least one of the following laboratory criteria is present:
  i. Platelet count higher than 100 x 10^9/L, or ≥50% improvement over baseline (without exogenous growth factors or transfusion)
  ii. Hemoglobin higher than 110 g/L, or ≥50% improvement over baseline (without exogenous growth factors or transfusions)
  iii. Absolute Neutrophil Count higher than 1.5 x 10^9/L, or ≥50% improvement over baseline (without exogenous growth factors)
- Reduction in tumor load documented by at least two of the following criteria, with exceptions in the following situations where only 1 criterion needs to be met: (a) lymphadenopathy is the only disease manifestation (b) only lymphocytosis without lymphadenopathy is present at baseline, (c) a bone marrow assessment at screening shows quantifiable bone marrow infiltration as the only site of disease. In situation (a) only criterion (ii) will be applicable, in situation (b) only criterion (i), and in situation (c) only criterion (v).
  i. In patients with lymphocytosis at baseline (ALC ≥4 x 10^9/L), decrease in the ALC by ≥50% or more compared to baseline, or a decrease to <4 x 10^9/L.
  ii. In patients with nodal disease at baseline, decrease of SPD of target lesions by ≥50% compared to baseline.
  iii. If spleen enlarged at baseline (LCCD >12 cm), decrease of LCCD by ≥50%, or to normal size (LCCD ≤12 cm).
  iv. If liver enlarged at baseline, (LCCD >18 cm), decrease of LCCD by ≥50%, or to normal size (LCCD ≤18 cm).
  v. Bone marrow infiltration of CLL decreases by ≥50% compared to baseline, either in diffuse infiltration, or in B-lymphoid nodules.
- No target lesion and no non-target lesion (if present at baseline) are unequivocally progressing. No increase in liver and/or spleen LCCD by ≥50%

Partial Response with Lymphocytosis (PR-L)

To define a PR-L, the following criteria must be met:

- No evidence of new disease
- At least one of the following laboratory criteria is present:
  i. Platelet count higher than 100 x 10^9/L, or ≥50% improvement over baseline (without exogenous growth factors or transfusion)

ii. Hemoglobin higher than 110 g/L, or ≥50% improvement over baseline (without exogenous growth factors or transfusions)
iii. Absolute Neutrophil Count higher than 1.5 x 10^9/L, or ≥50% improvement over baseline (without exogenous growth factors)

- Reduction in tumor load documented by at least two of the following criteria. In patients with only one localization at baseline, improvement of this single criterion is sufficient:
  i. In patients with nodal disease at baseline, decrease of SPD of target lesions by ≥50% compared to baseline.
  ii. If spleen enlarged at baseline (LCCD >12 cm), decrease of LCCD by ≥50%, or to normal size (LCCD ≤12 cm).
  iii. If liver enlarged at baseline, (LCCD >18 cm), decrease of LCCD by ≥50%, or to normal size (LCCD ≤18 cm).
  iv. Bone marrow infiltration of CLL decreases by ≥50% compared to baseline, either in diffuse infiltration, or in B-lymphoid nodules.
- No PD criterion met, i.e. no target lesion and no non-target lesion (if present at baseline) are unequivocally progressing, and no increase in liver and/or spleen LCCD by ≥50%.
- Lymphocytosis during therapy with ibrutinib if occurring in isolation without other objective evidence of progressive disease will not be considered evidence of PD and will not preclude a patient from the PR-L category.

