CLINICAL STUDY PROTOCOL

Study Title:	A Phase 1b/2 Study of Idelalisib in Combination with BI 836826 in Subjects with Chronic Lymphocytic Leukemia	
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404	
IND Number:	101254	
EudraCT Number:	Not applicable	
Indication:	Chronic Lymphocytic Leukemia (CLL)	
Protocol ID:	GS-US-312-1579	
Gilead Study Director or Clinical Program Manager:	Name: Telephone: Email:	PPD PPD PPD
Gilead Medical Monitor:	Name: Telephone: Mobile: Email:	PPD PPD PPD PPD
Protocol Version/Date:	Original: Amendment 1: Amendment 2: Amendment 3: Amendment 4:	05 May 2015 29 June 2015 07 June 2016 08 November 2016 15 June 2017

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

PROTOCOL SYNOPSIS
333 Lakeside Drive
Foster City, CA 94404

Study Title	Phase 1b/2 Study of Idelalisib in Combination with BI 836826 in Subjects with Chronic Lymphocytic Leukemia
IND Number	101254
EudraCT Number	Not applicable
Study Centers Planned	Approximately 8 centers in the United States
Objectives	*Enrollment to this study was closed on 26 April 2017 based on an updated feasibility assessment in relation to changes in standard of care. The 2 subjects enrolled as of this date may remain on study with a modified schedule of assessments.* *Subjects may remain on study through approximately Week 50 (to include 30-Day Follow-up after last dose of BI 836826).* *Due to the early study termination, the study objectives will not be met and the subjects enrolled will be assessed for safety only.* The primary objectives of this study are as follows: • Phase 1b: To determine the safety and tolerability of the combination of idelalisib with BI 836826 in subjects with relapsed and refractory (R/R) chronic lymphocytic leukemia (CLL), and to establish the high recommended Phase 2 combination dose (highRP2D) as well as an alternate lower recommended Phase 2 combination dose (lowRP2D) regimen. • Phase 2: To determine the rates of complete response (CR) and of minimal residual disease (MRD) negativity with the combination at the highRP2D and the lowRP2D. The secondary objectives of this study are as follows: • Phase 1b and 2: To evaluate Overall Response Rate (ORR), Progression-Free Survival (PFS), Duration of Complete Response (DCR), Duration of Response (DOR), and Overall Survival (OS). • Phase 2: To further characterize the safety and tolerability of the combination using the highRP2D as well as the lowRP2D regimen.

CCI [redacted]

Study Design

This study has been terminated, with 2 subjects enrolled in the Phase 1b portion of the study.

The Phase 1b portion of the study will evaluate various dose combinations of idelalisib and BI 836826 in sequential cohorts following an initial 7-day idelalisib monotherapy run-in period. The safety data from each cohort will be used as input into the Bayesian Logistic Regression Model (BLRM). The output from this model will be used by the Safety Review Team (SRT) to choose the dose combination for evaluation in the subsequent cohort. At completion of Phase 1b, 2 dose combinations will have been selected for further evaluation in Phase 2.

In the Phase 2 portion of the study, subjects with R/R CLL will be randomly assigned to receive 1 of the 2 dose combinations selected from Phase 1b following an initial 7-day idelalisib monotherapy run-in period.

Number of Subjects Planned

Approximately 42 evaluable subjects will be enrolled in the Phase 1b portion of the study and 50 evaluable subjects will be randomized in the Phase 2 portion of the study.

Target Population

Phase 1b and Phase 2: Adult subjects with R/R CLL

Duration of Treatment

This study has been terminated with 2 subjects enrolled. Subjects may remain on study through approximately Week 50 (to include 30-Day Follow-up after last dose of BI 836826).

Idelalisib will be administered twice daily (BID) continuously until disease progression or intolerable toxicity. In addition, if peripheral blood and bone marrow are negative at or after Week 50, idelalisib may be discontinued at the discretion of the investigator. BI 836826 will be administered as 18 doses from Week 2 through Week 46. Idelalisib administration will be continued only in subjects whose benefit-risk profile is deemed positive by the investigator.

Diagnosis and Eligibility Criteria

Inclusion Criteria

Subjects must meet all of the following inclusion criteria to be eligible for participation in this study:

1) Male or female ≥18 years of age.
2) Diagnosis of B-cell CLL, with diagnosis established according to modified International Workshop on Chronic Lymphocytic Leukemia (IWCLL) criteria and documented within medical records, and having received at least 2 prior treatment regimens.
3) CLL that warrants treatment (consistent with accepted IWCLL criteria for initiation of therapy). Any of the following conditions constitute CLL that warrants treatment:
    a) Evidence of progressive marrow failure as manifested by the onset or worsening of anemia and/or thrombocytopenia, or
    b) Massive (ie, lower edge of spleen ≥ 6 cm below the left costal margin), progressive, or symptomatic splenomegaly, or
    c) Massive (ie, ≥10 cm in the longest diameter), progressive, or symptomatic lymphadenopathy, or
    d) Progressive lymphocytosis in the absence of infection, with an increase in blood absolute lymphocyte count (ALC) ≥ 50% over a 2-month period or lymphocyte doubling time of < 6 months (as long as initial ALC was ≥ 30,000/L), or
    e) Autoimmune anemia and/or thrombocytopenia that is poorly responsive to corticosteroids or other standard therapy, or
    f) Constitutional symptoms, defined as any 1 or more of the following disease-related symptoms or signs occurring in the absence of evidence of infection:
        i) Unintentional weight loss of ≥ 10% within the previous 6 months, or
        ii) Significant fatigue (≥ Grade 2), or
        iii) Fevers >100.5 °F or 38.0 °C for ≥ 2 weeks, or
        iv) Night sweats for > 1 month.
4) Clinically quantifiable disease burden defined as:
    a) For Phase 1b subjects: ALC > 5000/µl in peripheral blood.
    b) For Phase 2 subjects: either at least 1 node ≥ 2 cm on computed tomography (CT) or magnetic resonance imaging (MRI) confirmed by the Independent Review Committee (IRC), or a bone marrow is performed at Screening and demonstrates quantifiable CLL.

5) Discontinuation of all cytotoxic chemotherapy and anti-CD20 antibody therapy for ≥ 4 weeks, alemtuzumab for ≥ 8 weeks, targeted therapy for ≥ 2 weeks, and investigational therapy for ≥ 3 weeks before enrollment (Phase 1b) or randomization (Phase 2). For subjects with relapsed CLL most recently treated with B-cell receptor (BCR) pathway inhibitors who, in the opinion of the investigator, will not tolerate waiting 3 weeks, a washout period of > 5 half-lives is allowed. If on a systemic corticosteroid, the dose must be stable for the prior 4 weeks.
6) All acute non-hematologic toxic effects of any prior antitumor therapy resolved to Grade ≤ 1 before enrollment with the exception of alopecia or neurotoxicity (Grade 1 or 2 neurotoxicity permitted).
7) Eastern Cooperative Oncology Group (ECOG) score of 0, 1, or 2.
8) Required baseline laboratory data (within 4 weeks prior to enrollment) as shown in the following table:

Organ System	Parameter	Required Value
Hematopoietic	ANC[a]	≥ 1×10^9/L
	Platelet	≥ 25×10^9/L
Hepatic	Serum total bilirubin	≤ 1.5 × ULN (unless elevated due to Gilbert's syndrome or hemolysis)
	Serum ALT	≤ 2.5 × ULN
	Serum AST	
Renal	C_{Cr}[b]	≥ 30 mL/min
Pregnancy	β-hCG[c]	Negative
Infection	HIV	Negative HIV antibody
	HBV	Negative HBsAg and negative HBc antibody, or positive HBc antibody and negative for HBV DNA
	HCV	Negative viral RNA (if HCV antibody is positive)
	CMV	Negative viral DNA

a ANC value to be obtained in the absence of growth factors
b As calculated by the Cockcroft-Gault formula or measured.
c For women of child-bearing potential only; serum β-hCG must be negative during Screening and urine pregnancy test must be negative prior to the first dose of study drug.

β-hCG = beta human chorionic gonadotropin, ALT = alanine aminotransferase, AST = aspartate aminotransferase, DNA = deoxyribonucleic acid, eCCr = estimated creatinine clearance, HBc antibody = anti-hepatitis B core antibody, HBsAg = hepatitis B surface antigen, HBV = hepatitis B virus, HCV = hepatitis C virus, HIV = human immunodeficiency virus, Ig = immunoglobulin, PCR = polymerase chain reaction, RNA = ribonucleic acid, ULN = upper limit of normal

9) For female subjects of child-bearing potential, willingness to use a protocol-recommended method of contraception from the Screening visit (Visit 1) throughout the study, and for 30 days from the last dose of idelalisib or 12 months from the last dose of BI 836826 (whichever is later).

10) For male subjects of reproductive potential, willingness to use a protocol-recommended method of contraception when having intercourse with females of child-bearing potential, and to refrain from sperm donation, from enrollment (Day 1) throughout the study and for 90 days following the last dose of idelalisib or 12 months from the last dose of BI 836826 (whichever is later).

11) In the judgment of the investigator, participation in the protocol offers an acceptable benefit-to-risk ratio when considering current CLL disease status, medical condition, and the potential benefits and risks of alternative treatments for CLL.

12) Willingness and ability to comply with scheduled visits, drug administration plan, imaging studies, laboratory tests, other study procedures, and study restrictions, including mandatory prophylaxis for PJP).

13) Evidence of a personally signed informed consent indicating that the subject is aware of the neoplastic nature of the disease and has been informed of the procedures to be followed, the experimental nature of the therapy, alternatives, potential benefits, possible side effects, potential risks and discomforts, and other pertinent aspects of study participation.

Exclusion Criteria

Subjects who meet any of the following exclusion criteria are not to be enrolled in this study:

1) Known histological transformation from CLL to an aggressive lymphoma (ie, Richter transformation).

2) Known presence of myelodysplastic syndrome.

3) History of a non-CLL malignancy except for the following: adequately treated local basal cell or squamous cell carcinoma of the skin, cervical carcinoma in situ, superficial bladder cancer, asymptomatic prostate cancer without known metastatic disease and with no requirement for therapy or requiring only hormonal therapy and with normal prostate-specific antigen for ≥ 1 year prior to enrollment, other adequately treated Stage 1 or 2 cancer currently in complete remission, or any other cancer that has been in complete remission for ≥ 2 years.

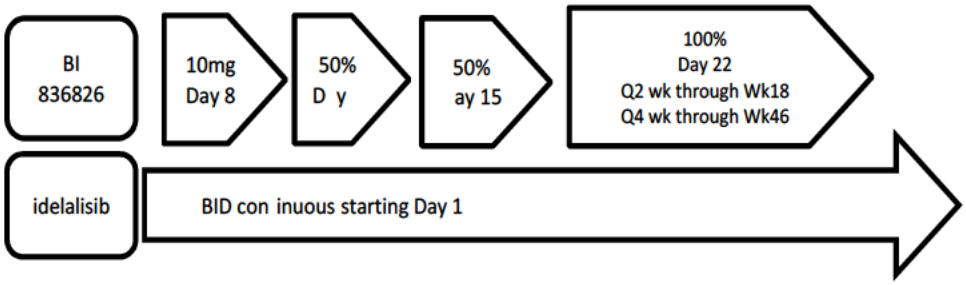
4) Known hypersensitivity or intolerance to any of the active substances or excipients in the formulations for either idelalisib or BI 836826.
5) Evidence of ongoing systemic bacterial, fungal, or viral infection at the time of enrollment.
6) Ongoing infection with, or treatment or prophylaxis for, CMV within the past 28 days.
7) Ongoing drug-induced liver injury, chronic active hepatitis C (HCV), chronic active hepatitis B (HBV), alcoholic liver disease, non-alcoholic steatohepatitis, primary biliary cirrhosis, extrahepatic obstruction caused by cholelithiasis, cirrhosis of the liver, or portal hypertension.
8) History of drug-induced pneumonitis.
9) Ongoing inflammatory bowel disease.
10) Ongoing alcohol or drug addiction.
11) Pregnancy or breastfeeding.
12) History of prior allogeneic bone marrow progenitor cell or solid organ transplantation.
13) Ongoing systemic immunosuppressive therapy other than corticosteroids.
14) History of prior therapy with any phosphatidylinositol 3-kinase (PI3K) inhibitor (including idelalisib), or any prior anti-CD37 agent.
15) Concurrent participation in another therapeutic clinical trial.
16) Prior or ongoing clinically significant illness, medical condition, surgical history, physical finding, electrocardiogram (ECG) finding, or laboratory abnormality that, in the investigator's opinion, could adversely affect the safety of the subject or impair the assessment of study results.

Study Procedures/ Frequency

This study has been terminated with 2 subjects enrolled. Subjects may remain on study through approximately Week 50 (to include 30-Day Follow-up after last dose of BI 836826). Study procedures have been modified, and the subjects enrolled will be assessed for safety only.

Screening will begin after obtaining subject's signed informed consent and will occur up to 28 days prior to first dose of study drug (Phase 1b) or randomization (Phase 2).

Treatment will begin with a 7-day idelalisib monotherapy run-in period starting on Day 1. BI 836826 will be initiated on Day 8. Subjects will be hospitalized overnight on Day 9 for monitoring and prophylaxis against tumor lysis syndrome (TLS). The investigator will assess disease status at Screening, Weeks 14, 26, 38, 50, and every 16 weeks thereafter, based on modified IWCLL criteria. Minimal residual disease (MRD) will be assessed in peripheral blood coinciding with central radiologic evaluation. MRD negativity in peripheral blood will be confirmed by bone marrow biopsy.

	Subjects will stay on study until disease progression, initiation of non-protocol anti-cancer therapy, or subject's refusal of treatment. Survival data will be collected annually for 5 years after End of Study.
Test Product, Dose, and Mode of Administration	**Idelalisib:** Idelalisib tablets will be administered BID by mouth. During the Phase 1b portion of the study, the following dose levels will be tested: 50 mg BID, 100 mg BID, and 150 mg BID; the starting dose level will be 50 mg BID. **BI 836826:** BI 836826 will be administered as a rate-controlled intravenous (IV) infusion. During the Phase 1b portion of the study, the starting dose level will be 100 mg IV. , and the highest possible dose tested will be 600 mg IV. Dosing Schema:  In both Phase 1b and Phase 2, iIdelalisib will be administered starting Week 1, Day 1. Following 7 days of idelalisib, BI 836826 administration will start Week 2 with an initial dose of 10 mg on Day 8; 50% of the assigned dose will be given on Days 9 and 15, and 100% of the assigned dose will be given on Day 22. Thereafter, 100% of the assigned dose will be administered every 2 weeks through Week 18, and every 4 weeks through Week 46.
Criteria for Evaluation	*Due to the early study termination, the endpoints will not be met and the subjects enrolled will be assessed for safety only. Planned analyses will not be performed and only safety related endpoints will be analyzed and reported for the subjects enrolled in the study.* <u>Phase 1b</u> The overall safety profile of each dosing cohort will be characterized by the type, frequency, severity, timing of onset, duration, and relationship to study treatment of any adverse events (AEs) or abnormalities of laboratory tests or ECGs. Primary Endpoint: • Incidence rate of DLTs during the first 7 weeks of study therapy at each combination dose level tested.

Secondary Endpoint:

- Description of any DLTs, serious adverse events (SAE), or AEs leading to discontinuation of study treatment.

This study has been terminated in Phase 1b and therefore Phase 2 will not occur.

Phase 2

The following endpoints will be evaluated within the highRP2D and lowRP2D groups. There will be no formal comparison between the 2 dose groups.

Primary Endpoints:

- Complete Response Rate (CRR) – defined as the proportion of subjects who achieve a CR.

MRD Negativity Rate in bone marrow by Week 50 – defined as the proportion of subjects with MRD level $< 10^{-4}$ malignant cells, assessed by flow cytometry in bone marrow, achieved by Week 50.

Secondary Endpoints:

- Description of SAEs or AEs leading to discontinuation of study treatment.
- Overall Response Rate (ORR) – defined as the proportion of subjects who achieve a complete response (CR) or partial response (PR).
- Duration of Complete Response (DCR) – defined as the interval from the first documentation of CR to the earlier of the first documentation of definitive disease progression or death from any cause.
- Duration of Response (DOR) – defined as the interval from the first documentation of CR or PR to the earlier of the first documentation of definitive disease progression or death from any cause.
- Progression-Free Survival (PFS) – defined as the interval from randomization to the earlier of the first documentation of definitive disease progression or death from any cause.
- Overall Survival (OS) – defined as the interval from the randomization to the date of death from any cause.
- Minimal Residual Disease (MRD) negativity rate in blood at any time – defined as the proportion of subjects with MRD level $< 10^{-4}$ malignant cells, assessed by flow cytometry in blood, at any time on study.
- MRD negativity rate in bone marrow at any time – defined as the proportion of subjects with MRD level $< 10^{-4}$ malignant cells, assessed by flow cytometry in bone marrow, at any time on study.

CCI [redacted]

Statistical Methods

This study has been terminated in Phase 1b based on an updated feasibility assessment in relation to changes in standard of care. The 2 subjects enrolled may remain on study with a modified schedule of assessments. Since only 2 subjects were enrolled at time of study termination, the statistical analysis will not be completed.

Analysis Methods

Dose escalation during the Phase 1b portion of the study is guided by a BLRM with overdose control. The incidence of dose-limiting toxicities (DLT), AEs, and clinically significant laboratory abnormalities will be evaluated and the toxicity probability at each dose combination will be calculated. The highRP2D will be determined by the SRT based on an assessment of the aggregate safety and PK data, and the output from the BLRM.

The highRP2D Analysis Set will include subjects in the Phase 1b portion of the study who either meet the minimum exposure criteria without experiencing a DLT, or experience a DLT following exposure to the combination of idelalisib and BI 836826 (at least 1 dose of each study drug). The Intent-to-Treat (ITT) Analysis Set for the Phase 1b portion of the study will include subjects who receive at least 1 dose of any study drug. The ITT Analysis Set for the Phase 2 portion of the study will include all subjects randomized, grouped by assigned treatment arm regardless of whether any study drug is administered. The Safety Analysis Set will comprise data from subjects who receive ≥1 dose of any study drug. The PK Analysis Set will comprise data from subjects in the Safety Analysis Set who have the necessary baseline and on-study measurements to provide interpretable results.

Subject characteristics and study results will be described and summarized for each dosing cohort.

Descriptive summaries will be prepared to mean, standard deviation, 95% confidence intervals (CI) on the mean, median, minimum, and maximum for continuous variables and counts, percentages, and 95% CIs on the percentage for categorical variables.

An IRC will review radiographic data and pertinent clinical data in order to provide expert evaluation of tumor status. The findings of the IRC will be considered primary for efficacy analyses.