Progressive Disease (PD)
Any of the following criteria constitutes the diagnosis of PD:

- Evidence of new disease:
  - any new pathologically enlarged lymph node (>1.5 cm in short axis) considered a manifestation of CLL
  - new or recurrent increase of the liver LCCD by ≥50%, with a minimum absolute liver LCCD of 20 cm
  - new or recurrent increase of the spleen LCCD by ≥50%, with a minimum absolute spleen LCCD of 14 cm
  - any new unequivocal extranodal non-target lesion (if the non-target lesion is an effusion without additional indication for progression of CLL, there should be histological or cytological evidence that this effusion is due to CLL)
  - unequivocal reappearance of an extranodal non-target lesion that had disappeared completely on treatment
- Evidence of worsening of disease
  - SPD increase of target lesions from baseline/nadir by ≥50%
  - Increase of LD in any individual nodal target lesion from baseline/nadir by ≥50%
  - Liver progression, i.e. enlargement of the liver LCCD by ≥50% from baseline/nadir (with a minimum increase of 2 cm and minimum total LCCD of 20 cm)
  - Spleen progression, i.e. enlargement of the spleen LCCD by ≥50% from baseline/nadir (with a minimum increase of 2 cm and minimum total LCCD of 14 cm)

  - unequivocal progression of non-target lesions overall (should not be based solely on worsening of a pleural effusion or ascites as the only location for disease progression)
  - transformation into a more aggressive histology (e.g. Richter's syndrome), diagnosed by cytology or histology
- Worsening in laboratory values attributable to CLL
  - Platelet count is less than 100 x 10^9/L and has decreased by ≥50% compared to the highest platelet count on study (values obtained within one day after a transfusion should be excluded)
  - Hemoglobin is <110 g/L and has decreased by > 20 g/L from the highest hemoglobin value on study (values obtained within one day after a transfusion should be excluded)
- Lymphocytosis during therapy with ibrutinib will only be considered evidence of worsening of disease if it is not occurring in isolation, but associated with other objective evidence of progressive disease as outlined above.

Worsening of constitutional symptoms in the absence of other objective evidence of worsening of CLL will not be considered disease progression, and other causes for constitutional symptoms, e.g. infections should be considered.

Ibrutinib can mobilize CLL cells from tissues into the peripheral blood. This characteristic pharmacologic action can be prominent early in therapy, but it can also persist over time, and should not be confused with PD unless the treated patient develops other CLL-related signs or symptoms of PD. In the absence of other objective evidence of PD, lymphocytosis alone should not be considered an indicator of PD. Patients with lymphocytosis and no other evidence of PD should continue therapy until they develop other definitive signs of or the occurrence of another reason to discontinue therapy.

During therapy, anemia and/or thrombocytopenia may be difficult to differentiate from drug related effects on PLT or hemoglobin. If there is uncertainty whether there is true progression, the patient should continue study treatment and remain under close observation, e.g. with additional unscheduled assessments, which should be captured in the eCRF. If subsequent evaluations indicate CLL progression, the date of progression should be the date at which progression was first documented.

Stable Disease (SD)
For SD, the following criteria must be met:

- No evidence of new disease
- There is neither sufficient evidence of tumor shrinkage to qualify for CR/CRi/PR/PR-L nor sufficient evidence of tumor growth to qualify for definitive PD

Non Evaluable (NE)
In a patient who does not have clinical evidence for PD based on CBC/Diff, the response assessment may be NE in the following situations:

- No imaging study performed.

- Inadequate imaging quality, or missing sections which do not allow assessment of all areas in which target lesions were selected. (PD may be assigned at any timepoint regardless of the extent of missing target lesions)
- Images of liver and/or spleen missing (exception: splenectomized patient).

10.5 PUBLICATIONS

The sponsor will have unrestricted publication rights on data resulting from the study and may give the data to third parties for publication.

In a multi-center study, the primary publication shall be a full publication of the study results from all appropriate study sites. If such a full publication is not submitted within twelve (12) months after conclusion of the study at all sites, or after the sponsor confirms there will be no primary full publication, investigator(s) may publish individually in accordance with this Section.
Any written, oral or audio-visual publication resulting from the study, either in part or in total (abstracts in journals or newspapers, oral presentations, posters etc.) by investigators and/or their representatives, including publications of experimental substudies, will require pre-submission review by the sponsor. The sponsor is entitled to delay any publication in order to protect patentable inventions and/or to avoid disclosure of proprietary matters which require protection, including but not limited to, trade secrets and know-how (for details, see contract). Moreover, the sponsor has the right to edit or remove confidential information, prior to submission for publication. In general, the sponsor will not veto any publication.

The International CI will have the unrestricted right to publish on data resulting from the study and will be given the choice to be the first author, or the last author. The selection and order of the subsequent authors (i.e. author(s) 2.-x.) will be based on (a) the numbers of recruitment, i.e. the number of subjects treated with BI 836826 in the study, (b) data quality and (c) significant scientific input to the study, unless otherwise agreed.

A representative of the sponsor substantially involved in the implementation of the study will serve as co-author in the primary full publication of the study, unless otherwise agreed. Moreover, the sponsor will retain the right to include in the authorship list up three (3) Boehringer Ingelheim authors.

For any interim publication(s,) the order of the authors will be determined in accordance with (a) the numbers of recruitment and (b) data quality, after consultation with the International CI.

For publication(s) of experimental substudies only, co-authorship will be offered to all authors according to their individual contributions, unless otherwise agreed. The sponsor shall have the right to publish results of the study in whole or in part for regulatory purposes, unless otherwise agreed.

All publications of the results of the study shall be compiled in adherence to the rules of Good Scientific Practice and the guidelines for publications of clinical Study data as outlined e. g. by editors of the major medical journals.

10.6 CALCULATION OF GLOMERULAR FILTRATION RATE

Glomerular Filtration Rate (GFR) may be estimated based on commonly used and accepted formula, i.e.

Cockroft Gault formula:

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

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

Modification of Diet in Renal Disease (MDRD) formula:

$$GFR = 170 \times Serum\ Creatinine^{-0.999} \times Age^{-0.176} \times BUN^{-0.170} \times Albumin^{+0.318} \times F_S$$

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

Variations of the MDRD formula:

$$GFR = 186 \times Serum\ Creatinine^{-1.154} \times Age^{-0.203} \times F_S$$

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

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

10.7 STATISTICAL APPENDIX INCLUDING MODEL PERFORMANCE AND DATA SCENARIOS

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

Hypothetical Data Scenarios
Hypothetical data scenarios are shown in Table 10.7:1. These scenarios reflect the potential on-study data constellations and related escalation as allowed by the model and the 100% escalation limit. For each scenario, the probability of overdose for the current dose, as well as the next potential dose and related probabilities of under-dosing, target toxicity and over-dosing are shown.

For example, scenario 1 represents the case that no DLT is observed in three patients at the starting dose of 420mg on Ibrutinib and 100mg of BI 836826. In this case, the next dose permitted by the model and by the 100% escalation rule is 420mg of Ibrutinib and 200mg of BI 836826. Similarly, scenario 6 represents the case that no DLT is observed in the first cohort of 3 patients at 420mg of Ibrutinib and 100mg of BI 836826, and 1 DLT is observed in the cohort of 3 patients at 420mg Ibrutinib and 200 mg of BI 836826. In this case, the model suggests re-enrolling patients at the current dose level of 200mg BI 836826.

In scenario 17, 1 DLT is observed with 6 patients at a BI 836826 dose of 200mg. Here, the model suggests to only increase the dose up to 300mg BI 836826 and to not use the 100% dose escalation. In scenario 22, it is assumed that at a dose of 1400mg BI 836826, 2 DLTs occur in 3 patients. Despite the fact that no DLTs have been observed in the previous 4 cohorts, the model reacts immediately to the data observed and requires de-escalation to 600mg. This case illustrates the adaptive behavior of the model in more extreme situations.