CRR, ORR, and MRD-negativity rate will be calculated along with the 95% CIs based on exact method. For the analyses of DCR, DOR, OS, and PFS, the Kaplan-Meier method will be used.

Based on the Safety Analysis Set, information regarding study treatment administration, study drug compliance, and safety variables will be described and summarized. CCI [redacted]

Sample Size Calculation

There is no formal hypothesis to be tested in this study; therefore, no formal sample size calculation was performed.

This study will be conducted in accordance with the guidelines of Good Clinical Practice (GCP) including archiving of essential documents.

GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

ADA	anti-drug antibody
ADCC	antibody-dependent cellular cytotoxicity
AE	adverse event
ALC	absolute lymphocyte count
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATP	adenosine triphosphate
BCR	B-cell receptor
β-HCG	beta human chorionic gonadotropin
BID	twice daily
BLRM	Bayesian logistic regression analysis
B-NHL	B-cell non-Hodgkin lymphoma
CBC	complete blood count
CDC	complement-dependent cytotoxicity
CFR	Code of Federal Regulations
CI	confidence interval
CLL	chronic lymphocytic leukemia
CMV	Cytomegalovirus
CR	complete response
CRi	complete response with incomplete marrow recovery
CRO	contract research organization
CRR	complete response rate
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DCR	duration of complete response
DLT	dose limiting toxicity
DNA	deoxyribonucleic acid
DOR	duration of response
DSPH	Drug Safety and Public Health
E2	depressed estradiol
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EOS	end of study

EOT	end of treatment
EU	European Union
FD&C	Food, Drug, and Cosmetics Act
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
G-CSF	granulocyte colony-stimulating factor
GCP	good clinical practice
GM-CSF	granulocyte-macrophage colony-stimulating factors
HBc antibody	anti-hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
HDPE	high-density polyethylene
HiB	Haemophilus influenza Type B
highRP2D	high recommended Phase 2 dose
HIV	human immunodeficiency virus
HLGT	High-Level Group Term
HLT	High-Level Term
HMG-CoA	3-hydroxy-3-methyl-glutaryl-Coenzyme A
HSP	hysterosalpingogram
lowRP2D	low recommended Phase 2 dose
IB	investigator's brochure
ICH	International Conference on Harmonisation
IEC	independent ethics committee
Ig	immunoglobulin
IHC	immunohistochemsitry
IRB	independent review board
IRC	independent review committee
IRR	infusion-related reaction
ITT	intent-to-treat
IUD	intrauterine device
IV	intravenous
IWCLL	International Working Group on CLL
IWRS	interactive web response system
LD	longest dimension
LLT	Lower-Level Term
Mab	monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
MRD	minimal residual disease

MRI	magnetic resonance imaging
MTD	maximum tolerated dose
N	number in analysis set
N	number of subjects
NCI	National Cancer Institute
NCCN	National Comprehensive Cancer Network
ND	no disease
NE	not evaluable
ORR	overall response rate
OS	overall survival
PBMC	peripheral blood mononuclear cells
PCR	polymerase chain reaction
PD	progressive disease
PDE5	phosphodiesterase-5
PE	physical exam
PET	positron-emission tomography
PFS	progression-free survival
PI3K	phosphatidylinositol 3-kinase
PJP	*Pneumocystis jirovecii* pneumonia
PK	pharmacokinetic
PPD	product of the perpendicular dimensions
PR	partial response
PT	Preferred Term
PVA	polyvinyl alcohol
QA	quality assurance
RNA	ribonucleic acid
R/R	relapsed/refractory
SADR	serious adverse drug reaction
SAE	serious adverse event
SD	stable disease
SOC	System Organ Class
SOP	standard operating procedure
SRT	Safety Review Team
SUSAR	suspected unexpected serious adverse reactions
TEAE	treatment-emergent adverse event
TLS	Tumor Lysis Syndrome
ULN	upper limit of normal
US	United States
WES	whole exome sequencing

1. INTRODUCTION

1.1. Background

1.1.1. Chronic Lymphocytic Leukemia

Chronic lymphocytic leukemia (CLL) is a neoplastic condition resulting from the progressive accumulation of functionally incompetent monoclonal B lymphocytes in blood, bone marrow, lymph nodes, spleen, and liver {Dighiero 2008}. Chronic lymphocytic leukemia constitutes the most commonly occurring leukemia in Europe and the United States (US) {Sant 2010, Surveillance Epidemiology and End Results (SEER) Program 2011}. Symptoms may include fever, night sweats, weight loss, and there may be lymphadenopathy, splenomegaly, or hepatomegaly. The natural history of CLL is highly variable, with a median survival of more than 10 years in low-risk patients compared with 2 years in high-risk patients. CLL is largely a disease of the elderly; at diagnosis, 70% of patients are ≥ 65 years of age and the median age is 72 years {Surveillance Epidemiology and End Results (SEER) Program 2011}. New cytotoxic-free combinations are needed for patients with relapsed or refractory CLL. In patients with treatment-naive CLL, chemotherapy or chemoimmunotherapy are commonly employed to control disease manifestations {Gribben 2011}. Such therapies typically contain some combination of a purine analog, an alkylating agent, and an anti-CD20 monoclonal antibody (eg, rituximab) and can be effective in providing durable remissions {Byrd 2005, Catovsky 2007, Hallek 2010, Robak 2010}. However, these treatments are not curative; the disease will usually relapse and further intervention is required to obtain and maintain tumor control. The studies that have established the best results in response rate and progression free survival (PFS) in treatment naïve patients have generally included subjects who are not representative of the average CLL patient in the community. For example, the German CLL Study Group CLL-8 study of FC (fludarabine plus cyclophosphamide) vs FCR (FC plus rituximab) {Hallek 2010} included a subject population that was only 30% ≥ 65 years, and 10% ≥ 70 years. For patients who have significant comorbidities ("unfit") and/or are elderly, the benefit of FCR or bendamustine plus rituximab (BR) administered in less than standard dosing/schedule has not been established. There is also a need for new cytotoxic-free combination therapies for previously untreated CLL patients not suitable for intensive chemoimmunotherapy.

1.1.2. Phosphatidylinositol 3-Kinase in Lymphoid Malignancies

Phosphatidylinositol 3-kinases (PI3Ks) are enzymes that regulate several cellular functions including motility, proliferation, survival, metabolism and migration {Okkenhaug 2003b}. PI3K activation recruits and activates numerous intracellular signaling enzymes. The most important of these is the serine/threonine kinase, Akt, which mediates a positive pleiotropic effect on cell survival, proliferation, growth, and metabolism {Engelman 2006} acting by signaling through mammalian target of rapamycin (mTOR) {Hay 2005, Osaki 2004}.

PI3K signaling is mediated by 4 catalytic isoforms of the p110 subunit of the enzyme – α, β, γ, and δ. PI3K p110δ (PI3Kδ) shows an expression pattern that is particularly prominent in cells of hematopoietic origin {Vanhaesebroeck 2005}. Mice deficient in PI3Kδ have no gross abnormalities, are fertile, fecund, live a normal life span without an increased susceptibility to infections but develop colitis {Okkenhaug 2002}. The B-lymphocyte population in these animals shows a decrease in maturation, diminished B-cell receptor-induced proliferation, and deficient T-cell dependent and independent immune response. Conversely, mice with aberrantly elevated PI3K signaling develop lymphadenopathy and have an increased incidence of lymphoma {Donahue 2004}. In CLL, sustained activation of the PI3K/Akt pathway has been shown to promote malignant B-cell survival through mechanisms that are dependent on the PI3Kδ isoform {Herman 2010, Lannutti 2011}.

PI3Kδ is critical for multiple signaling pathways that are hyperactive in B-cell malignancies. Inhibition of PI3Kδ modulates B-cell receptor (BCR) signaling as well as signaling through cytokine and chemokine receptors and integrins. These signaling pathways act via downstream enzymes (most importantly Akt) to regulate proliferation, apoptosis, homing, and retention of malignant B cells in lymphoid tissues and bone marrow compartments. By inhibiting PI3Kδ-dependent signaling, idelalisib inhibits proliferation survival and homing in many B-cell malignancies.

Knowledge of the critical importance of PI3Kδ in B-cell biology and neoplasia has encouraged a search for selective inhibitors of this enzyme that could provide new options in the therapy of lymphoid malignancies, including CLL.

1.1.3. CD37 in Mature B-cell Malignancies

CD37, a member of the tetraspanin superfamily, is a glycosylated cell surface protein with 4 transmembrane domains and 2 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 {Barrena 2005, Schuurman 1987}. Low level expression of CD37 has been reported for monocytes, T cells, macrophages, and granulocytes {Moore 1987, Schwartz-Albiez 1988, van Spriel 2004}. The majority of malignant cells in patients with B-cell non-Hodgkin lymphoma (B-NHL) and CLL express the CD37 antigen {Barrena 2005, Norton 1987, Schuurman 1987, Schwartz-Albiez 1988, Smith 1989}. The physiological function of CD37 in humans remains largely unknown {Moldenhauer 2000, Schwartz-Albiez 1988}. 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 {Knobeloch 2000}. Studies with $CD37^{-/-}$ T cells suggest a role for CD37 in T-cell proliferation and regulation of IgA response {van Spriel 2004, van Spriel 2009}. 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 {Lapalombella 2012}.

CD37 is expressed on normal B cells and in B-cell malignancies such as CLL and B-NHL.

1.2. Idelalisib

1.2.1. General Information

Idelalisib (Zydelig) was first approved in the US on July 23, 2014 for the treatment of relapsed CLL, follicular lymphoma, and small lymphocytic lymphoma, followed by approval in the European Union (EU) on September 18, 2014 (centrally authorized). Zydelig is currently approved in 35 countries, including the US, EU, Switzerland, Australia, and Canada.

Idelalisib is a potent competitive inhibitor of the adenosine triphosphate (ATP) binding site of the PI3Kδ catalytic domain, which has been shown to be prominently expressed in cells of hematopoietic origin {Okkenhaug 2003a, Vanhaesebroeck 2005}. The effects of p110δ on lymphocyte activation/function, cellular proliferation, and protection from apoptosis provide the rationale for targeting this isoform as a therapy for hematologic malignancies.

Further details on the preclinical pharmacology, toxicology, metabolism, and PK of idelalisib can be found in the idelalisib Investigator's Brochure (IB).

1.3. BI 836826

1.3.1. General Information

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

1.3.2. BI 836826 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 in vitro, but lacks complement-dependent cytotoxicity (CDC) activity. The pro-apoptotic activity of BI 836826 does not depend on IgG cross-linking. BI 836826 is able to deplete endogenous, normal B cells, Ramos Burkitt lymphoma cells, and CLL cells from human blood without affecting endogenous T cells and monocytes {Heider 2011, Krause 2012, Zenz 2010}.

The combination of BI 836826 with chemotherapeutics (bendamustine, chlorambucil, fludarabine) or with the anti-CD20 Mab rituximab in vitro results in additive or synergistic apoptosis induction on lymphoma cell lines and primary CLL cells {Heider 2012}. Combination studies with idelalisib in primary CLL cells ex vivo demonstrated that the combination of idelalisib and BI 836826 showed more direct cytotoxicity in high risk (p53 dysfunctional) patient samples than either agent alone {Stephens 2014}.

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 2 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 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 (IV) exposure to BI 836826 in HuCD37 mice and to the surrogate BI 836847 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 natural killer (NK) cells at low to moderate doses. T cells, granulocytes, and platelets 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 (IL-) 6 and IL-8 in monkeys and of IL-6 and TNFα in the in vitro study using the human blood solid phase assay.

1.3.3. Clinical Trials of BI 836826

Preliminary data from 2 ongoing Phase 1 monotherapy trials are available, 1 in relapsed CLL and the other in relapsed NHL. As of June 2015, 77 subjects have been treated with BI 836826, 36 in the CLL trial and 41 in the NHL trial.

In the CLL trial (1270.1) 36 subjects were exposed to BI 836826, administered intravenously at escalating doses in a 2-week schedule. The median age of subjects 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, 3, and 9 mg contained 1 intravenous infusion of BI 836826 at a fixed rate over 3 hours on Day 1 of a 14-day treatment course. Due to the occurrence of infusion-related reactions (IRR) 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 2 portions delivered on 2 consecutive treatment days (Day 1 and 2 of Course 1) to mitigate the risk for severe IRR. This schedule was applied to 3 additional subjects at 9 mg, and all subjects treated at dose tiers of 25 mg and above. During the dose escalation all subjects 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 subjects have completed 8 or more treatment courses.

Infusion-Related Reaction was the most frequent adverse event (AE), reported in 25 subjects (69%). With mandatory premedication and an infusion schedule using a split of the first dose over 2 consecutive treatment days and a slowly increasing infusion rate the IRRs reported have been manageable at all dose tiers. The majority of IRRs were Grade 1 or 2, only 3 subjects experienced a Grade 3 reaction, which in 2 cases led to discontinuation of the trial drug.

Decrease in leukocytes, neutrophils, thrombocytes, and haemoglobin have frequently been reported in subjects. Drug-related neutropenia was reported in 41% (15/36) of the subjects, with a worst Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 or 4 in 14/36 subjects (32%). Drug-related thrombocytopenia was reported in 31% (11/36), with a worst CTCAE Grade of 3 or 4 in 8 subjects (22%). Corresponding laboratory data showed that neutrophils and thrombocytes declined immediately after the infusion. Anemia was considered drug-related in 28% of the subjects and the highest Grade was CTCAE Grade 3. A drug-related increase of alanine aminotransferase (ALT) was reported in 4 subjects (11%), and an increase of aspartate aminotransferase (AST) was reported in 5 subjects (14%). ALT and AST elevations were Grade 1 and 2 in all subjects except for 1 subject with a Grade 3 ALT elevation. The corresponding laboratory data in these subjects 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 Overall Response Rate (ORR) was 40% (12/30 subjects); all responses were partial responses. In addition, the decline in absolute lymphocyte count (ALC) was analyzed to assess effect of BI 836826 on CLL tumor load in 25 subjects treated at doses ≥ 9 mg, who had an elevated ALC at baseline and received at least 1 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 of the subjects) and a reduction to $< 4 \times 10^9$/L were observed in 56% (14/25) of the subjects.

Additional clinical data for BI 836826 is available from an ongoing Phase 1 trial in subjects with B-NHL. The treatment schedule involves weekly intravenous infusions of BI 836826 on Days 1, 8, 15, and 22 of each treatment cycle. The first 2 treatment cycles have a duration of 7 weeks, and the third cycle is 12 weeks. Subjects were allowed to receive up to 3 treatment cycles (12 administrations of BI 836826). Dose tiers of 1, 9, 25, 50, and 100 mg were completed without dose-limiting toxicities (DLT). At the dose tier of 200 mg, 1 subject experienced a DLT (oral herpes, stomatitis and febrile neutropenia, all CTCAE Grade 3). Because 4 additional subjects at this dose level experienced prolonged Grade 3-4 neutropenia lasting 7 days or more, it was decided that the 200 mg dose level exceeded the maximum tolerated dose (MTD). An intermediate dose of 150 mg was tested, and a total of 6 subjects were enrolled at this dose. One subject at the 150 mg dose experienced Grade 3 hypocalcemia and Grade 3 hypokalemia, and an additional 2 subjects experienced hypophosphatemia Grade 4. Based on DLT criteria, those laboratory abnormalities were classified as DLTs, and the MTD was established at 100 mg, which is the recommended dose for the expansion cohort.

For further information on BI 836826 please refer to the current IB.

1.4. Rationale for This Study

This study has been terminated in Phase 1b based on an updated feasibility assessment in relation to changes in standard of care. There will be no determination of highRP2D or lowRP2D in this study.

Idelalisib and BI 836826 are 2 agents for which there is a theoretical basis for synergy against CLL. This is related to the observation that 2 distinct downstream pathways are activated after ligation of the CD37 surface protein by antibodies, a SHP-1 dependent cell death pathway and a PI3Kδ-dependent cell survival pathway. Consequently, combination of CD37 ligation and PI3Kδ inhibition may lead to synergistic pro-apoptotic activity {Lapalombella 2012}. Enhanced cytotoxicity with the combination of idelalisib and BI 836826 in CLL clinical samples, especially in P53 null specimens, has been described {Stephens 2014}. Finally, the largely non-overlapping toxicity of idelalisib and BI 836826 makes this combination attractive for clinical evaluation.

Two dose combinations will be evaluated in this study. The first, higher recommended Phase 2 dose (highRP2D), will be the maximally tolerated doses of the 2 agents predicted by the Bayesian Logistic Regression Model (BLRM) and assessed by the Safety Review Team (SRT) as tolerable in the Phase 2 component of the study. The second, lower recommended Phase 2 (lowRP2D), will be chosen to evaluate whether similar efficacy can be achieved with lower toxicity.

1.5. Compliance

This study will be conducted in compliance with this protocol, Good Clinical Practice (GCP), and all applicable regulatory requirements.

2. OBJECTIVES

Enrollment to this study was closed on 26 April 2017 based on an updated feasibility assessment in relation to changes in standard of care. The 2 subjects enrolled as of this date may remain on study with a modified schedule of assessments.

Subjects may remain on study through approximately Week 50 (to include 30-Day Follow-up after last dose of BI 836826).

Due to the early study termination, the study objectives will not be met and the subjects enrolled will be assessed for safety only.

The primary objectives of this study are as follows:

- Phase 1b: To determine the safety and tolerability of the combination of idelalisib with BI 836826 in subjects with relapsed/refractory (R/R) CLL, and to establish the maximum recommended Phase 2 combination dose (highRP2D) as well as an alternate lower recommended Phase 2 combination dose (lowRP2D).

- Phase 2: To determine the rates of Complete Response (CR) and of minimal residual disease (MRD) negativity with the combination at the highRP2D and the lowRP2D.

The secondary objectives of this study are as follows:

- Phase 1b and 2: To evaluate ORR, PFS, Duration of Complete Response (DCR), Duration of Response (DOR), and Overall Survival (OS).

- Phase 2: To further characterize the safety and tolerability of the combination using the highRP2D and the lowRP2D.

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3. STUDY DESIGN

Enrollment to this study was closed on 26 April 2017 based on an updated feasibility assessment in relation to changes in standard of care. The 2 subjects enrolled as of this date may remain on study with a modified schedule of assessments.

Subjects may remain on study through approximately Week 50 (to include 30-Day Follow-up after last dose of BI 836826).

3.1. Endpoints

Due to the early study termination, the endpoints will not be met and the subjects enrolled will be assessed for safety only. Planned analyses will not be performed and only safety related endpoints will be analyzed and reported for the subjects enrolled in the study.

The Phase 1b primary endpoint is:

- Incidence rate of DLTs during the first 7 weeks of study therapy at each combination dose level tested

The Phase 1b secondary endpoint is:

- Description of any DLTs, serious adverse events (SAE), or AE leading to discontinuation of study treatment.

This study has been terminated in Phase 1b and therefore Phase 2 will not occur.

The Phase 2 primary endpoints are:

- Complete Response Rate (CRR) – defined as the proportion of subjects who achieve a Complete Response (CR)

- Minimal Residual Disease (MRD) Negativity Rate in bone marrow by Week 50 – defined as the proportion of subjects with MRD level $< 10^{-4}$ malignant cells, assessed by flow cytometry in bone marrow, achieved by Week 50

The Phase 2 secondary endpoints are:

- Description of SAEs, or AEs leading to discontinuation of study treatment

- ORR – defined as the proportion of subjects who achieve a CR or Partial Response (PR)

- DCR – defined as the interval from the first documentation of CR to the earlier of the first documentation of definitive disease progression or death from any cause

- DOR – defined as the interval from the first documentation of CR or PR to the earlier of the first documentation of definitive disease progression or death from any cause
- PFS – defined as the interval from randomization to the earlier of the first documentation of definitive disease progression or death from any cause
- OS – defined as the interval from the randomization to the date of death from any cause
- MRD negativity rate in blood at any time – defined as the proportion of subjects with MRD level < 10^{-4} malignant cells, assessed by flow cytometry in blood, at any time on study
- MRD negativity rate in bone marrow at any time – defined as the proportion of subjects with MRD level < 10^{-4} malignant cells, assessed by flow cytometry in bone marrow, at any time on study

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3.2. Study Design

This study has been terminated with 2 subjects enrolled in the Phase 1b portion of the study.

The Phase 1b portion of the study will evaluate various dose combinations of idelalisib and BI 836826 in sequential cohorts following an initial 7-day idelalisib monotherapy run-in period. The safety data from each cohort will be used as input in the BLRM. The output from this model will be used by the Safety Review Team (SRT) to choose the dose combination for evaluation in the subsequent cohort. At the completion of Phase 1b, 2 dose combinations will have been selected for further evaluation in Phase 2.

In the Phase 2 portion of the study, subjects with R/R CLL will be randomly assigned to receive 1 of the 2 dose combinations selected from Phase 1b following an initial 7-day idelalisib monotherapy run-in period.

3.2.1. Phase 1b

The Phase 1b dose escalation portion of the study will enroll approximately 42 evaluable subjects with R/R CLL. Determination of the dose levels tested in each cohort will be based on the posterior probability of DLT estimated by a 5-parameter BLRM with overdose control (Appendix 6). Subjects are evaluable for dose selection analysis during the 7week- safety evaluation period if either of the following conditions are met:

- A DLT (Section 5.5) occurs at any time during the final 6 weeks of the 7-week safety evaluation period (once combination treatment has begun). Events occurring during the initial 7-day idelalisib monotherapy run-in period and resolving by Day 8 will not be included.

- A minimum exposure to each of the drugs has been attained. Minimum exposure for safety evaluability during the 7 week safety evaluation period is defined as 4 weeks of the assigned dose of idelalisib after the first infusion of BI 836826 and 2/3 of the intended dose of BI 836826.

A minimum of 3 evaluable subjects will be enrolled into each sequential cohort. For each cohort, the BLRM will be run based on data collected through14 days after the second full dose of BI 836826 for the final evaluable subject. In each run, the estimate of parameters will be updated with accumulated data and the toxicity probability at each dose level will be calculated based on the posterior distributions of the model parameters. The BLRM-recommended dose for the next cohort will be chosen out of the dose candidates satisfying the overdose control criterion, based on the conditions listed in Appendix 6. Overdose control criterion is set as the probability of excessive toxicity to be less than 25%; however, the maximum allowable dose increment for the subsequent cohort will be no more than 100% for each drug. The SRT will review all safety data and the BLRM outputs to confirm the combination of doses for the next cohort.

For the final highRP2D to be declared, more than 6 subjects will be evaluated at that level, posterior probability of targeted toxicity will exceed 40% at that level, and a minimum of 12 subjects will be treated in total at all dose levels. The highRP2D will be determined by the SRT based on the dose candidate identified by the BLRM and an assessment of the aggregate safety and pharmacokinetic data.

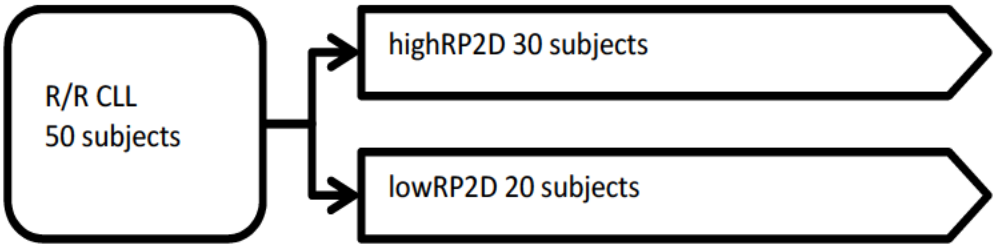
In addition, a supplemental cohort of approximately 6 subjects will be enrolled to evaluate a lowRP2D, determined by assessing the combination of a sub-maximal dose of BI 836826 (yet a dose which yields a desirable ALC-lowering and effect on biomarkers), and/or a lower dose of idelalisib. For this supplemental cohort, treatment will be initiated at the highRP2D dose and the lowRP2D first administered Week 8, following the second 100% dose of BI 836826 at the highRP2D.

Following completion of enrollment into the lowRP2D cohort and until the safety and efficacy analysis of this cohort is complete, an expansion cohort of up to 6 additional subjects may be enrolled at the highRP2D.

3.2.2. Phase 2

The Phase 2 portion of the study will begin enrolling after data is available for selection of the highRP2D and lowRP2D. Approximately 50 subjects with R/R CLL will be randomly assigned to receive either the highRP2D or the lowRP2D in a 3:2 ratio.

Phase 2 Study Design:



The expected accrual duration is approximately 24 months. The primary analysis of the Phase 2 portion will be conducted once the last subject has completed BI 836826 treatment and received a response and MRD assessment. The final analysis will be conducted after the last subject completes study participation.

3.3. Study Treatments

The study drugs, idelalisib and BI 836826, will be supplied by Gilead Sciences. Formulation, packaging, and dosing regimens are further described in Section 5.

3.4. Duration of Treatment

This study has been terminated with 2 subjects enrolled. Subjects may remain on study through approximately Week 50 (to include 30-Day Follow-up after last dose of BI 836826).

The planned treatment duration with BI 836826 is 46 weeks. The last BI 836826 infusion must be administered no later than Week 48.If the bone marrow evaluation at Week 50 is MRD positive ($\geq 10^{-4}$), idelalisib should be continued until disease progression, intolerable toxicity, or a subsequent negative bone marrow/peripheral blood MRD. Idelalisib dosing may, at the investigators discretion, be discontinued following the completion of BI 836826 if the MRD assessment in bone marrow and peripheral blood are both negative ($< 10^{-4}$) at Week 50 or later. Idelalisib administration will be continued only in subjects whose benefit-risk profile is deemed positive by the investigator.

3.5. Study Discontinuation Criteria

The study may be discontinued at any time based on reviews of safety and efficacy data by Gilead. Subject discontinuation criteria are described in Section 6.6

3.6. Source Data

The subject identification number and randomization number captured by the interactive web response system (IWRS) are considered source data.

3.7. Biomarker Testing

This study has been terminated in Phase 1b based on an updated feasibility assessment in relation to changes in standard of care. The 2 subjects enrolled may remain on study with a modified schedule of assessments. Since only 2 subjects were enrolled at time of study termination, biomarker samples will no longer be collected or analyzed.

3.7.1. Biomarker Samples to Address the Study Objectives

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Minimal residual disease will be evaluated in peripheral blood and/or bone marrow, depending on the time point of the assessment. Minimal residual disease assessments will be done by multi-parameter flow cytometry with a sensitivity of at least 1 leukemic cell per 10,000 leukocytes (10^{-4}), the level defined as MRD negative status. The laboratory procedures, instrument settings and antibody panels will be fully standardized in order to achieve maximally comparable results among the different central labs.

Minimal residual disease will be assessed in peripheral blood at Screening, Weeks 14, 26, 38, 50 and then every 16 weeks through End of Treatment at the same time as imaging studies and overall disease assessment. Additionally peripheral blood mononuclear cells (PBMC) will be biobanked for MRD assessment by next generation sequencing methods if necessary.

Minimal residual disease will be assessed in bone marrow at Week 50. In addition, if a peripheral blood specimen is MRD negative at any time, a marrow specimen should be obtained within 30 days following the achievement of peripheral blood MRD. Once marrow MRD negativity is achieved, the subject should be followed with peripheral blood sampling only, according to the schedule of procedures (Appendix 2). MRD may also be assessed by DNA sequencing.

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4. SUBJECT POPULATION

Enrollment to this study was closed on 26 April 2017 based on an updated feasibility assessment in relation to changes in standard of care. The 2 subjects enrolled as of this date may remain on study with a modified schedule of assessments.

Subjects may remain on study through approximately Week 50 (to include 30-Day Follow-up after last dose of BI 836826).

4.1. Number of Subjects and Subject Selection

Approximately 42 evaluable subjects will be treated during the Phase 1b portion of the study. The Phase 2 portion of the study will enroll approximately 50 subjects.

4.2. Inclusion Criteria

Subjects must meet all of the following inclusion criteria to be eligible for participation in this study:

1) Male or female ≥ 18 years of age.

2) Diagnosis of B-cell CLL, with diagnosis established according to modified International Workshop on Chronic Lymphocytic Leukemia (IWCLL) criteria and documented within medical records, and having received at least 2 prior treatment regimens.

3) CLL that warrants treatment (consistent with accepted IWCLL criteria for initiation of therapy). Any of the following conditions constitute CLL that warrants treatment:

    a) Evidence of progressive marrow failure as manifested by the onset or worsening of anemia and/or thrombocytopenia, or

    b) Massive (ie, lower edge of spleen ≥ 6 cm below the left costal margin), progressive, or symptomatic splenomegaly, or

    c) Massive (ie, ≥ 10 cm in the longest diameter), progressive, or symptomatic lymphadenopathy, or

    d) Progressive lymphocytosis in the absence of infection, with an increase in blood absolute lymphocyte count (ALC) ≥ 50% over a 2-month period or lymphocyte doubling time of < 6 months (as long as initial ALC was ≥ 30,000/L), or

    e) Autoimmune anemia and/or thrombocytopenia that is poorly responsive to corticosteroids or other standard therapy, or

f) Constitutional symptoms, defined as any 1 or more of the following disease-related symptoms or signs occurring in the absence of evidence of infection:

i) Unintentional weight loss of ≥ 10% within the previous 6 months, or

ii) Significant fatigue (≥ Grade 2), or

iii) Fevers >100.5 °F or 38.0 °C for ≥ 2 weeks, or

iv) Night sweats for > 1 month.

4) Clinically quantifiable disease burden defined as:

a) For Phase 1b subjects: ALC > 5000/µL in peripheral blood.

b) For Phase 2 subjects: either at least 1 node ≥ 2 cm on computed tomography (CT) or magnetic resonance imaging (MRI) confirmed by the Independent Review Committee (IRC), or a bone marrow is performed at Screening and demonstrates quantifiable CLL.

5) Discontinuation of all cytotoxic chemotherapy and anti-CD20 antibody therapy for ≥ 4 weeks, alemtuzumab for ≥ 8 weeks, targeted therapy for ≥ 2 weeks, and investigational therapy for ≥ 3 weeks before enrollment (Phase 1b) or randomization (Phase 2). For subjects with relapsed CLL most recently treated with BCR pathway inhibitors who, in the opinion of the investigator, will not tolerate waiting 3 weeks, a washout period of > 5 half-lives is allowed. If on a systemic corticosteroid, the dose must be stable for the previous 4 weeks.

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

7) Eastern Cooperative Oncology Group (ECOG) score of 0, 1, or 2.

8) Required baseline laboratory data (within 4 weeks prior to enrollment) as shown in the following table:

Organ System	Parameter	Required Value
Hematopoietic	ANCa	≥ 1 × 109/L
	Platelets	≥ 25 × 109/L
Hepatic	Serum total bilirubin	≤ 1.5 × ULN (unless elevated due to Gilbert's syndrome or hemolysis)
	Serum ALT	≤ 2.5 × ULN
	Serum AST	
Renal	CCrb	≥ 30 mL/min
Pregnancy	β-hCGc	Negative
Infection	HIV	Negative HIV antibody
	HBV	Negative HBsAg and negative HBc antibody, or positive HBc antibody and negative for HBV DNA
	HCV	Negative viral RNA (if HCV antibody is positive)
	CMV	Negative viral DNA

a ANC value to be obtained in the absence of growth factors
b As calculated by the Cockcroft-Gault formula or measured.
c For women of child-bearing potential only; serum β-hCG must be negative during Screening and urine pregnancy test must be negative prior to the first dose of study drug

β-hCG = beta human chorionic gonadotropin, ALT = alanine aminotransferase, AST = aspartate aminotransferase, DNA = deoxyribonucleic acid, eCCr = estimated creatinine clearance, HBc antibody = anti-hepatitis B core antibody, HBsAg = hepatitis B surface antigen, HBV = hepatitis B virus, HCV = hepatitis C virus, HIV = human immunodeficiency virus, Ig = immunoglobulin, PCR = polymerase chain reaction, RNA = ribonucleic acid, ULN = upper limit of normal

9) For female subjects of child-bearing potential, willingness to use a protocol-recommended method of contraception from the Screening visit throughout the study, and for 30 days from the last dose of idelalisib or 12 months from the last dose of BI 836826 (whichever is later).

10) For male subjects of reproductive potential a willingness to both: 1) use a protocol-recommended method of contraception, when having intercourse with females of child bearing potential, and 2) to refrain from sperm donation, from enrollment (Day 1) throughout the study and for 90 days following the last dose of idelalisib or 12 months from the last dose of BI 836826 (whichever is later).

11) In the judgment of the investigator, participation in the protocol offers an acceptable benefit-to-risk ratio when considering current CLL disease status, medical condition, and the potential benefits and risks of alternative treatments for CLL.

12) Willingness and ability to comply with scheduled visits, drug administration plan, imaging studies, laboratory tests, other study procedures, and study restrictions, including mandatory prophylaxis for PJP.

13) Evidence of a personally signed informed consent indicating that the subject is aware of the neoplastic nature of the disease and has been informed of the procedures to be followed, the experimental nature of the therapy, alternatives, potential benefits, possible side effects, potential risks and discomforts, and other pertinent aspects of study participation.

4.3. Exclusion Criteria

Subjects who meet *any* of the following exclusion criteria are not to be enrolled in this study:

1) Known histological transformation from CLL to an aggressive lymphoma (ie, Richter transformation).

2) Known presence of myelodysplastic syndrome.

3) History of a non-CLL malignancy except for the following: adequately treated local basal cell or squamous cell carcinoma of the skin, cervical carcinoma in situ, superficial bladder cancer, asymptomatic prostate cancer without known metastatic disease and with no requirement for therapy or requiring only hormonal therapy and with normal prostate-specific antigen for ≥1 year prior to enrollment, other adequately treated Stage 1 or 2 cancer currently in complete remission, or any other cancer that has been in complete remission for ≥ 2 years.

4) Known hypersensitivity or intolerance to any of the active substances or excipients in the formulations for either idelalisib or BI 836826.

5) Evidence of ongoing systemic bacterial, fungal, or viral infection at the time of enrollment.

6) Ongoing infection with, or treatment or prophylaxis for, CMV within the past 28 days.

7) Ongoing drug-induced liver injury, chronic active hepatitis C (HCV), chronic active hepatitis B (HBV), alcoholic liver disease, non-alcoholic steatohepatitis, primary biliary cirrhosis, extrahepatic obstruction caused by cholelithiasis, cirrhosis of the liver, or portal hypertension.

8) History of drug-induced pneumonitis.

9) Ongoing inflammatory bowel disease.

10) Ongoing alcohol or drug addiction.

11) Pregnancy or breastfeeding.

12) History of prior allogeneic bone marrow progenitor cell or solid organ transplantation.

13) Ongoing systemic immunosuppressive therapy other than corticosteroids.

14) History of prior therapy with any PI3K inhibitor (including idelalisib), or any anti-CD37 agent.

15) Concurrent participation in another therapeutic clinical trial.

16) Prior or ongoing clinically significant illness, medical condition, surgical history, physical finding, electrocardiogram (ECG) finding, or laboratory abnormality that, in the investigator's opinion, could adversely affect the safety of the subject or impair the assessment of study results.

5. STUDY TREATMENTS

5.1. Randomization, Blinding, and Treatment Codes

5.1.1. Interactive Web Response System

An IWRS will be employed to manage the conduct of the trial. In Phase 1b and/or Phase 2, the IWRS will be used to maintain a central log documenting enrollment, to implement randomization, to manage dose modifications, to assess current inventories of study drug, to initiate any necessary resupply of study drug, and to document discontinuation of study drug and study participation.

5.2. Description and Handling of Idelalisib

5.2.1. Formulation

Idelalisib will be provided in tablets intended for oral administration. Each tablet contains 150 mg, 100 mg, or 50 mg of active idelalisib.

The 150 mg tablets are oval and pink; the 100 mg tablets are oval and orange; and the 50 mg tablets are round and pink. All tablets are film-coated, and include the following inactive excipients: microcrystalline cellulose, hydroxypropyl cellulose, croscarmellose sodium, sodium starch glycolate, magnesium stearate, FD&C Yellow #6/ Sunset Yellow FCF Aluminum Lake (100 mg tablets only), red iron oxide (150 mg and 50 mg only), polyethylene glycol, talc, polyvinyl alcohol (PVA), and titanium dioxide.

5.2.2. Packaging and Labeling

Idelalisib tablets are packaged in white, high density polyethylene (HDPE) bottles. Each bottle contains 60 tablets and polyester packing material. Each bottle is enclosed with a white, continuous thread, child resistant polypropylene screw cap with an induction-sealed and aluminum faced liner.

5.2.3. Storage and Handling

Idelalisib tablets should be stored at controlled room temperature of 25 °C (77 °F); excursions are permitted between 15 °C and 30 °C (59 °F and 86 °F). Storage conditions are specified on the label. Until dispensed to the subjects, all bottles of study drugs should be stored in a securely locked area, accessible only to authorized site personnel. To ensure the stability and proper identification, the study drug should be stored in the containers in which they were supplied.

5.3. Description and Handling of BI 836826

5.3.1. Formulation

BI 836826 concentrate for solution for infusion is a clear to slightly opalescent, colourless to yellowish liquid, with an osmolality of 260 - 340 mOsm/kg and a pH of 5.7 – 6.7. Concentration is 10 mg/mL in vials with 10 mL, dilution is required prior to administration.