Table 10.7:1 Hypothetical data scenarios

Scenario	Dose Ibrutinib, Bi 836826 [mg]	# DLT	# Pat	Current dose:	Next dose Ibrutinib, BI 836826 [mg]	Next dose		
				P(over dosing)		P(under dosing)	P(target toxicity)	P(over dosing)
1	420,100	0	3	0.036	420, 200	0.577	0.304	0.119
2	420,100	1	3	0.201	420, 100	0.431	0.394	0.174
3	420,100	2	3	0.491	NA	NA	NA	NA
4	420,100	0	2	0.055	420,200	0.541	0.316	0.144
5	420, 100 420, 200	0 0	3 3	0.033	420, 400	0.498	0.254	0.248
6	420, 100 420, 200	0 1	3 3	0.208	420, 200	0.418	0.418	0.163
7	420, 100 420, 200	0 2	3 3	0.426	420, 100	0.429	0.43	0.141
8	420, 100 420, 100	1 1	3 3	0.227	420, 100	0.304	0.47	0.227
9	420, 100 420, 100	1 0	3 3	0.063	420, 200	0.399	0.401	0.2
10	420, 100 420, 100	1 2	3 3	0.487	NA	NA	NA	NA
11	420, 100 420, 100	2 0	3 3	0.227	420, 100	0.304	0.47	0.227
12	420, 100 420, 100	2 1	3 3	0.497	NA	NA	NA	NA
13	420, 100 420, 200 420, 400	0 0 0	3 3 3	0.056	420, 800	0.622	0.168	0.209

Table 10.7:1 (cont.) Hypothetical data scenarios

Scenario	Dose Ibrutinib, Bi 836826 [mg]	# DLT	# Pat	Current dose:	Next dose Ibrutinib, BI 836826 [mg]	Next dose		
14	420, 100 420, 200 420, 400	0 0 1	3 3 3	0.284	420, 300	0.455	0.419	0.125
15	420, 100 420, 200 420, 300	0 0 0	3 3 3	0.039	420, 600	0.589	0.193	0.218
16	420, 100 420, 200 420, 300	0 0 1	3 3 3	0.194	420, 300	0.409	0.397	0.194
17	420, 100 420, 200 420, 200	0 1 0	3 3 3	0.061	420, 300	0.401	0.377	0.223
18	420, 100 420, 200 420, 200	0 1 1	3 3 3	0.206	420, 200	0.291	0.503	0.206
19	420, 100 420, 200 420, 200	0 1 2	3 3 3	0.44	420, 100	0.401	0.473	0.126
20	420, 100 420, 200 420, 400 420, 800	0 0 0 2	3 3 3 3	0.721	420, 400	0.258	0.541	0.201

Table 10.7:1 (cont.) Hypothetical data scenarios

Scenario	Dose Ibrutinib, Bi 836826 [mg]	# DLT	# Pat	Current dose:	Next dose Ibrutinib, BI 836826 [mg]	Next dose		
				P(over dosing)		P(under dosing)	P(target toxicity)	P(over dosing)
21	420, 100 420, 200 420, 400 420, 800	0 0 0 0	3 3 3 3	0.035	420, 1400	0.833	0.083	0.084
22	420, 100 420, 200 420, 400 420, 800 420, 1400	0 0 0 0 2	3 3 3 3 3	0.651	420,600	0.321	0.552	0.127

Operational Characteristics

Operating characteristics are a way to assess the long-run behavior of a model. Under an assumed true dose-toxicity curve, metrics such as the probability of recommending a dose with true DLT rate in the target interval can be approximated via simulations. Table 10.7.2. describes 4 assumed true dose-toxicity scenarios which were used to assess the operating characteristics of the model. These scenarios reflect a wide range of possible cases as follows:

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

Table 10.7: 2 Dose-toxicity scenarios

Scenario		**BI 836826 dose (mg)**					
	P(DLT)	**100**	**200**	**400**	**600**	**800**	**1400**
1 (Prior)		0.13	0.18	0.30	0.40	0.47	0.63
2 (High Tox)		0.24	0.30	0.40	0.50	0.63	0.75
3 (Low Tox)		0.08	0.13	0.20	0.22	0.25	0.30
4 (Low-High)		0.08	0.13	0.20	0.40	0.50	0.63

For each of these scenarios, 1000 trials were simulated. It was then assessed how often a dose was declared as MTD with true DLT rate in the under-, targeted or over-dose range. Furthermore, the average, minimum and maximum number of patients per trial and the average number of DLTs per trial are reported. Results are shown in Table 10.7:3.