5.3.2. Packaging and Labeling

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 contains 100 mg active ingredients (10 mg/mL). Each vial is enclosed with a rubber stopper and sealed with an aluminum flip-off cap.

5.3.3. Storage and Stability

BI 836826 should be stored at 2-8 °C (36-46 °F); do not freeze. Storage conditions are specified on the label. Until dispensed, all vials of study drug should be stored in a securely locked area, accessible only to authorized site personnel. To ensure the stability and proper identification, the study drug should be stored in the containers in which it was supplied.

Prepared solution for infusion is stable for 48 hours at room temperature (up to 25°C/77°F). Solution for infusion should be administered as soon as possible after preparation.

5.3.4. Solution Preparation and Dispensing

Before use, vials of BI 836826 should be inspected for particulate matter or discoloration. Any vial with evidence of particulates or discoloration should not be used.

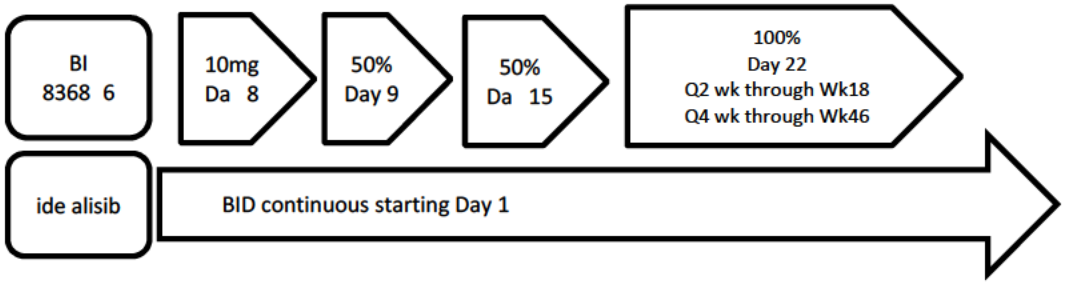
For preparation of the BI 836826 solution, the contents of the vial of BI 836826 will be diluted in 0.9% sodium chloride. The final prepared volume of the infusion bags will be 250 mL for doses of 10 and 50 mg, and 500 mL for all other doses prepared. The content of up to 6 vials will be needed for administration of the highest possible dose of 600 mg.

The intravenous solution should be prepared and dispensed by the clinical research center pharmacist and should be infused by a qualified nurse with experience in monitoring the administration of chemotherapeutic agents.

5.4. Dosage and Administration

This study has been terminated, with 2 subjects enrolled in the Phase 1b portion of the study. The 2 subjects enrolled may remain on study at the current dose levels for both treatments.

Dosing (Phase 1b and Phase 2):



5.4.1. Idelalisib

Idelalisib will be taken orally twice daily (BID). At each dose administration, the idelalisib tablet is to be swallowed whole with 120 to 240 mL (approximately 4 to 8 ounces) of water. In case of breakage of the tablet in the oral cavity, additional water should be taken as a rinse.

During Phase 1b the initial BLRM will use the following dose levels for idelalisib: 50 mg BID, 100 mg BID, and 150 mg BID; the starting dose level will be idelalisib 50 mg BID.

Idelalisib may be taken with or without food. There are no known dietary restrictions related to idelalisib use.

On days of BI 836826 dosing, idelalisib will be administered in the clinic approximately 60 minutes before the start of the infusion and appropriately timed relative to blood sampling for idelalisib PK. Prior to these visits, subjects should be reminded not to take their morning dose of study drug before coming into the clinic. Subjects should also be reminded to bring their study drug with them to clinic for dosing. Clinic staff should record idelalisib administration information, including the exact clock time of each dose, for doses of study drug administered in the clinic or hospital.

Thereafter, subjects will be given an adequate supply of tablets to take at home. At home, idelalisib should be taken at approximately the same time each day. Ideally, doses should be taken at approximately 12 hour intervals (eg, at 7 AM and at 7 PM). While it is realized that variations in dosing schedule may occur in the outpatient setting, the prescribed regimen should be followed as closely as possible.

Subjects who have a delay in administration of a dose of idelalisib of < 6 hours should take the planned dose as soon as possible after the intended time of administration. For subjects who have a delay in administration of study drug of ≥ 6 hours, the dose should not be taken. Study drug administration may continue but the missed dose should not be made up and the planned timing of subsequent study drug dosing should not be altered.

5.4.2. BI 836826

BI 836826 is administered intravenously as a rate controlled infusion. Administration will start on Week 2 with an initial of 10 mg on Day 8, 50% of the assigned dose on Days 9 and Day 15, and 100% of the assigned dose on Day 22. Thereafter, 100% of the assigned dose will be administered every 2 weeks through Week 18, and every 4 weeks through Week 46. During the Phase 1b portion of the study, subjects will be hospitalized overnight on Day 9 (first 50% dose) for monitoring and prophylaxis against tumor lysis syndrome (TLS).

In the Phase 1b portion of the study, the initial BLRM will use the following dose levels for BI 836826: 100 mg, 200 mg, and 400 mg; the starting dose level will be 100 mg. The BLRM may subsequently be modified to include additional BI 836826 doses through 600 mg, dependent on safety data from this study and from Boehringer Ingelheim study 1270.1.

Subjects should receive 18 infusions of BI 836826 over the course of the study. There will be no intra-subject dose escalation.

There is no limit on the length of time BI 836826 may be held to allow resolution of toxicity. If both idelalisib and BI 836826 are held during the same period, when appropriate both drugs should be restarted on the same day rather than dosing with idelalisib for 7 days prior to restarting BI 836826. If administration of BI 836826 is delayed by more than 4 weeks, when infusions are restarted pre-medication must be administered for the first 8 weeks. The last BI 836826 infusion must be administered no later than Week 48.

Surveillance of the subject during and until at least 2 hours after the end of the infusion is required for the first 4 BI 836826 infusions (through the first infusion of 100% of the assigned dose). Surveillance should be prolonged as clinically indicated to monitor or treat AEs. Mandatory surveillance can be reduced to at least 1 hour in the fifth and subsequent infusions if no AE occurs during the infusion or the 1 hour surveillance period. Prophylaxis against IRR is required prior to administration (Section 5.8.2.1).

5.4.2.1. BI 836826 Infusion Rates

Table 5-1 provides a tabular summary of BI 836826 infusion rates.

Table 5-1. BI 836826 Infusion Rates

Day of Treatment	Dose of BI 836826	Rate of Infusion	Maximum Allowed Infusion Duration	Maximum Allowed Infusion Rate
Week 2 Day 8	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
Week 2 Day 9	50% of assigned 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
Week 3 Day 15	50% of assigned 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
Week 4 Day 22	100% of assigned dose	≤ 50 mg/hr x 60 min Escalate by ≤ 50 mg/hr every 30 min as tolerated to maximum allowed rate; slower start rate or smaller increments allowed at investigator's discretion	24 hr	400 mg/hr
Week 6 Day 36	100% of assigned 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; slower start rate or smaller increments allowed at investigator's discretion	24 hr	500 mg/hr

- Week 2, Day 8: BI 836826 Initial Dose of 10 mg

BI 836826 administration will start with an initial dose of 10 mg on Week 2, Day 8. Premedication (Section 5.8.2) is mandatory. The recommended initial infusion rate to mitigate the risk for severe IRRs is 2 mg/hr for the first 60 minutes. The rate can be escalated every 30 minutes by increments of 1 mg/hr to a maximum rate of 5 mg/hr in the absence of IRRs. In subjects with high risk for IRRs, occurrence of an IRR during the infusion, or a high risk for TLS, the infusion may be given extremely slowly over a longer period of time not exceeding 24 hours.

- Week 2, Day 9 and Week 3, Day 15: BI 836826 to 50% of Assigned Dose

Pre-medication (Section 5.8.2) is mandatory. The recommended initial infusion rate to mitigate the risk for severe IRRs should not exceed 50 mg/hr for the first 60 minutes. The rate can be escalated every 30 minutes by increments of 50 mg/hr or less to a maximum rate of 400 mg/hr 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 subjects with high risk for IRRs, occurrence of an IRR during the infusion, or a high risk for TLS, the infusion may be given extremely slowly over a longer period of time not exceeding 24 hours.

- Week 4, Day 22: BI 836826 at the Assigned Dose

Pre-medication (Section 5.8.2) is mandatory. The recommended initial infusion rate to mitigate the risk for severe IRRs should not exceed 50 mg/hr for the first 60 minutes. The rate can be escalated every 30 minutes by increments of 50 mg/hr or less to a maximum rate of 400 mg/hr 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.

- Week 6, Day 36 and Subsequent Doses of BI 836826

In the absence of infusion related reactions during the administration of the previous full dose, subsequent administration of BI 836826 is recommended to start at a rate of 50 mg/hr or less for the first 30 minutes, followed by a rate of 100 mg/hr or less for 30 minutes. Incremental steps thereafter may be larger depending on individual tolerability, but must not exceed 100 mg/hr. A maximum rate of 500 mg/hr 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 5.8.2.

5.4.2.2. BI 836826 Infusion Rate Response to Infusion-Related Reaction

If symptoms of an IRR occur while BI 836826 is administered, the following instructions for rate changes and interruptions of BI 836826 should be followed. Table 5-2 provides a tabular summary of procedures that may be employed to manage IRRs.

Table 5-2. BI 836826 Management of Infusion-Related Reactions

NCI CTCAE Grade of IRR	Action	Continuing BI 836826 [1]	
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; supportive treatment may be administered as indicated	After resolution of symptoms	Resume infusion at a slower rate than that at which the reaction occurred
Grade 3	Interrupt infusion; supportive treatment is typically indicated, glucocorticoids should be considered for management	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	

1. Once subject is stable after reintroduction of initial infusion rate, proceed per Section 5.4.2, Dosage and Administration of BI 836826

- In the case of an IRR 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 IRR 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 IRR of CTCAE Grades 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.

5.4.2.3. Criteria for Administration of BI 836826 at 100% of the Assigned Dose (Day 22 and Following)

Prior to each administration of a 100% assigned dose of BI 836826, AEs and complete blood count (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 (Table 5-3)

In case any 1 of these criteria is not fulfilled, blood counts and/or the AE should be regularly re-evaluated. See section 5.6 for information on dose modification in response to toxicity.

If an infusion cannot be administered within the protocol-specified procedure window (see Appendix Table 1, Visit Window) the dose should be skipped. Doses may be made up if a minimum interval of 2 weeks is maintained between infusions. The last infusion of BI 836826 may be given no later than Week 48.

5.5. Dose-Limiting Toxicity

All AEs, including SAEs and deaths, will be carefully analyzed by the SRT. Dose-limiting toxicities will be those clinically relevant AEs which are unexpected in severity or frequency considering the mode of action and known toxicities of the individual agents, are not manifestations of underlying disease or background events typical of the study population, and are any of the following: debilitating, non-reversible, not manageable, or which lead to a fatal outcome, where evidence suggests that there was a reasonable possibility that the drug combination caused the AE.

The following drug-related hematologic adverse events will be considered DLT:

- Grade 4 neutropenia lasting more than 7 days
- Grade 4 febrile neutropenia, and Grade 3 febrile neutropenia not resolving within 48 hrs with appropriate treatment (antibiotics, antivirals, antifungals, growth factor support)
- Grade 4 thrombocytopenia lasting more than7 days, or Grade 3-4 thrombocytopenia with clinically significant bleeding
- Grade 4 anemia
- Any Grade 5 hematologic AE

Non-hematologic, drug-related AEs of Grade 3 or higher will be considered DLTs except:

- Grade 3 ALT or AST elevation
- Grade 3 diarrhea that responds to therapy within 7 days
- Grade 3 rash that improves within 7 days following supportive therapy and discontinuation of idelalisib
- Grade 3 pneumonia or localized infection that responds to therapy within 7 days
- Any other Grade ≥ 3 lab abnormalities that, in the opinion of the investigator, are attributable to the underlying disease process
- Infusion-related reaction, any grade

5.6. Safety Monitoring and Study Drug Interruption/Dose Modification/Discontinuation

Required and recommended actions for discontinuation or dose modification for both drugs, including the combination regimen, are provided in Table 5-3. The requirements and recommendations are based on the drug and the CTCAE grade of specific toxicities, focusing on the types of events most commonly attributed to each of the study agents.

In cases of uncertainty, the study medical monitor should be contacted.

There is no limit on the length of time either idelalisib or BI 836826 may be held during the study (eg, to allow resolution of toxicity). If both idelalisib and BI 836826 are held during the same period, when appropriate both drugs should be restarted on the same day rather than dosing with idelalisib for 7 days prior to restarting BI 836826. During the combination therapy period (through Week 46), if either study drug is permanently discontinued, the other study drug should also be permanently discontinued. See Section 6.6.1 for recommended follow-up.

Table 5-3. Requirements and Recommendations for Discontinuation or Modification of Study Treatment in Response to Adverse Events

NCI CTCAE Grade[1]	Idelalisib	BI 836826
HEMATOLOGICAL ADVERSE EVENT		
Neutropenia		
Grade ≤2 neutropenia	Maintain current dose and schedule.	Maintain current dose level and schedule.
Grade 3 neutropenia	*Required action:* Blood counts must be monitored at least weekly until neutropenia Grade ≤ 2.	Maintain current dose level and schedule. Consider G-CSF support. If febrile neutropenia not resolving within 48 hrs with appropriate treatment, decrease subsequent dose by 50%[2].
Grade 4 neutropenia (or occurrence of neutropenic fever or infection)	*Required action:* Interrupt idelalisib. Blood counts must be monitored at least weekly until neutropenia is ≤ Grade 2. *Recommended action:* May resume idelalisib at lower dose level when neutropenia is Grade ≤ 3[2].Neutropenia should be managed according to established clinical guidelines.	If Gr 4 neutropenia lasts >7 days, or febrile neutropenia not resolving within 48 hrs with appropriate treatment, decrease subsequent dose by 50% [3] Otherwise, maintain current dose level and schedule and consider G-CSF support.
Thrombocytopenia		
Grade ≤2 thrombocytopenia	Maintain current dose and schedule.	Maintain current dose level and schedule.
Grade 3 thrombocytopenia	Maintain current dose and schedule.	Maintain current dose level and schedule; unless associated with significant bleeding, in which case decrease subsequent dose by 50% [3]
Grade 4 thrombocytopenia	*Required action:* During continuing single agent therapy period, withhold for bruising or bleeding until Grade ≤ 3. *Recommended action:* During combination therapy period, maintain current dose level. If withheld during continuing therapy period, may resume at same or reduced dose level at investigator discretion [2].	If lasts > 7 days or associated with significant bleeding, decrease subsequent dose by 50% [3].
Anemia		
Grade ≤3	Maintain current dose and schedule.	Maintain current dose level and schedule.
Grade 4	If all other possible etiologies of anemia have been ruled out, idelalisib may be withheld at investigator discretion.	Decrease subsequent dose by 50%[3].

NCI CTCAE Grade[1]	Idelalisib	BI 836826
NON-HEMATOLOGICAL ADVERSE EVENT		
Rash		
Grade ≤ 2	Maintain current dose and schedule.	Maintain current dose level and schedule.
Grade ≥ 3	*Required action:* Withhold idelalisib until Grade ≤ 1. *Recommended action:* May resume at lower dose or discontinue idelalisib at investigator discretion [2].	Delay BI 836826 until Grade ≤ 1. Thereafter, may resume at full dose.
Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis		
Any Grade	*Required action:* Discontinue idelalisib. Interrupt coadministered medications potentially associated with SJS or TEN. Institute treatment per institutional standards.	Discontinue BI 836826. Institute treatment per institutional standards.
Bowel Perforation		
Any Grade	Discontinue idelalisib.	Discontinue BI 836826.
Diarrhea or Colitis		
Any Grade (in addition see below for response to specific CTCAE grades)	*Required action:* See Section 5.7.2.1 for required assessments. *Recommended action:* Ensure good hydration status and provide anti-diarrheal; maintain current dose level. See Section 5.7.2.2 for recommended evaluations.	See below.
Grade ≤ 1	*Required action:* See Section 5.7.2.1 for required assessments. *Recommended action:* Provide anti-diarrheal (eg, loperamide) and maintain current idelalisib dose and schedule.	Maintain current dose level and schedule.
Grade 2 (unless clinical diagnosis is established from medical history and physical examination)	*Required action:* See Section 5.7.2.1 for required assessments and Section 6.1.8.9 for required testing. *Recommended action:* See Section 5.7.2.2 for recommended evaluations. Maintain current dose level.	Delay BI 836826 until Grade ≤ 1. Thereafter, may resume at full dose.
Grade ≥ 3 (or persistent Grade 2 diarrhea or colitis without clear etiology)	*Required action:* Withhold idelalisib. See Section 5.7.2.1 for required assessments and Section 6.1.8.9 for required testing. Consider anti-diarrheal (eg, loperamide) and/or addition of anti-inflammatory agent (eg, sulfasalazine, budesonide). *Recommended action:* See Section 5.7.2.2 for recommended evaluations. At Grade ≤1, may resume at lower dose level [2] or discontinue study drug at investigator discretion.	If diarrhea Grade ≥ 3 recurs despite interruption of idelalisib, reduce BI 836826 to 50% [3]. BI 836826 may be increased to 100% upon resolution to Grade ≤ 1 at investigator discretion.