Table 10.7:3 Min/Max number of patients per trial and average number of DLTs

Scenario	% of trials declaring the MTD with true DLT rate in				# Patients	# DLTs
	underdose	Target toxicity	overdose	Stopped (too toxic	Mean (Min-Max)	Mean (Min-Max)
1 (Prior)	12.1	75.8	3.6	8.5	16.10 (3-42)	3.12 (2-11)
2 (HighTox)	0	67.1	2.5	30.4	11.58 (3-36)	3.25 (2-10)
3 (Low Tox)	56.9	41.0	0	2.1	19.47 (3-45)	2.30 (1-9)
4 (Low-High)	61.5	27.6	8.8	2.1	18.66 (3-42)	3.22 (1-10)

In scenario 1, which reflects the case that the true dose-toxicity is aligned with prior means, 75.8% of the simulated trials declared a dose as MTD with the true DLT rate in the targeted dose range. Considering that 100mg has a DLT probability of 0.13 which is relatively close to the lower bound of the target toxicity interval (0.16), one could consider this as an MTD as well, and the target rate would thus be even higher.

In scenario 2 (high toxicity), the starting dose already has a >20% probability of a DLT in the first cohort. This contributes to the high percentage (30.4%) of all simulated trials for which

the trial is stopped since none of the doses is considered tolerable anymore. This is an expected situation for a high-toxicity scenario.

In scenario 3 (low toxicity scenario), nearly 60% of trials declare a dose in the under-dose interval as the MTD. Since the 200mg cohort has a DLT probability of 0.13 which is relatively close to the lower bound of the target toxicity interval (0.16), one could consider this as an MTD as well, and the target rate would thus be much higher than the formal 41% target rate.

In scenario 4, even though formally only 27.6% of simulated trials declared a dose as MTD with the true DLT rate in the target interval, as in Scenario 1 and 3, considering the dose with a true DLT rate of 0.13 also as target interval, the target rate would be much higher.
The mean patient numbers range from 11.58 (high-toxicity scenario) to 19.47 patients (low-toxicity scenario) and the maximum number of patients was 45. Therefore, the patient numbers are as expected and increase when moving away from the high-toxicity scenario. In summary, the considered data scenarios show a reasonable behavior of the model and the operating characteristics demonstrate a good precision of MTD determination.

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

Number of global amendment		1
Date of CTP revision		18 Jul 2018
EudraCT number		Not Applicable
BI Trial number		1270.15
BI Investigational Product(s)		BI 836826
Title of protocol		A Phase Ib, Open label, Single Arm, Multi-center, Dose Escalation Trial of Intravenous BI 836826 in Combination with ibrutinib in Patients with Relapsed/Refractory Chronic Lymphocytic Leukemia
To be implemented only after approval of the IRB / IEC / Competent Authorities		☒
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		☐
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		☐
Section to be changed		2.1 Rationale for Performing the Trial
Description of change		Added: "Note: Due to the rapid evolution of the treatment landscape of CLL, further development of BI 836826 has been discontinued. Recruitment of trial participants will be stopped, however, current subjects on treatment will be allowed to complete the trial as per the protocol. Trial procedures and endpoint analysis has been amended due to the early termination of the trial."
Rationale for change		Early termination of trial, discontinue recruitment of new trial subjects, and completion of treatment for current subjects as per protocol.

Section to be changed		Throughout the document
Description of change		Any reference to Phase II of the study including (but not limited to) sections on study rationale, Objectives, Number of patients, data collection and analysis, primary and secondary end points for phase II has been deleted. Phase Ib also removed in most sections as the removal of Phase II eliminates the need to differentiate between phases.
Rationale for change		Phase II of the study will not be conducted.
Section to be changed		Throughout the document
Description of change		Number of patients included in the study changed from 60 patients to 20 patients.
Rationale for change		Phase II of the study will not be conducted.
Section to be changed		Throughout the document
Description of change		Extended Follow up period removed. Study will be completed once all patients complete REP.
Rationale for change		Extended Follow up period will not be necessary, since further analysis of trial data will not be completed.
Section to be changed		Throughout the document
Description of change		.

Rationale for change		
Section to be changed		Flowchart- Screening to Cycle 12 and Cycle 13-Cycle 24 and associated footnotes
Description of change		Trial medication listed separately as BI 836826 investigational drug and backbone therapy, ibrutinib
Rationale for change		Ibrutinib is a non-investigational medicinal product in this trial and therefore does not qualify as trial medication.
Section to be changed		Flowchart-Screening to Cycle 12 and Cycle 13-Cycle 24
Description of change		Assessments have been reduced. Footnotes updated to match the flowchart
Rationale for change		Phase II of the study will not be conducted. Trial data will not be analysed. Hence assessments have been reduced.
Section to be changed		Flowchart- Day 1and Day 15 of Cycle 2 to Cycle 12, Response evaluation at the end of cycle 3,6,9 and 12 and Day 1 of Cycle 13-cycle 24
Description of change		A -2/ +14 day window has been added to day I of cycles 2-12 and cycles 13-24.
Rationale for change		Broader window period provided to make it less stringent for the patient and site.
Section to be changed		Footnotes 20 and 21 in flowchart for Cycle 1 to Cycle 12, throughout the document where PK sampling and pharmacogenetics sampling is referenced, and footnote in Table 10.3.1
Description of change		
Rationale for change		
Section to be changed		

Description of change		
Rationale for change		
Section to be changed		Section 4.2.1.2
Description of change		Deleted sentence "After the REP, only concomitant therapy indicated for treatment of a BI 836826 related SAE or Adverse Event of Special Interest (AESI) has to be reported."
Rationale for change		Once REP is completed the patient will end the study per the amendment. No data will be collected after REP.
Section to be changed		Section 4.2.1.2.2
Description of change		Cairo- Bishop Classification has been removed
Rationale for change		This classification and methodology was planned but not implemented in the trial.
Section to be changed		Section 5.1, 7.3 and throughout the document
Description of change		
Rationale for change		
Section to be changed		Section 5.2.1
Description of change		Sentence deleted-"The next scheduled disease assessment time point may be used for response confirmation."
Rationale for change		With the termination of the trial, confirmatory disease assessments for response are no longer needed.
Section to be changed		Section 5.2.4
Description of change		Following sentences have been deleted from this section-Physical examination with clinical assessment of all nodal disease locations amenable to clinical examination. The size of the liver and spleen, as assessed by palpation, should be documented in cm below costal margin if enlarged. Liver and spleen are not considered enlarged if palpation below costal margin is not possible. Now reads as: "At Day 1 of each treatment cycle, a physical examination will be performed to assess

		disease progression. In case Progressive Disease (PD) is suspected based on physical examination, imaging should be performed."
Rationale for change		With the termination of the trial, clinical disease assessments for response are no longer needed.
Section to be changed		Section 5.3.6.1 AEs considered "Always serious"
Description of change		Added "Note: Every new occurrence of cancer of new histology must be classified as serious event regardless of the time since the discontinuation of the trial medication and must be reported as described in 5.3.7 , subsections "AE collection" and "AE reporting to sponsor and timelines".
Rationale for change		Updated to reflect BI's reporting requirement that cancer of new histology should always be reported regardless of time since discontinuation of trial medication.
Section to be changed		Section 5.3.6.1 Causal relationship of AEs
Description of change		Updated sentence to remove the backbone medication ibrutinib as an IMP and the requirement to provide causal relationship of SAEs .for this treatment.
Rationale for change		Modified to show ibrutinib is a non-investigational medicinal product in this trial and therefore does not require reporting of causal relationship assessment for SAEs.
Section to be changed		Section 5.3.7
Description of change		Under AE collection-Modified section to read as all AEs (non-serious and serious), and all AESIs will be collected and documented on the appropriate eCRF from signing the informed consent onwards through REP, until individual patient's end of trial. After the individual patient's end of trial: the investigator does not need to actively monitor the patient for new AEs. Word "new" added. Deleted second bullet "From the end of the REP until the last visit of the extended follow-up, all BI 836826 related SAEs and BI 836826 related AESIs
Rationale for change		Updated as per BI reporting requirements. Deleted second bullet since extended follow up period is no