NCI CTCAE Grade[1]	Idelalisib	BI 836826
Hepatic Adverse Events (elevations in ALT, AST)		
Grade ≤1 (ALT/AST ≤ 3 × ULN; Bilirubin ≤ 1.5xULN)	Maintain current dose and schedule.	Maintain current dose level and schedule.
Grade 2 (ALT/AST ≤ 3-5 × ULN; Bilirubin > 1.5- ≤ 3xULN)	Maintain current dose and schedule. *Recommended action:* Monitor ALT, AST, ALP, and bilirubin at least 1x per week until all abnormalities are Grade ≤ 1.	Delay BI 836826 until Grade ≤ 1. Thereafter resume at full dose.
Grade 3 (ALT/AST > 5-20 × ULN; Bilirubin > 3-10xULN)	*Recommended action:* Withhold idelalisib. Monitor ALT, AST, alkaline phosphatase (ALP), and bilirubin at least 1x per week until all abnormalities are Grade ≤1. If bilirubin abnormality was Grade <3 resume idelalisib at same dose level. If bilirubin abnormality was Grade ≥3, resume at lower dose level [2].	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 and idelalisib at reduced dose, reduce BI 836826 to 50% [3]. Upon resolution of ALT/AST to Grade ≤1 BI 836826 may be re-escalated to 100% at investigator discretion.
Grade 4 (ALT/AST > 20 × ULN; Bilirubin > 10xULN)	*Required action:* Withhold idelalisib. Monitor ALT, AST, ALP, and bilirubin at least 1x per week until all abnormalities are Grade ≤1. If bilirubin abnormality was Grade 4, discontinue idelalisib. *Recommended action:* If bilirubin abnormality was Grade <4 resume idelalisib at lower dose level[2].	Withhold BI 836826. Monitor ALT, AST, ALP, and bilirubin at least 1x per week until all abnormalities are Grade ≤1. If bilirubin abnormality was Grade 4, discontinue BI 836826.
Pneumonitis (with new onset or worsening of baseline dyspnea, cough, or hypoxia without obvious infectious cause)		
Grade 1 (asymptomatic)	*Required action:* Withhold idelalisib until resolution to baseline. May resume at lower dose level or discontinue at investigator discretion.	Maintain current dose level and schedule.
Grade ≥ 2	*Required action:* Discontinue idelalisib permanently in subjects with any severity of symptomatic pneumonitis and institute therapy as clinically appropriate.	Discontinue BI 836826.
***Pneumocystis jirovecii* pneumonia (PJP)**		
Any Grade	*Required action:* Discontinue idelalisib.	Discontinue BI 836826.
CMV Infection/Reactivation [4]		
Any Grade	*Required action:* Interrupt idelalisib upon unequivocal clinical or laboratory evidence of CMV infection. Treat according to established clinical guidelines. If the benefits of resuming idelalisib are judged to outweigh the risks, consider pre-emptive CMV therapy.	Discontinue BI 836826.
Hepatitis B Reactivation		
Any Grade	*Required action:* Discontinue idelalisib.	Discontinue BI 836826.

NCI CTCAE Grade[1]	Idelalisib	BI 836826
OTHER NONHEMATOLOGICAL ADVERSE EVENTS		
Grade ≤ 2	Maintain current dose level and schedule.	Maintain current dose level and schedule.
Grade ≥ 3	Withhold study drug until Grade ≤ 1. May resume study drug at initial or next lower dose[2] or discontinue study drug at investigator discretion.	Withhold study drug until Grade ≤ 1. May resume study drug at initial or at 50% [3] or discontinue study drug at investigator discretion.

1. CTCAE, Version 4.03.
2. If assigned idelalisib dose level is 50 mg BID, dose reduction is not possible and idelalisib should be interrupted.
3. Dose reduction of BI 836826 by 50% may be performed twice. If still not tolerated, BI 836826 should be discontinued.
4. CMV should be diagnosed using clinical or laboratory criteria per established institutional standard

5.7. Requirements and Recommendations Regarding Specific Adverse Events or Conditions

5.7.1. Transaminase Elevations

Consistent with observations in a dog toxicology study, reversible asymptomatic ALT/AST increases were observed early in the idelalisib program in phase 1 studies (101-02 and 101-07) in subjects with hematologic malignancies. Transaminase elevations generally occurred within 4 to 12 weeks of drug initiation, and resolved spontaneously over a period of 2 to 4 weeks with drug being continued for Grade 1 and 2 elevations and drug withheld for Grade 3 or 4 elevations until resolution. These early observations are consistent with the ongoing experience with idelalisib treatment and transaminase elevations are now well characterized as most frequently asymptomatic, transient and occurring within the first 3 months of treatment.

Grade 1 or 2 elevations commonly resolve despite continued idelalisib treatment and Grade 3 or 4 elevations can be managed by temporarily withholding idelalisib. Successful rechallenge after resolution at either the same or lower dose level of idelalisib has been achieved in the majority of subjects. There has been no evidence of impaired synthetic function. Close monitoring of hepatic laboratory tests during therapy is important to allow for appropriate idelalisib interruption and reinstitution so that subjects may continue with study drug treatment.

Cholangitis manifest as hyperbilirubinemia out of proportion to serum transaminase elevations has been observed. While disease-related factors, neutropenia, toxicity from prior therapies, effects of ongoing supportive care, or pre-existing cholelithiasis may have initiated such events, it is possible that idelalisib played a contributory role. In such subjects, rechallenge with idelalisib has been possible and has not been associated with other severe adverse events.

In selected subjects who experience more complicated hepatic AEs, further workup may be warranted particularly in subjects who first experience a serum ALT/AST elevation ≥12 weeks from the start of study drug therapy, who have an elevation in serum bilirubin concentration or coagulation parameters, or who have other characteristics that suggest an atypical change in transaminase values. Hepatic AEs that require additional workup should be discussed with the Gilead Sciences Medical Monitor.

5.7.2. Gastrointestinal Events

Isolated cases of gastrointestinal inflammation (eg, stomatitis, colitis, cecitis) have been noted in subjects receiving idelalisib. Rare cases of gastrointestinal perforation have occurred, generally in the setting of occult carcinoma, mesenteric embolus or diverticular disease. Study treatment must be discontinued in subjects who experience bowel perforation.

For study subjects who develop severe abdominal pain the possibility of a bowel obstruction or perforation should be considered. Appropriate clinical and radiographic examination should be performed and supportive care or surgical intervention should be considered.

Subjects who have developed evidence of enteritis during idelalisib therapy have been successfully treated with antidiarrheals (eg, loperamide) and with enteric steroidal (eg, budesonide) or non-steroidal (eg sulfasalazine [Azulfidine®]) anti-inflammatory agents and have been able to continue or resume idelalisib.

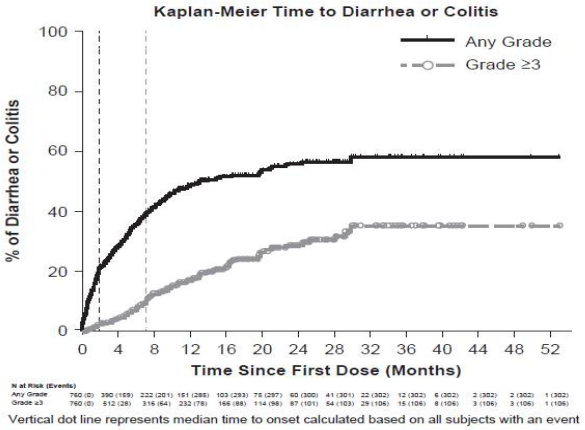
For study subjects who develop persistent diarrhea, causes related to concomitant medications or gastrointestinal infections such as *Clostridium difficile* (particularly for patients recently treated with broad spectrum antibiotics), *Shigella, Campylobacter, Yersinia* and CMV should be considered and treated if appropriate. Depending upon the clinical circumstances, endoscopy and biopsy, with bacterial and viral immunohistochemical (IHC) staining should be considered. For Grade ≥ 3 or persistent Grade 2 colitis or diarrhea without clear etiology (eg, *C. difficile* enterocolitis), endoscopy with biopsy is strongly recommended. See Section 6.1.8.9 for required testing. In the event that an infectious cause is not identified, an antimotility agent (eg, loperamide) may lessen symptoms and intervention with enteric steroidal (eg, budesonide) or non-steroidal (eg, sulfasalazine) anti-inflammatory agents should be considered. In such subjects, rechallenge with idelalisib at a lower dose level has resulted in recurrence of symptoms in some but not all subjects and has not been associated with other severe adverse events.

Investigation for Idelalisib Late Onset or Severe Diarrhea/Colitis

See CTCAE Version 4.03 for definitions of colitis and diarrhea.

Among idelalisib-treated patients who reported diarrhea or colitis, the median time to onset of any grade diarrhea or colitis was 1.9 months (range, 0.0–29.8), of Grade 1 or 2 was 1.5 months (range, 0.0–15.2), and of Grade 3 or 4 was 7.1 months (range, 0.5–29.8). Kaplan–Meier curves of time to onset of diarrhea or colitis are shown for all idelalisib-treated patients in Figure 5-1 {Coutre 2015}.

Figure 5-1. Kaplan-Meier Time to Diarrhea or Colitis



Idelalisib-associated severe diarrhea responds poorly to antimotility agents, however, median time to resolution ranged between 1 week and 1 month across trials following interruption of idelalisib treatment and, in some instances, initiation of corticosteroid treatment {Gilead Sciences Inc 2014}

5.7.2.1. Required Assessments for Diarrhea/Colitis

For any grade diarrhea/colitis, obtain history of onset and duration of diarrhea, including description of number of stools and stool composition (eg, watery, bloody, nocturnal), travel history, dietary changes and a medication review to identify possible diarrheogenic agents; perform physical examination including assessment for fever, dizziness, abdominal pain/cramping, and weakness (ie, evaluate for sepsis, bowel obstruction, dehydration).

5.7.2.2. Recommended Assessments for Diarrhea/Colitis

Differentiation between small-bowel and large-bowel diarrhea may be possible on a clinical basis. If unclear, consider upper and lower tract endoscopy with biopsy.

- Small bowel diarrhea is characterized by large volume diarrhea (more than 1 per day), possible associated dehydration weight loss and paraumbilical pain. Consider an endoscopic small-bowel biopsy and evaluate other etiologies such as celiac disease.

- Large-bowel diarrhea may present with lower pelvic pain, tenesmus, generally smaller stool volume with gross blood frquently found in the stool. Consider a colonoscopic evaluation and biopsy.

For Grade ≥ 3 or persistent Grade 2 colitis or diarrhea without clear etiology (eg, *C. difficile* enterocolitis), endoscopy with biopsy is strongly recommended. All biopsy samples should include immunohistochemistry and PCR for CMV, Adenovirus. If ileal biopsy is performed, consider Acid Fact Bacillus staining.

5.7.3. Dermatological Events

Subjects receiving idelalisib with ≥ Grade 3 rash have generally presented with a maculopapular rash on the trunk and extremities that is occasionally associated with fever and/or pruritus and responded to treatment with diphenhydramine and/or topical or oral corticosteroids.

For subjects who develop a Grade ≥ 3 rash for which an underlying etiology cannot be identified (eg, infection, co-suspect drug), study drug must be interrupted. Resumption of study drug should be considered once rash resolves.

Severe cutaneous reactions, including fatal events of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), have been reported in subjects receiving idelalisib.

Assessment of potential causal association between idelalisib and the occurrence of SJS or TEN has been confounded by the coadministration of antineoplastic agents (eg, bendamustine, rituximab) and/or other concomitant medications known to be associated with SJS or TEN (eg, allopurinol). If SJS or TEN is suspected, idelalisib must be discontinued and all coadministered medications associated with SJS or TEN should be interrupted, and the subject treated per institutional standards.

5.7.4. Pulmonary Events

Documented bacterial, fungal, viral, and pneumocystis pneumonias have been observed in patients receiving idelalisib, primarily in patients with CLL. Some study subjects receiving idelalisib alone or in combination have developed evidence of pneumonitis without documented pulmonary infection.

Given the potential for infectious or drug-related pulmonary adverse events, clinicians should be particularly observant for evidence of respiratory events in subjects participating in this trial. Subjects who describe pulmonary symptoms (eg, dyspnea on exertion, cough, shortness of breath); manifest a decline from baseline of ≥5% in oxygen saturation, or demonstrate evidence of pulmonary inflammation (eg, focal or diffuse interstitial pattern or ground-glass opacities on chest CT) should be evaluated. Potential bacterial, fungal, or viral etiologies should be assessed. Noninfectious etiologies such as pulmonary edema or thromboembolism should also be considered.

As appropriate for the clinical situation and culture results, subjects should be treated empirically or given specific antibiotics, antifungals, or antiviral agents for a cultured organism. Supportive care, including oxygen or mechanical ventilation, should be provided as necessary.

For subjects with suspected Grade 1 pneumonitis, withhold idelalisib until resolution to baseline. Upon resolution to baseline, idelalisib may be resumed at lower dose level or discontinued at investigator discretion. For subjects with suspected Grade ≥ 2 pneumonitis (eg, new onset or worsening of baseline cough, dyspnea, hypoxia and/or a diffuse interstitial pattern or ground-glass opacities on chest imaging without obvious infectious etiology), idelalisib must be discontinued permanently and therapy initiated as clinically appropriate.

5.7.5. Hematological and Immunological Events

In the Phase 1 experience with idelalisib in patients with NHL and CLL, subjects with Grade ≥3 neutropenia, anemia, and/or thrombocytopenia were enrolled to clinical trials. Decreased levels of neutrophil counts, hemoglobin, or platelet counts during idelalisib administration were largely due to minor fluctuations in these parameters among subjects with pre-existing hematological abnormalities due to disease or prior therapy. Thus, idelalisib did not appear to induce overt myelosuppression. Obvious patterns of drug-mediated reductions in circulating CD4+ lymphocyte counts or suppression of serum IgG levels were also not observed.

Treatment-emergent Grade 3 or 4 neutropenia events, including those accompanied by fever or infection, have occurred in subjects treated with idelalisib. All subjects should have their blood counts monitored at least every 2 weeks for the first 6 months of idelalisib treatment. For subjects who develop neutropenia Grade 3, blood counts must be monitored at least weekly until neutropenia is Grade ≤ 2. For subjects who develop neutropenia Grade 4, idelalisib must be interrupted and blood counts monitored at least weekly until neutropenia is Grade ≤ 2. Idelalisib dosing may be resumed at lower dose level when neutropenia is Grade ≤ 3. Neutropenia should be managed according to established clinical guidelines.

No modification of either study drug for changes in circulating CD4+ counts or Ig levels is planned.

5.7.6. Infectious Events

Patients with lymphoid cancers receiving idelalisib have developed serious and fatal infections during therapy. Opportunistic infections, most notably *Pneumocystis jirovecii* pneumonia (PJP) and CMV infection, have most frequently occurred within the first 6 months of treatment with idelalisib and are increased in the context of concurrent myelosuppressive therapy such as bendamustine.

Subjects must receive prophylaxis for PJP throughout the course of idelalisib treatment, and for 2 to 6 months after idelalisib treatment ends (see Section 5.8.1). Subjects must permanently discontinue idelalisib upon diagnosis of PJP.

Cytomegalovirus (CMV) surveillance for active disease (quantitative PCR or PP65 antigen) must be conducted approximately every 4 weeks throughout the course of idelalisib treatment. CMV viral load testing should be performed from the same specimen type whenever possible and caution should be exercised when comparing CMV viral load results across different testing centers. If unequivocal clinical or laboratory evidence of CMV infection is present, the subject must interrupt idelalisib treatment and undergo effective antiviral treatment according to established clinical guidelines. If the benefits of resuming idelalisib are judged to outweigh the risks, consider pre-emptive CMV therapy.

In high-risk subjects (history of recurrent infection, allogeneic transplant, treatment with alemtuzumab, hypogammaglobulinemia) other infection prophylaxis should be considered per consensus guidelines. Administration of intravenous immunoglobulin is permitted per standard institutional practice {Raanani 2009}. For subjects who develop an infection, appropriate medical therapy should be instituted in a timely manner.

5.7.7. Secondary Malignancies

Subjects receiving idelalisib for CLL or iNHL have developed pre-malignant and secondary malignant diseases, such as basal cell carcinoma, myelodysplastic syndrome, myeloproliferative disorders, and more aggressive lymphoid malignancies (eg, have had Richter transformation). Generally this has occurred in subjects who have received multiple previous lines of therapy and when idelalisib is combined with other therapies such as rituximab or bendamustine. The specific association of the therapeutic agents with these types of events has not been determined.

5.7.8. Ultraviolet Exposure

In vitro studies indicate enhanced cytotoxicity when embryonic murine fibroblasts treated with GS-563117 (the major metabolite of idelalisib) are simultaneously exposed to ultraviolet light. While nonclinical findings suggest the hypothetical potential for phototoxicity in humans, available clinical data do not reveal a photosafety concern. Although specific clinical correlates for these nonclinical data are not available, investigators and study subjects should be observant for the possibility that study participants may have exaggerated sunburn reactions (eg, burning, erythema, exudation, vesicles, blistering, edema) involving areas of skin exposed to ultraviolet light.

5.7.9. Pregnancy, Lactation, and Reproduction

Idelalisib has induced embryo lethality and teratogenicity when administered to pregnant female rats at maternally toxic doses. However, definitive reproductive toxicology studies in animals have not yet been performed and the specific effects of idelalisib on human embryogenesis or fetal development are unknown. Whether idelalisib is excreted in human breast milk is unknown. General toxicology studies of idelalisib in rats and dogs indicated dose-dependent reductions in testicular weights, with persistent minimal to mild degeneration of the seminiferous tubules and decreased spermatozoa in rats and hypospermatogenesis in dogs. The implications of these testicular changes for animal or human fertility are unknown.

Given the potential the risks to a fetus or infant as a result of exposure to idelalisib, women of reproductive potential entering this study must have a negative serum pregnancy test at baseline and must not be breastfeeding. Males and females of childbearing potential should abstain from sexual intercourse or use an effective form of contraception (see Appendix 5). If a female study participant becomes pregnant or decides to breastfeed during the course of the study, all study therapy (idelalisib//BI836826) must be discontinued.

5.7.10. *Pneumocystis jirovecii* Pneumonia Prophylaxis

Trimethoprim sulfamethoxazole is rated a Pregnancy Category C agent. In rats, oral doses of 533 mg/kg or 200 mg/kg produced teratologic effects manifested mainly as cleft palates. One survey found no congenital abnormalities in 35 children whose mothers had received oral sulfamethoxazole and trimethoprim at the time of conception or shortly thereafter. Because sulfamethoxazole and trimethoprim may interfere with folic acid metabolism it should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Dapsone is rated a Pregnancy Category C agent. Extensive, but uncontrolled experience and 2 published surveys on the use of Dapsone in pregnant women have not shown that Dapsone increases the risk of fetal abnormalities if administered during all trimesters of pregnancy or can affect reproduction capacity. Because of the lack of animal studies or controlled human experience, Dapsone should be given to a pregnant woman only if clearly needed. Dapsone is excreted in breast milk in substantial amounts. Hemolytic reactions can occur in neonates. Because of the potential for tumorgenicity shown for Dapsone in animal studies a decision should be made whether to discontinue nursing or discontinue Dapsone, taking into account the importance of drug to the mother.

Atovaquone is rated a Pregnancy Category C agent. Atovaquone is teratogenic and did not cause reproductive toxicity in rats at plasma concentrations up to 2 to 3 times the estimated human exposure. Atovaquone can cause maternal toxicity in rabbits at plasma concentrations that were approximately one half the estimated human exposure. Mean fetal body lengths and weights were decreased and there were higher numbers of early resorption and post-implantation loss per dam. It is not clear whether these effects are caused by atovaquone directly or are secondary to maternal toxicity. Concentrations of atovaquone in rabbit fetuses averaged 30% of the concurrent maternal plasma concentrations. There are no adequate and well-controlled studies in pregnant women. Atovaquone should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. It is not known whether atovaquone is excreted into human milk. Because many drugs are excreted into human milk, caution should be exercised when Atovaquone is administered to a nursing woman. In a rat study, atovaquone concentrations in the milk were 30% of the concurrent atovaquone concentrations in the maternal plasma.

Aerosolized Pentamidine (NebuPent) is a Pregnancy Category C agent. There are no adequate and well controlled studies of NebuPent in pregnant women. One literature report indicated that intravenously administered pentamidine in pregnant rats at 4 mg/kg/day was embryolethal; however, teratogenicity was not observed in this study. It is unknown whether pentamidine administered via the aerosolized route crosses the placenta at clinically significant concentrations. It is not known whether NebuPent can cause fetal harm when administered to a pregnant woman. NebuPent should be given to a pregnant woman only if clearly needed. It is not known whether NebuPent is excreted in human milk. NebuPent should not be given to a nursing mother unless the potential benefits are judged to outweigh the unknown risks.

5.7.11. Risk of Hepatitis B Reactivation

Hepatitis B Virus (HBV) reactivation can occur in patients treated with anti-CD20 antibodies, and this risk may be assumed to apply also to anti-CD37 antibodies. Subjects whose Screening labs show anti-hepatitis B core antibody (HBc antibody) positivity, but have negative HBV DNA by PCR are eligible to enroll on this study. Although some subjects who are HBc antibody positive with negative PCR may have had passive transfer of antibody from intravenous IgG, it cannot be known for certain that any such subject did not have natural HBV infection. Therefore, all subjects who are HBc antibody positive at screening should receive Hepatitis B prophylaxis with lamivudine, entecavir, or tenofovir per National Comprehensive Cancer Network (NCCN) infection guidelines. These subjects will also be monitored for potential HBV reactivation (manifest as detectable HBV DNA by quantitative PCR). Subjects will be tested monthly,

starting at Week 8, for the duration of BI 836826 therapy and every 3 months thereafter for 1 year from the last dose of BI 836826 during study participation. Following the completion of study participation, monitoring for HBV reactivation will be conducted per standard of care, at the discretion of the investigator. If there is evidence of HBV reactivation, immediately discontinue BI 836826 and idelalisib.

5.7.12. Further Safety Information

Further safety information regarding the study drug may be found in the idelalisib and BI 836826 IBs.

5.8. Prior and Concomitant Medications

5.8.1. Idelalisib

Subjects must receive trimethoprim-sulfamethoxazole or other established prophylaxis for PJP throughout the course of idelalisib treatment. Prophylaxis will continue for a minimum period of 2-6 months after idelalisib discontinuation and until the CD4+ T-cell count is documented to be >200 cells/mcL. The duration of prophylaxis should be based on clinical judgment and may take into account risk factors such as concomitant corticosteroid treatment and prolonged neutropenia after idelalisib treatment ends.

5.8.2. BI 836826

5.8.2.1. Infusion-Related Reactions

Infusion-Related Reactions are related to cytokine-release resulting from the interaction of antibody with antigen on circulating hematopoietic cells, with increasing risk at higher infusion dose rates or increments. Pre-medication is mandatory 30-120 minutes prior to the administration of BI 836826 to mitigate the risk for IRR, see Table 5-4. In case a contra-indication for 1 of the drug exists, the drug may be replaced or omitted.

If BI 836826 has been well tolerated without signs of IRRs during the sixth or a later administration (ie, in Week 8 or later), the glucocorticoid dose may be stepwise reduced during subsequent infusions while the other drugs are maintained. If BI 836826 is tolerated without IRR after pre-medication according to Table 5-4 Level -2, the investigator may individually decide whether to administer pre-medication for subsequent treatments and which of the recommended drugs to use.

If IRRs are observed at infusions with reduced pre-medication, the pre-medication triplet at doses as outlined for the first 4 infusions should continue to be used for all administrations.

Table 5-4. Premedication for BI 836826

Week	Subjects Requiring Premedication	Premedication	Completion Prior to BI 836826
2-8	all subjects	Analgesic/Antipyretic PO or IV [1] Antihistamine PO or IV [2] Glucocorticoid IV, equivalent to prednisolone 100 mg	60-120 minutes
10-46	all subjects with IRR in the previous infusion or with ALC ≥ 25000/µL	Analgesic/Antipyretic PO or IV [1] Antihistamine PO or IV [2] Glucocorticoid IV, equivalent to prednisolone 100 mg	60-120 minutes
10-46	subjects without IRR in previous infusion and ALC < 25000/µL	Premedication Level -1: Analgesic/Antipyretic PO or IV [1] Antihistamine PO or IV [2] Glucocorticoid IV, equivalent to prednisolone 50 mg	30-120 minutes
10-46	subjects with ALC < 25000/µL and without IRR and premedication at level -1 at previous infusion	Premedication Level -2: Analgesic/Antipyretic PO or IV [1] Antihistamine PO or IV [2] Glucocorticoid IV, equivalent to prednisolone 25 mg	30-120 minutes
12-46	subjects 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 1000 mg
2. equivalent to diphenhydramine 50 mg IV

5.8.2.2. Tumor Lysis Syndrome

Subjects 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 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 (eg, rasburicase) starting ≥ 24 hours prior to the first infusion should be considered. Subjects should continue to receive repeated prophylaxis with allopurinol and adequate hydration prior to each subsequent infusion, if deemed appropriate by the investigator. Older and frail subjects will need special individualized care in fluid management, as 3 liters per day may not be tolerated. Rasburicase may be particularly indicated in such subjects. For all subjects, electrolytes should be monitored and corrected, fluid balance and renal function should be monitored, and supportive care should be administered, including dialysis as indicated.

5.8.2.3. Hepatitis B

All subjects who are HBc antibody positive at screening should receive Hepatitis B prophylaxis. Refer to Section 5.7.11 for specific treatment recommendations.

5.8.3. Anticancer or Experimental Therapies Other than Idelalisib or BI 836826

No other anticancer therapies (including systemic chemotherapy, radiation, antibody therapy, immunotherapy, or other experimental therapies) of any kind are permitted while the subject is participating in the study. Subjects are not allowed to participate concurrently in any other therapeutic clinical study.

5.8.4. Granulocyte Colony-Stimulating Factors and Erythropoietin

Granulocyte-macrophage colony-stimulating factors (GM-CSF) should not be administered given the potential for GM-CSF-related inflammatory symptoms. The use of supportive care agents such as Granulocyte colony-stimulating factor (G-CSF) agents or erythropoietic agents are permitted in compliance with regional prescribing information.

5.8.5. Corticosteroids

Subjects may receive topical or inhaled corticosteroids while on study. The use of systemic corticosteroids is discouraged because their potential antineoplastic activity in subjects with CLL may confound interpretation of idelalisib-mediated antitumor effects. However, subjects who develop severe or life-threatening conditions that may be alleviated by systemic corticosteroid therapy are permitted to receive such drugs and are not required to discontinue study participation. Systemic corticosteroids in addition to premedication should be used as indicated to treat infusion related reactions. Hydrocortisone for prevention or treatment of IRRs is not recommended as it has not been effective in reducing the rate of infusion reactions with other Fc-engineered antibodies.

5.8.6. Drug-Drug Interactions

Consistent with nonclinical data indicating that GS-563117(the major metabolite of idelalisib) is a reversible and time-dependent inhibitor of CYP3A, coadministration with idelalisib resulted in higher midazolam systemic exposures, indicating that idelalisib is a strong inhibitor of CYP3A. Accordingly, coadministration of CYP3A substrates with idelalisib may result in an increase in their systemic exposures (eg, certain antiarrhythmics, calcium channel blockers, benzodiazepines, HMG-CoA reductase inhibitors, phosphodiesterase-5 [PDE5] inhibitors, and warfarin). Avoid coadministration of idelalisib with drugs that are narrow therapeutic index CYP3A substrates (eg, alfentanil, cyclosporine, sirolimus, tacrolimus, cisapride, pimozide, fentanyl, quinidine, ergotamine, dihydroergotamine, astemizole, and terfenadine).

Data indicate that when coadministered with rifampin, a highly potent inducer of CYP3A, idelalisib exposures are approximately 75% lower. Coadministration of potent inducers of CYP3A (rifampin, carbamazepine, phenytoin, and St. John’s wort) with idelalisib should be avoided.

5.9. Investigational Medicinal Product Accountability (Idelalisib and BI 836826)

The investigator is responsible for ensuring adequate accountability of all used and unused study drug containers (idelalisib bottles and BI 836826 vials). This includes acknowledgement of receipt of each shipment of study drug (quantity and condition).

Study drug accountability records for idelalisib and BI 836826 will be provided to each study site to:

- Record receipt into pharmacy: date, quantity, and lot and/or bottle number(s) received.
- Record dispensing from the pharmacy: date, subject number, subject initials, and lot and/or bottle number dispensed.
- Record return: date, quantity of used and unused study drug/containers, along with the initials of the person recording the information.

Institution specific accountability records may be used if they capture the same information listed above.

5.9.1. Investigational Medicinal Product Return and Disposal (Idelalisib and BI 836826)

5.9.1.1. Idelalisib

Used and unused idelalisib and containers should be retrieved at the end of each dispensing interval. The quantity of idelalisib and the date returned by the subject should be recorded in the study drug accountability records. All idelalisib and containers returned by the subject should be retained for review by the study site monitor prior to destruction.

5.9.1.2. BI 836826

Used and unused BI 836826 and containers should be retrieved at the end of each infusion. The quantity of used/unused BI 836826 and containers should be recorded in the study drug accountability records. All BI 836826 and containers remaining after the infusion should be retained for review by the study site monitor prior to destruction.

6. STUDY PROCEDURES

This study has been terminated with 2 subjects enrolled. Subjects may remain on study through approximately Week 50 (to include 30-Day Follow-up after last dose of BI 836826). Study procedures have been modified, and the subjects enrolled will be assessed for safety only.

The study procedures to be conducted for each subject enrolled in the study are presented in tabular form in Appendix 2 and described in the text that follows.

The investigator must document any deviation from protocol procedures and notify the sponsor or contract research organization (CRO).

Safety and tolerability assessments will include regular monitoring of AEs, changes from baseline in laboratory variables, physical examinations, vital signs, and special safety assessments such as ECGs.

From the time of obtaining informed consent through the first administration of investigational medicinal product, record all SAEs, as well as any non-serious AEs related to protocol-mandated procedures, on the adverse events electronic Case Report Form (eCRF). All other untoward medical occurrences observed during the Screening period, including exacerbation or changers in medical history, are to be captured on the medical history eCRF. See Section 7 for additional details.

6.1. Description of Study Procedures

During the study, following Days 8 and 9 all visits must be performed within a period of ±1 day through Week 6, then ±2 days through Week 18, then ± 3 days through Week 46 then ±7 days through 30-Day Follow-up/End of Study.

6.1.1. Informed Consent

All subjects must sign and date the Independent Review Board/Independent Ethics Committee (IRB/IEC) approved informed consent form before any study procedures are performed except where noted in the protocol in relation to standard of care procedures. CCI [redacted]

6.1.2. Subject Enrollment and Treatment Assignment

Subject eligibility will be established at the conclusion of the Screening evaluations. In Phase 2, subjects will be randomized to receive either the highRP2D or lowRP2D and the unique subject enrollment identifier will be assigned by the IWRS.

6.1.3. Medical & Medication History

A complete medical and surgical history will be obtained prior to enrollment and recorded on the eCRF, including a history of the subject's CLL.

A history of medications taken within the 3 months prior to Screening and during the Screening period will be obtained prior to enrollment and recorded on the eCRF.

6.1.4. Physical Examination

The physical examination (PE) will be performed by a physician, physician's assistant or nurse practitioner qualified to perform the assessment.

At Screening, a complete PE will be performed including height, body weight, and clinical signs, and symptoms. Height and body weight assessments will be performed per institutional practice and will be recorded in the eCRF. Physical examination findings during the Screening period will either be reported as medical history or adverse events based on the requirements in Section 7.1.1.

At subsequent study visits, the PE will include body weight and assessment of disease related clinical signs and symptoms.

More frequent examinations may be performed at the investigator's discretion, if clinically indicated.

6.1.5. Vital Signs

Vital signs will include pulse, systolic and diastolic blood pressure, and body temperature. Vital signs should be collected per institutional practice.

6.1.6. Eastern Cooperative Oncology Group Performance Status

Performance status will be scored using the ECOG criteria (see Appendix 3).

6.1.7. Electrocardiogram Assessment

A standard 12-lead ECG will be performed at Screening per standard institutional practice, at week 26 and 30-Day Follow-Up/End of Study, and whenever clinically indicated at the discretion of the Investigator.

6.1.8. Laboratory Assessments

Due to the early study termination, several blood samples are no longer being collected, however the subjects enrolled will continue to be assessed for safety. Refer to the modified Table 6-1 *and* Appendix 2 *for changes to Laboratory Assessments. Certain subsections in Section 6.1.8 may no longer apply.*

Blood samples for laboratory assessments will be sent to a central/local laboratory for analysis. Analytes to be tested are listed in Table 6-1. Laboratory samples will be collected and analyzed on the scheduled day as specified in Appendix 2, even if study medication is being held. More frequent examinations may be performed at the investigator's discretion if medically indicated. In addition to the required central laboratory tests, laboratory tests may be performed locally at the discretion of the investigator to facilitate treatment decisions.

Any samples collected as specified in Appendix 2 may be analyzed for any tests necessary to ensure subject safety. Specific instructions for processing, labeling, and shipping samples will be provided in a central laboratory manual.

When abnormal laboratory values or test results constitute an AE, they must be recorded on the eCRF AE page.

Table 6-1. Analytes

Chemistry	Urinalysis	Hematology	Other Analytes
Albumin	Dipstick	RBC	Genotyping
Alkaline phosphatase	pH	Hematocrit	Serum β-hCG pregnancy test [b]
ALT/SGPT	Occult blood	Hemoglobin	Urine pregnancy test [be]
AST/SGOT	Protein	Platelets	β-2 microglobulin
BUN	Glucose	WBC	Immune monitoring[e]:
Calcium	Ketones	Differential	· Lymphocyte subset panel
Chloride	Bilirubin	Neutrophils	· Quantitative immunoglobulins: IgG, IgM, IgA
Cholesterol	Urobilirubin	Bands/stabs	· Total hemolytic complement (CH50)
Creatinine [a]	Nitrite	Eosinophils	Hepatitis B surface antigen
GGT	Leukocyte esterase	Basophils	Hepatitis B core antibody
Glucose		Lymphocytes	Hepatitis B DNA[e]
LDH		Monocytes	Hepatitis C antibody
Phosphorus	Microscopic [c]	**Coagulation**	Hepatitis C viral RNA
Potassium	WBC/HPF		HIV antibody
Sodium	RBC/HPF	PT /INR	CMV DNA
Total bilirubin		aPTT	MRD[e]
Total protein			Biomarkers [d,e]
Triglycerides			Plasma concentration of idelalisib and BI 836826 [e]
Uric acid			Anti-drug Antibodies

ANC = absolute neutrophil count; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CMV=cytomegalovirus; HiB=Haemophilus influenza Type B; LDH = lactate dehydrogenase; MRD=minimal residual disease; RBC = red blood cell; WBC = white blood cell
Note: Additional components, abnormal, and/or atypical cells will also be reported if present
a Estimated creatinine clearance/glomerular filtration rate will be calculated based on the Cockroft-Gault formula
b If applicable.
c To be performed only if the dipstick results are abnormal
d See Section 3.7
e These tests have been removed in Amendment 4. The one female subject enrolled is not of child bearing potential. CD4 monitoring will continue. The 2 subjects enrolled were negative for HBc antibody.

6.1.8.1. Chemistry and Hematology

Chemistry and hematology will be obtained a minimum of 3 times in the first week following the first 50% dose of BI 836826, and once after the first full dose of BI 836826, then a minimum of weekly x 6 weeks, then prior to each BI 836826 dose.

6.1.8.2. Immune Monitoring

Immune monitoring will be conducted at Baseline prior to the first dose of idelalisib, Weeks 4, 12, 22, 38, 46, and at 30-Day Follow-up/ End of Study. With the implementation of Amendment 4, immune monitoring will include CD4 quantitation only.

6.1.8.3. Bone Marrow Aspirate and/or Biopsy

In both the Phase 1b and Phase 2 portions of the study, a bone marrow biopsy and aspirate may be performed at investigator discretion to assess extent of disease involvement and bone marrow cellularity at Screening.

Post-screening, a bone marrow biopsy and aspirate will be performed in the following circumstances:

- For MRD testing:
  - within 30 days of the first MRD negativity in peripheral blood
  - at Week 50
- To confirm CR or Progressive Disease (PD):
  - throughout study as indicated by CT/MRI and hematologic parameters

CCI [redacted]

In the Phase 2 portion of the study only, a bone marrow biopsy and aspirate will be performed at Screening and at Weeks 14, 26, 38, and 50 to confirm the presence of quantifiable CLL for subjects without at least 1 LN $\geq$ 2 cm confirmed by the IRC at screening.

6.1.8.4. Pregnancy Test

All females of childbearing potential (see Appendix 5) will have a serum pregnancy test at Screening. Additional pregnancy tests will be performed as specified in Appendix 2.

CCI [redacted]

6.1.8.6. Immunogenicity Testing

Blood samples will be collected for anti-drug antibodies (ADA) against BI 836826 as specified in Appendix 2. Details of sample collection, preparation, storage and shipment are described in the Laboratory Manual.

6.1.8.7. CMV Monitoring

CMV surveillance for active disease (quantitative PCR or PP65 antigen) must be conducted approximately every 4 weeks throughout the course of idelalisib treatment. See Section 5.7.6 for testing requirements.

6.1.8.8. Hepatitis B reactivation Monitoring

All subjects who are HBc antibody positive at screening will be monitored for potential HBV reactivation. See Section 5.7.11 for testing requirements.

6.1.8.9. Required Evaluations for Gastrointestinal Events/Colitis

For Grade $\geq$ 2 colitis and diarrhea (unless clinical diagnosis is established from medical history and physical examination), the following testing is required:

- Stool culture for routine pathogens (Salmonella, Shigella, Campylobacter species, *Clostridium difficile* toxin, Rotavirus, Cytomegalovirus (CMV), Adenovirus)
- Stool for Ova and Parasites (*Cryptosporidium parvum*, *Isospora belli*, *Enterocytozoon bieneusi*, *Septata intestinalis*, Strongyloides, Microsporidia, *Entamoeba histolytica*, Cyclospora, Giardia antigen

CCI [redacted]

[redacted]

CCI [redacted]

[redacted]

6.2. Disease Assessments

The investigator will assess the overall CLL response at timepoints specified in Appendix 2. This will be based on modified IWCLL criteria (Appendix 4) and will require consideration of the CBC. Physical exam and any imaging to be performed per standard of care.