		longer required as per the amendment.
Section to be changed		Section 5.3.7
Description of change		Schematic representation of study deleted. Deleted sentences- "BI 836826 related events which occurred after the REP will be considered as post treatment events. Events attributed to ibrutinib only or not-related events will not be reported after the REP." Modified paragraph on Information required to read as "For each AE, the Investigator should provide the information requested on the appropriate (e)CRF pages and the BI SAE form (if applicable)" and deleted the remainder of the paragraph. Paragraph on exemptions to SAE reporting: However, when there is evidence suggesting a causal relationship between the study drug and the progression of the underlying malignancy, the event must be reported as an (S)AE on the SAE form and on the (e)CRF.
Rationale for change		Since there is no extended follow up period after the REP, section has been updated. Section on " AE collection", "Information required" and "exemptions to SAE reporting" has been updated to reflect current BI reporting practices.
Section to be changed		
Section to be changed		Section 5.5.1.1
Description of change		
Rationale for change		Deleted to mirror the flow chart.
Section to be changed		Section 5.5.2 modified and 5.5.3 deleted
Description of change		

Rationale for change		
Section to be changed		Section 6.2.3 and 6.2.3.2
Description of change		Trial completion for an individual patient has been clarified.
Rationale for change		Extended Follow up period has been removed. Section clarified to indicate criteria for trial completion.
Section to be changed		Section 7.3
Description of change		Removal of the sub-group analysis
Rationale for change		Since the trial is being stopped prior to reaching the MTD, the subgroup analysis will not be performed.
Section to be changed		Section 7.4
Description of change		Sentence deleted- “In addition, after determination of the RP2D in the Phase Ib part of this trial, s synoptic interim report will be written to justify the RP2D”.
Rationale for change		Since Phase II of the trial will not be conducted, an interim report will not be prepared.
Section to be changed		Section 8.4.2
Description of change		Expedited Reporting of Adverse Events section updated.
Rationale for change		Section updated to reflect current BI reporting requirements.
Section to be changed		Section 8.6
Description of change		Last patient last visit primary endpoint: Section modified to delete first bullet point-“ All patients without PD have completed the 1st follow up visit (of the follow-up for PD). Second bullet point modified to delete “with PD” from sentence “all patients with PD have completed the REP”
Rationale for change		Follow up visit has been deleted from the protocol. Study will end once all patients complete the REP.

APPROVAL / SIGNATURE PAGE

Document Number: c03032933 **Technical Version Number:2.0**

Document Name: clinical-trial-protocol-version-02

Title: A Phase Ib, Open label, Single Arm, Multi-center, Dose Escalation Trial of Intravenous BI 836826 in Combination with ibrutinib in Patients with Relapsed/Refractory Chronic Lymphocytic Leukemia

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Author-Trial Clinical Monitor		24 Jul 2018 16:13 CEST
Author-Pharmacokinetics		24 Jul 2018 16:30 CEST
Approval-Team Member Medicine		24 Jul 2018 16:53 CEST
Author-Trial Statistician		24 Jul 2018 17:04 CEST
Approval-Therapeutic Area		25 Jul 2018 08:42 CEST
Verification-Paper Signature Completion		26 Jul 2018 00:21 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	**Signed by**	**Date Signed**