6.2.1. CT Scan/MRI

With the early termination of this study, CT/MRI scans have been discontinued for the rest of the study. Imaging assessments should follow standard of care per investigator discretion.

Subjects will be imaged for neck, chest, abdomen, and pelvis with either contrast-enhanced CT or gadolinium-enhanced MRI. If MRI is chosen, subjects will have an MRI of neck, abdomen and pelvis, but will need a non-contrast enhanced CT of the chest. Chest x-ray, ultrasound, endoscopy, laparoscopy, positron-emission tomography (PET), radionuclide scans, or tumor markers will not be considered for response assessment.

For radiographic evaluations, the same method of assessment and the same technique (eg, scan type, scanner, subject position, dose of contrast, injection/scan interval) should be used to characterize each identified and reported lesion at baseline and during the study and follow-up. Furthermore, the use of IV contrast should be consistent across time points. In the event that the Screening/baseline CT scan of the neck, chest, abdomen and pelvis is performed without IV contrast, follow-up time points should be performed with IV contrast. Subjects who develop an allergy to CT contrast dye may have subsequent scans without contrast. All relevant clinical and radiographic information required to make each assessment must be made available for source verification and for submission to the IRC (see Section 8.12).

During the Phase 2 portion of the study, the IRC will evaluate the Screening CT/MRI to assess for measurable lesions and subjects who do not have a lesion ≥ 2 cm confirmed by IRC will need a bone marrow biopsy demonstrating quantifiable CLL per inclusion criterion 4).

CT/MRIs performed as standard of care prior to signing the ICF and within 42 days of enrollment (Phase 1b) or randomization (Phase 2) may be used to fulfill the Screening requirement. If this option is used, the scans must follow the same conditions set above.

Investigators will assess the status of each subject's CLL using the criteria in Appendix 4. If CLL progression is suspected, the IRC will be notified and will review radiographic and pertinent clinical data in order to provide expert interpretation (see Section 8.12). The findings of the IRC will be considered primary for analyses of efficacy endpoints

6.2.2. Minimal Residual Disease

With the implementation of Amendment 4, MRD assessments will not be performed.

Minimal residual disease will be evaluated in peripheral blood and/or bone marrow, depending on the time point of the assessment. MRD assessments will be done by multi-parameter flow cytometry with a sensitivity of at least 1 leukemic cell per 10,000 leukocytes (10^{-4} malignant cells), the level defined as MRD negative status. The laboratory procedures, instrument settings and antibody panels will be fully standardized in order to achieve maximally comparable results among the different central labs.

Minimal residual disease will be assessed in peripheral blood at Screening, Weeks 14, 26, 38, 50 and then every 16 weeks through End of Study at the same time as imaging studies and overall disease assessment.

Minimal residual disease will be assessed in bone marrow at Week 50. In addition, if a peripheral specimen is MRD negative at any time, a marrow specimen should be obtained within 30 days following the achievement of peripheral blood MRD negativity at any time point. Once marrow MRD negativity is achieved, the subject will be followed with peripheral blood sampling only, according to the schedule of procedures.

6.3. Screening

The Screening date is defined as the date the subject signs the informed consent form. The Screening period starts once a subject has provided written informed consent to participate in the study, and ends on the day the subject is enrolled (Phase 1b) or randomized (Phase 2). Screening evaluations will be performed within 28 days of confirming eligibility for participation in the study (unless specifically noted below or for a particular procedure). CT/MRIs performed as standard of care, prior to signing the ICF, and within 42 days of randomization, may be used to fulfill this Screening requirement.

Screening tests and procedures indicated in Appendix 2 will be performed to determine eligibility. Please refer to the IWRS study reference manual for the process of subject number assignment.

Subjects failing to meet eligibility or complete the initial Screening will be registered as a Screen Failure and permitted to rescreen 1 time. Laboratory assessments may be repeated 1 time during the Screening period for confirmation prior to registering the subject as a Screen Failure. Rescreening requirements are the same as the Screening requirements. Assessments from the first Screening attempt that fall within the allowed timeframes do not need to be repeated.

From the time of obtaining informed consent through the first administration of investigational medicinal product, record all SAEs, as well as any AEs related to protocol-mandated procedures on the AE eCRF. All other untoward medical occurrences observed during the Screening period, including exacerbation or changes in medical history are to be captured on the medical history eCRF. See Section 7 for additional details.

6.4. Enrollment

This study was terminated in Phase 1b and therefore Phase 2 will not occur.

It is the responsibility of the investigator to ensure that each subject is eligible for the study before enrollment.

During the Phase 2 portion of the study, a site must confirm eligibility by IRC review of imaging and, if applicable, bone marrow for quantifiable CLL prior to randomizing the subject. The IWRS will assign study medication at the time of randomization.

The site will train the subject on the dosing schedule for each medication at the time of dispensing. Day 1 for the purposes of calculating future visits is defined as the date of the first dose of any study drug. The subject's baseline status for the study is defined by tests and procedures done prior to receipt of any study drug. Some of these tests are performed during the Screening period and some are performed after enrollment but prior to the first dose of any study drug. The following laboratory tests are performed at Week 1, Day 1 after enrollment and prior to receipt of any study drug (refer to Appendix 2):

- Urine pregnancy test
- Physical exam and vital signs
- Chemistry
- β-2 microglobulin
- Hematology
- [redacted]
- [redacted]

6.5. Treatment and Post-Treatment Period Assessments

Study days will be determined based on the first administration of idelalisib on Week 1, Day 1. All subjects will receive 7 days of idelalisib monotherapy followed by a period of combination therapy with idelalisib plus intermittent BI 836826 infusions. After the final BI 836826 infusion subjects will continue to receive idelalisib monotherapy for 4 weeks, through completion of Week 50 assessments.

6.6. Criteria for Discontinuation from Treatment or Study

6.6.1. Criteria for Discontinuation of Study Drug

Study drug may be discontinued in the following instances, in consultation with the Gilead Medical Monitor:

- Disease progression

- Initiation of non-study specific anti-cancer therapy in the absence of progression
- If, in the investigator's opinion, it is not in the subject's best interest to continue.
- Pregnancy or breastfeeding begins during the study
- Subject non-compliance
- Subject request to discontinue study drug, for any reason
- Any subject is unable to tolerate a second rechallenge for the same AE
- Toxicity for which the protocol specifies discontinuation of study drug
- Any subject whose benefit-risk profile is not deemed positive by the investigator must discontinue study drug
- During the combination therapy period (through Week 46), if either study drug is permanently discontinued, the other study drug should also be permanently discontinued

End of Treatment (EOT) assessments as specified in Appendix 2 will be performed when a subject permanently discontinues both BI 836826 and idelalisib.

Subjects who permanently discontinue study drug for a reason other than disease progression should continue with disease assessments per the schedule of procedures until disease progression, study participation has ended, or another anticancer or experimental therapy is initiated (see Appendix 2).

6.6.2. Criteria for Discontinuation from Study

Discontinuation from the study may occur in the following instances:

- Disease progression
- Initiation of non-study specific systemic anti-cancer therapy in the absence of progression
- If, in the investigator's opinion, and in consultation with Gilead Sciences, it is determined not to be in the subject's best interest to continue.
- Pregnancy begins during the study
- Death
- Discontinuation of the study at the request of Gilead, a regulatory agency, or an institutional review board or independent ethics committee (IRB/IEC) occurs

- Withdrawal of consent
- Subject is lost to follow-up

If a subject discontinues the study for reasons other than withdrawal of full consent, lost to follow-up, or death, the subject will complete a 30-Day Follow-up/End of Study visit (see Section 6.7). Note that pregnancies are monitored until the conclusion of the pregnancy even after discontinuation from the study (see Section 7.7.2.1).

6.7. 30-Day Follow-up/End of Study Visit

A 30-Day Follow-up/End of Study assessment will be performed 30 days following the last dose of BI 836826 (no later than Week 50) however, it may be waived for subjects who have permanently discontinued study drug and have had a study visit > 30 days after the last dose.

6.8. Unscheduled Visits

Unscheduled visits may occur at any time while the subject is enrolled on study. Vital signs, laboratory assessments, ECG, physical examination, radiographic assessments, and bone marrow aspiration/biopsy may be conducted at these visits. Data relevant to the study generated during an unscheduled visit will be collected on the eCRF.

7. ADVERSE EVENTS AND TOXICITY MANAGEMENT

7.1. Definitions of Adverse Events, Adverse Reactions, and Serious Adverse Events

7.1.1. Adverse Events

An AE is any untoward medical occurrence in a clinical study subject administered a medicinal product, which does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and/or unintended sign, symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. AEs may also include pre- or post-treatment complications that occur as a result of protocol specified procedures, lack of efficacy, overdose, drug abuse/misuse reports, or occupational exposure. Preexisting events that increase in severity or change in nature during or as a consequence of participation in the clinical study will also be considered AEs.

An AE does not include the following:

- Medical or surgical procedures such as surgery, endoscopy, tooth extraction, and transfusion. The condition that led to the procedure may be an adverse event and must be reported.
- Pre-existing diseases, conditions, or laboratory abnormalities present or detected before the Screening visit that do not worsen
- Situations where an untoward medical occurrence has not occurred (e.g., hospitalization for elective surgery, social and/or convenience admissions)
- Overdose without clinical sequelae (see Section 7.7.1)
- Any medical condition or clinically significant laboratory abnormality with an onset date before the consent form is signed and not related to a protocol-associated procedure is not an AE. It is considered to be pre-existing and should be documented on the medical history eCRF.

7.1.2. Serious Adverse Events

An SAE is defined as an event that, at any dose, results in the following:

- Death
- Life-threatening (Note: The term “life-threatening” in the definition of “serious” refers to an event in which the subject 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 it were more severe.)
- In-patient hospitalization or prolongation of existing hospitalization

- Persistent or significant disability/incapacity
- A congenital anomaly/birth defect
- A medically important event or reaction: such events may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent 1 of the other outcomes constituting SAEs. Medical and scientific judgment must be exercised to determine whether such an event is a reportable under expedited reporting rules. Examples of medically important events include intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; and development of drug dependency or drug abuse. For the avoidance of doubt, infections resulting from contaminated medicinal product will be considered a medically important event and subject to expedited reporting requirements.

7.1.2.1. Protocol-Specific Serious Adverse Event Instructions

The following events related to the disease under study, if assessed as unrelated to study drug, will not be considered SAEs:

- Progression of CLL
- Death related to progression of CLL

Disease progression and death from disease progression should be reported as SAEs by the investigator only if it is assessed that the investigational medicinal product (IMP)(s) caused or contributed to the disease progression (i.e., by a means other than lack of effect). Unrelated disease progression should be captured on the eCRF.

These events will be reported, as appropriate, in the final clinical study report and in any relevant aggregate safety reports.

7.1.3. Clinical Laboratory Abnormalities and Other Abnormal Assessments as Adverse Events or Serious Adverse Events

Laboratory abnormalities without clinical significance are not recorded as AEs or SAEs. However, laboratory abnormalities (eg, clinical chemistry, hematology, and urinalysis) that require medical or surgical intervention or lead to IMP interruption, modification, or discontinuation must be recorded as an AE, as well as an SAE, if applicable. In addition, laboratory or other abnormal assessments (eg, electrocardiogram, x-rays, vital signs) that are associated with signs and/or symptoms must be recorded as an AE or SAE if they meet the definition of an AE or SAE as described in Sections 7.1.1 and 7.1.2. If the laboratory abnormality is part of a syndrome, record the syndrome or diagnosis (eg, anemia), not the laboratory result (ie, decreased hemoglobin).

For specific information on handling of clinical laboratory abnormalities in this study, please refer to Section 7.5.

7.2. Assessment of Adverse Events and Serious Adverse Events

The investigator or qualified subinvestigator is responsible for assessing AEs and SAEs for causality and severity, and for final review and confirmation of accuracy of event information and assessments.

7.2.1. Assessment of Causality for Study Drugs and Procedures

The investigator or qualified subinvestigator is responsible for assessing the relationship to each study drug independently, using clinical judgment and the following considerations:

- **No:** Evidence exists that the adverse event has an etiology other than the IMP. For SAEs, an alternative causality must be provided (eg, pre-existing condition, underlying disease, intercurrent illness, or concomitant medication)

- **Yes:** There is reasonable possibility that the event may have been caused by the investigational medicinal product

It should be emphasized that ineffective treatment should not be considered as causally related in the context of adverse event reporting.

The relationship to study procedures (eg, invasive procedures such as venipuncture or biopsy) should be assessed using the following considerations:

- **No:** Evidence exists that the adverse event has an etiology other than the study procedure

- **Yes:** The adverse event occurred as a result of protocol procedures, (eg, venipuncture)

7.2.2. Assessment of Severity

The severity of AEs will be graded using the CTCAE, Version 4.03 in study manual and available at

http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

For each episode, the highest severity grade attained should be reported.

If a CTCAE criterion does not exist, the investigator should use the grade or adjectives: Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), Grade 4 (life-threatening), or Grade 5 (fatal) to describe the maximum intensity of the AE. For purposes of consistency with the CTCAE, these intensity grades are defined in Table 7-1.

Table 7-1. Grading of Adverse Event Severity

Grade	Adjective	Description
Grade 1	Mild	Sign or symptom is present, but it is easily tolerated, is not expected to have a clinically significant effect on the subject's overall health and well-being, does not interfere with the subject's usual function, and is not likely to require medical attention.
Grade 2	Moderate	Sign or symptom causes interference with usual activity or affect clinical status, and may require medical intervention.
Grade 3	Severe	Sign or symptom is incapacitating or significantly affects clinical status and likely requires medical intervention and/or close follow-up.
Grade 4	Life-threatening	Sign or symptom results in a potential threat to life.
Grade 5	Fatal	Sign or symptom results in death.

The distinction between the seriousness and the severity of an AE should be noted. Severe is a measure of intensity; thus, a severe reaction is not necessarily a serious reaction.

7.3. Investigator Requirements and Instructions for Reporting Adverse Events and Serious Adverse Events to Gilead

7.3.1. Requirements for Collection Prior to Study Drug Initiation

After the subject has signed the informed consent form, but prior to initiation of study medication, the following types of events should be reported on the eCRF:

- All SAEs, and AEs related to protocol-mandated procedures

7.3.2. Adverse Events

Following initiation of study medication, collect all AEs, regardless of cause or relationship, until 30 days after last administration of idelalisib or BI 836826 (whichever is discontinued last), and report in the eCRF database as instructed.

All AEs should be followed up until resolution or until the adverse event is stable, if possible. Gilead Sciences may request that certain AEs be followed beyond the protocol defined follow up period.

7.3.3. Serious Adverse Events

All SAEs, regardless of cause or relationship, which occur after the subject first consents to participate in the study (ie, signing the informed consent) and throughout the duration of the study, including the protocol-required post treatment follow-up period, must be reported to the eCRF database and Gilead Drug Safety and Public Health (DSPH) as instructed. This also includes any SAEs resulting from protocol-associated procedures performed after informed consent is signed.

Any SAEs and deaths which occur after the post treatment follow-up visit but within 30 days of the last dose of study drug (idelalisib or BI 836826, whichever is later), regardless of causality, should also be reported.

Investigators are not obligated to actively seek SAEs after the protocol defined 30-day follow up period. However, if the investigator learns of any SAEs that occur after study participation has concluded and the event is deemed relevant to the use of IP, he/she should promptly document and report the event to Gilead DSPH.

All AEs and SAEs will be recorded in the eCRF database within the timelines outlined in the eCRF completion guideline.

7.3.4. Electronic Serious Adverse Event (eSAE) Reporting Process

Site personnel record all SAE data in the eCRF database and from there transmit the SAE information to Gilead DSPH within 24 hours of the investigator's knowledge of the event. Detailed instructions can be found in the eCRF completion guidelines.

If for any reason it is not possible to record the SAE information electronically, ie, the eCRF database is not functioning, record the SAE on the paper serious adverse event reporting form and submit within 24 hours of the investigator's knowledge of the event to:

Gilead DSPH:	Fax:	PPD
	Email:	PPD

As soon as it is possible to do so, any SAE reported via paper must be transcribed into the eCRF Database according to instructions in the eCRF completion guidelines.

If an SAE has been reported via a paper form because the eCRF database has been locked, no further action is necessary.

All AEs and SAEs will be recorded in the eCRF database within the timelines outlined in the eCRF completion guideline.

For fatal or life-threatening events, copies of hospital case reports, autopsy reports, and other documents are also to be submitted by e-mail or fax when requested and applicable. Transmission of such documents should occur without personal subject identification, maintaining the traceability of a document to the subject identifiers.

Additional information may be requested to ensure the timely completion of accurate safety reports.

Any medications necessary for treatment of the SAE must be recorded onto the concomitant medication section of the subject's eCRF and the event description section of the SAE form.

7.4. Gilead Reporting Requirements

Depending on relevant local legislation or regulations, including the applicable US FDA Code of Federal Regulations (CFR), the EU Clinical Trials Directive (2001/20/EC) and relevant updates, and other country-specific legislation or regulations, Gilead may be required to expedite to worldwide regulatory agencies reports of SAEs, serious adverse drug reactions (SADRs), or suspected unexpected serious adverse reactions (SUSARs). In accordance with the EU Clinical Trials Directive (2001/20/EC), Gilead or a specified designee will notify worldwide regulatory agencies and the relevant IRB/IEC in concerned Member States of applicable SUSARs as outlined in current regulations.

Assessment of expectedness for SAEs will be determined by Gilead using reference safety information specified in the IB or relevant local label as applicable.

All investigators will receive a safety letter notifying them of relevant SUSAR reports. The investigator should notify the IRB/IEC of SUSAR reports as soon as is practical, where this is required by local regulatory agencies, and in accordance with the local institutional policy.

7.5. Clinical Laboratory Abnormalities and Other Abnormal Assessments as Adverse Events or Serious Adverse Events

Laboratory abnormalities are usually not recorded as AEs or SAEs. However, laboratory abnormalities (eg, clinical chemistry, hematology, coagulation, and urinalysis) that require medical or surgical intervention or lead to study drug interruption or discontinuation must be recorded as an AE, as well as an SAE, if applicable. If the laboratory abnormality is part of a syndrome, record the syndrome or diagnosis (eg, anemia) not the laboratory result (ie, decreased hemoglobin).

Severity should be recorded and graded according to the CTCAE Version 4.03.

For AEs associated with laboratory abnormalities, the event should be graded on the basis of the clinical severity in the context of the underlying conditions; this may or may not be in agreement with the grading of the laboratory abnormality.

7.6. Toxicity Management

Please refer to the current IBs for idelalisib and BI 836826 for information related to toxicity management. See Section 5.6 for additional information related to recommended dose modifications associated with toxicities.

7.7. Special Situations Reports

7.7.1. Definitions of Special Situations

Special situation reports include all reports of medication error, abuse, misuse, overdose, reports of adverse events associated with product complaints, and pregnancy reports regardless of an associated AE. Reports of adverse reactions in infants following exposure from breastfeeding, and reports of adverse reactions associated with product complaints and reports arising from occupational exposure are also considered special situation reports.

- A pregnancy report form is used to report any pregnancy in female subjects and female partners of male subjects on study
- Medication error is any unintentional error in the prescribing, dispensing, or administration of a medicinal product while in the control of the health care provider, subject, or consumer.
- Abuse is defined as persistent or sporadic intentional excessive use of a medicinal product by a subject.
- Misuse is defined as any intentional and inappropriate use of a medicinal product that is not in accordance with the protocol instructions or the local prescribing information.
- An overdose is defined as an accidental or intentional administration of a quantity of a medicinal product given per administration or cumulatively which is above the maximum recommended dose as per protocol or in the product labelling (as it applies to the daily dose of the subject in question). In cases of a discrepancy in drug accountability, overdose will be established only when it is clear that the subject has taken the excess dose(s). Overdose cannot be established when the subject cannot account for the discrepancy except in cases in which the investigator has reason to suspect that the subject has taken the additional dose(s).
- Product complaint is defined as complaints arising from potential deviations in the manufacture, packaging, or distribution of the medicinal product.

7.7.2. Instructions for Reporting Special Situations

7.7.2.1. Instructions for Reporting Pregnancies

The investigator should report pregnancies in female study subjects that are identified after initiation of study medication and throughout the study, including the post study drug follow-up period, to Gilead DSPH using the pregnancy report form within 24 hours of becoming aware of the pregnancy.

Refer to the eCRF completion guidelines for full instructions on the mechanism of pregnancy reporting.

The pregnancy itself is not considered an AE nor is an induced elective abortion to terminate a pregnancy without medical reasons.

Any premature termination of pregnancy (eg, a spontaneous abortion, an induced therapeutic abortion due to complications or other medical reasons) must be reported within 24 hours as an SAE. The underlying medical reason for this procedure should be recorded as the AE term.

A spontaneous abortion is always considered to be an SAE and will be reported as described in Sections 7.1.1 and 7.1.2. Furthermore, any SAE occurring as an adverse pregnancy outcome post study must be reported to Gilead DSPH.

The subject should receive appropriate monitoring and care until the conclusion of the pregnancy. The outcome should be reported to Gilead DSPH using the pregnancy outcome report form. If the end of the pregnancy occurs after the study has been completed, the outcome should be reported directly to Gilead DSPH. Gilead DSPH contact information is as follows: Email: PPD or Fax: PPD

Pregnancies of female partners of male study subjects exposed to idelalisib or BI 836826 must also be reported and relevant information should be submitted to Gilead DSPH using the pregnancy and pregnancy outcome forms within 24 hours. Monitoring of the subject should continue until the conclusion of the pregnancy. If the end of the pregnancy occurs after the study has been completed, the outcome should be reported directly to Gilead DSPH. Gilead DSPH contact information is as follows: Email: PPD or Fax: PPD.

Refer to Appendix 5 for Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Requirements.

7.7.2.2. Reporting Other Special Situations

All other special situation reports must be reported on the special situations report form and forwarded to Gilead DSPH within 24 hours of the investigator becoming aware of the situation. These reports must consist of situations that involve study drug and/or Gilead concomitant medications, but do not apply to non-Gilead concomitant medications.

Special situations involving non-Gilead concomitant medications does not need to be reported on the special situation report form; however, for special situations that result in AEs due to a non-Gilead concomitant medication, the AE should be reported on the AE eCRF.

Any inappropriate use of concomitant medications prohibited by this protocol should not be reported as “misuse,” but may be more appropriately documented as a protocol deviation.

Refer to the CRF/eCRF completion guidelines for full instructions on the mechanism of special situations reporting.

All clinical sequelae in relation to these special situation reports will be reported as AEs or SAEs at the same time using the AE CRF/eCRF and/or the SAE report form. Details of the symptoms and signs, clinical management, and outcome will be reported, when available.

8. STATISTICAL CONSIDERATIONS

Due to the early study termination, the endpoints will not be met and the subjects enrolled will be assessed for safety only. Planned analyses will not be performed and only safety- related endpoints will be analyzed and reported for the subjects enrolled in the study.

8.1. Primary Endpoint

The primary endpoint of the Phase 1b portion of the study is the incidence rate of DLTs during the first 7 weeks of study therapy at each combination dose level tested.

In the Phase 2 portion of the study, the primary endpoints are CRR and MRD negativity rate in bone marrow achieved by Week 50 as defined in Section 3.1.

8.2. Secondary Endpoint

The secondary endpoint of the Phase 1b portion of the study is description of any DLTs, SAEs, and AEs leading to discontinuation of study treatment.

The secondary endpoints of the Phase 2 portion of the study include ORR, DCR, DOR, PFS, OS, MRD negativity rate in blood at any time on study, MRD negativity rate in bone marrow at any time on study, and safety profile of the combined study drugs.

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8.4. Analysis Conventions

8.4.1. Analysis Sets

8.4.1.1. Intent-to-Treat Analysis Set

The Intent-to-Treat (ITT) Analysis Set will include all subjects who received at least 1 dose of any study drug (Phase 1b) or who were randomized (Phase 2). Treatment group for the Phase 2 portion of the study will be designated according to randomization regardless of whether any study drug is administered. This analysis set will be used for the analysis of efficacy endpoints.

8.4.1.2. Safety Analysis Set

The Safety Analysis Set will consist of all subjects receiving at least 1 dose of any study drug, with treatment group designated according to the actual treatment received. This analysis set will be used in the analyses of safety endpoints and study treatment exposure**.**

8.4.1.3. HighRP2D Analysis Set

In the Phase 1b portion of the study, the highRP2D Analysis Set will include all subjects from the safety set who either (i) meet the minimum exposure criteria without experiencing a DLT, or (ii) experience a DLT following exposure to the combination of idelalisib and BI836826 (at least 1 dose of each study drug). Minimum exposure criteria during the 7-week safety evaluation period is defined as 4 weeks of the assigned dose of idelalisib after the first infusion of BI 836826 and 2/3 of the intended dose of BI 836826.

Subjects who are not evaluable for highRP2D determination will be replaced, under timely consideration by the SRT and study investigators. Subjects enrolled in the expansion and supplemental cohorts of the Phase 1b portion of the study are not included in the highRP2D Analysis Set. This analysis set will be used for the determination of highRP2D.

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[redacted]

8.5. Data Handling Conventions

Summary tables for continuous variables will contain the following statistics: N (number in analysis set), n (number with data), mean, standard deviation, 95% confidence intervals (CIs) on the mean, median, minimum, and maximum. Summary tables for categorical variables will include: N, n, percentage, and 95% CIs on the percentage. Analyses will be based upon the observed data unless methods for handling missing data are specified. Data from all sites will be pooled and the summary will be presented for each dosing cohort and total, as appropriate.

8.6. Demographic Data and Baseline Characteristics

Demographic and baseline measurements will be summarized using standard descriptive methods based on the ITT analysis set.

8.7. Efficacy Analysis

This study has been terminated in Phase 1b based on an updated feasibility assessment in relation to changes in standard of care. The 2 subjects enrolled as of this date may remain on study with a modified schedule of assessments. Since only 2 subjects were enrolled at time of study termination, the statistical analysis will not be completed.

8.7.1. Primary Analysis

In the Phase 2 portion of the study, complete response rate and MRD negativity rate in bone marrow by Week 50 will be calculated along with its 95% CIs based on exact method. In the analyses of CRR and MRD negativity rate, subjects who do not have sufficient on-study tumor assessment to characterize response will be counted in the denominator.

8.7.2. Secondary Analyses

ORR will be calculated along with its 95% CIs based on exact method. In the analyses of ORR, subjects who do not have sufficient on-study tumor assessment to characterize response will be counted in the denominator.

For the analyses of DCR, DOR, PFS and OS, the Kaplan-Meier method will be used. For the DCR, DOR and PFS analyses, subjects who withdraw from the study or are lost to follow-up without disease progression or death will be censored on the date of the last visit that lack of disease progression was documented. Subjects who start a new antitumor treatment other than study treatment before disease progression will be censored on the last visit that lack of disease progression was objectively documented before the start of new antitumor treatment. Subjects who have CLL progression or die after ≥ 2 consecutive missing tumor assessments will be censored at the last time prior to the missing assessments that lack of definitive CLL progression was objectively documented. Subjects without any adequate post-baseline disease assessment will be censored on the date of first study dose (Phase 1b) and date of randomization (Phase 2).

8.8. Safety Analysis

Due to study termination, the endpoints will not be met and the subjects enrolled will be assessed for safety. Planned analyses will not be performed and only safety related endpoints will be analyzed and reported for the subjects remaining in the study.

8.8.1. Phase 1b Portion of the Study Only

Five-parameter BLRM will be used with overdose control (Appendix 6). Dose recommendation will be based on the posterior distribution of DLT in the highRP2D Analysis Set. The highRP2D will be determined by the SRT based on an assessment of the aggregate safety and PK data, and the highRP2D as the identified by the BLRM.

8.8.2. Extent of Exposure

A subject's extent of exposure to idelalisib and BI 836826 will be generated from the study drug administration data. Exposure data and study drug compliance will be summarized based on safety analysis set.

Idelalisib compliance will be described in terms of the amount actually taken based on returned pill count relative to the amount that was dispensed (taking into account physician-prescribed reductions and interruptions).

BI 836826 compliance will be described in terms of the number of doses actually administered relative to the expected number of doses planned, and as the cumulative dose of BI actually administered relative to the planned cumulative dose.

8.8.3. Adverse Events

All AEs will be listed. The focus of AE summarization will be on treatment-emergent adverse events (TEAEs). A TEAE is defined as an AE that occurs or worsens in the period from the first dose of study treatment (idelalisib, BI 836826) to 30 days after the last dose of study treatment.

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). System Organ Class (SOC), High-Level Group Term (HLGT), High-Level Term (HLT), Preferred Term (PT), and Lower-Level Term (LLT) will be attached to the clinical database. The severity of AEs will be graded by the investigator according to the CTCAE, Version 4.03, whenever possible. If a CTCAE criterion does not exist for a specific type of AE, the grade corresponding to the appropriate adjective will be used by the investigator to describe the maximum intensity of the AE: Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), Grade 4 (life threatening), or Grade 5 (fatal). The relationship of the AE to the study drug will be categorized as related or unrelated.

Summaries (number and percentage of subjects) of treatment-emergent AEs (by SOC and PT) will be provided. A subject who reports multiple treatment-emergent AEs within the same PT (or SOC) is counted only once for that PT (or SOC) using the worst severity grade. AE descriptions will be presented by decreasing frequency for a given SOC and PT.

Following summaries (number and percentage of subjects) of TEAEs will be provided:

- All AEs
- AEs related to study drug
- AEs that are Grade ≥ 3 in severity
- AEs leading to study drug modification (interruption/reduction)
- AEs leading to study drug discontinuation
- AEs leading to death
- SAEs
- IRRs and related symptoms

8.8.4. Laboratory Evaluations

All laboratory data will be listed. Summaries of laboratory data will be based on observed data. The focus of laboratory data summarization will be on treatment-emergent laboratory abnormalities. A treatment-emergent laboratory abnormality is defined as an abnormality that,

compared to baseline, worsened by ≥ 1 grade in the period from the first dose of study treatment to 30 days after the last dose of study treatment. If baseline data are missing, then any graded abnormality (ie, an abnormality that is Grade ≥ 1 in severity) will be considered treatment emergent.

Hematological, serum biochemistry, and urine data will be graded according to CTCAE severity grade, when applicable. For parameters for which a CTCAE scale does not exist, reference ranges from the central laboratory (or textbook ranges if the result is from a local laboratory) will be used to determine programmatically if a laboratory parameter is below, within, or above the normal range for the subject's age, sex, etc.

Hematological and serum biochemistry and their changes from baseline will be summarized by visit. Summary tables will be presented for each relevant assay to show the number of subjects by CTCAE severity grade with corresponding percentages. Subjects will be characterized only once for a given assay, based on their worst severity grade observed during a period of interest.

Shift tables for hematology and serum biochemistry will also be presented by showing change in CTCAE severity grade from baseline to the worst grade post baseline.

8.8.5. Other Safety Evaluations

DLT will be listed for all dosing cohorts.

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[redacted]

8.11. Sample Size

There is no formal hypothesis to be tested in this study and therefore, no formal sample size calculation is performed. In the Phase 1b portion of the study, a minimum of 3 evaluable subjects will be enrolled in each dose cohort. Approximately 15 subjects are expected to be treated at the highRP2D, including subjects for the expansion cohort. Additionally, approximately 6 evaluable subjects will be treated for the determination of lowRP2D. In total, approximately 42 evaluable subjects are estimated to be enrolled. However, the actual number of subjects will depend on the number of dose cohorts tested.

In the Phase 2 portion of the study, approximately 50 subjects with R/R CLL will be enrolled (20 lowRP2D / 30 highRP2D) .

8.12. Independent Review Committee

An IRC will be established to provide a review of radiographic data and pertinent clinical data in order to provide expert interpretation of changes in disease status. The IRC will include at least two independent board-certified radiologists and at least 1 independent board-certified hematologist or oncologist.

9. RESPONSIBILITIES

9.1. Investigator Responsibilities

9.1.1. Good Clinical Practice

The investigator will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki (as amended in Edinburgh, Tokyo, Venice, Hong Kong, and South Africa), International Conference on Harmonisation (ICH) guidelines, or with the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the study subject. These standards are consistent with the European Union Clinical Trials Directive 2001/20/EC and Good Clinical Practice Directive 2005/28/EC.

The investigator will ensure adherence to the basic principles of GCP, as outlined in 21 CFR 312, subpart D, "Responsibilities of Sponsors and Investigators," 21 CFR, part 50, 1998, and 21 CFR, part 56, 1998.

The investigator and all applicable subinvestigators will comply with 21 CFR, Part 54, 1998, providing documentation of their financial interest or arrangements with Gilead, or proprietary interests in the investigational drug under study. This documentation must be provided prior to the investigator's (and any subinvestigator's) participation in the study. The investigator and subinvestigator agree to notify Gilead of any change in reportable interests during the study and for 1 year following completion of the study. Study completion is defined as the date when the last subject completes the protocol-defined activities.

9.1.2. Institutional Review Board/Independent Ethics Committee Review and Approval

The investigator (or sponsor as appropriate according to local regulations) will submit this protocol, informed consent form, and any accompanying material to be provided to the subject (such as advertisements, subject information sheets, or descriptions of the study used to obtain informed consent) to an IRB (for studies conducted in the United States) or IEC (for studies conducted outside of the United States). The investigator will not begin any study subject activities until approval from the IRB/IEC has been documented and provided as a letter to the investigator.

Before implementation, the investigator will submit to and receive documented approval from the IRB/IEC any modifications made to the protocol or any accompanying material to be provided to the subject after initial IRB/IEC approval, with the exception of those necessary to reduce immediate risk to study subjects.

9.1.3. Informed Consent

The investigator is responsible for obtaining written informed consent from each individual participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study and before undertaking any study-related procedures. The investigator must use the most current IRB- or EC-approved consent form for documenting

written informed consent. Each informed consent (or assent as applicable) will be appropriately signed and dated by the subject or the subject's legally authorized representative and the person conducting the consent discussion, and also by an impartial witness if required by IRB/IEC or local requirements. The consent form will inform subjects about pharmacogenomic testing and sample retention, and their right to receive clinically relevant pharmacogenomic analysis results.

9.1.4. Confidentiality

The investigator must assure that subjects' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. Only subject initials, date of birth, another unique identifier (as allowed by local law) and an identification code will be recorded on any form or biological sample submitted to the Sponsor, IRB/IEC, or laboratory. Laboratory specimens must be labeled in such a way as to protect subject identity while allowing the results to be recorded to the proper subject. Refer to specific laboratory instructions. NOTE: The investigator must keep a Screening log showing codes, names, and addresses for all subjects screened and for all subjects enrolled in the trial. Subject data will be processed in accordance with all applicable regulations.

The investigator agrees that all information received from Gilead, including but not limited to the investigator brochure, this protocol, CRF, the IMP, and any other study information, remain the sole and exclusive property of Gilead during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from Gilead. The investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the study site to any third party or otherwise into the public domain.

9.1.5. Study Files and Retention of Records

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into at least the following two categories: (1) investigator's study file, and (2) subject clinical source documents.

The investigator's study file will contain the protocol/amendments, eCRF and query forms, IRB/IEC, and governmental approval with correspondence, informed consent, drug records, staff curriculum vitae and authorization forms, and other appropriate documents and correspondence.

The required source data should include sequential notes containing at least the following information for each subject:

- Subject identification (name, date of birth, gender)
- Documentation that subject meets eligibility criteria, ie, history, PE, and confirmation of diagnosis (to support inclusion and exclusion criteria)
- Documentation of the reason(s) a consented subject is not enrolled

- Participation in study (including study number)
- Study discussed and date of informed consent
- Dates of all visits
- Documentation that protocol specific procedures were performed
- Results of efficacy parameters, as required by the protocol
- Start and end date (including dose regimen) of IMP, including dates of dispensing and return
- Record of all adverse events and other safety parameters (start and end date, and including causality and severity)
- Concomitant medication (including start and end date, dose if relevant; dose changes)
- Date of study completion and reason for early discontinuation, if it occurs

All clinical study documents must be retained by the investigator until at least 2 years or according to local laws, whichever is longer, after the last approval of a marketing application in an ICH region (ie, United States, Europe, or Japan) and until there are no pending or planned marketing applications in an ICH region; or, if no application is filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and regulatory authorities have been notified. Investigators may be required to retain documents longer if specified by regulatory requirements, by local regulations, or by an agreement with Gilead. The investigator must notify Gilead before destroying any clinical study records.

Should the investigator wish to assign the study records to another party or move them to another location, Gilead must be notified in advance.

If the investigator cannot provide for this archiving requirement at the study site for any or all of the documents, special arrangements must be made between the investigator and Gilead to store these records securely away from the site so that they can be returned sealed to the investigator in case of an inspection. When source documents are required for the continued care of the subject, appropriate copies should be made for storage away from the site.

9.1.6. Case Report Forms

For each subject consented, an eCRF will be completed by an authorized study staff member whose training for this function is documented according to study procedures. Subsequent to data entry, a study monitor will perform source data verification within the electronic data capture (EDC) system. Original entries as well as any changes to data fields will be stored in the audit trail of the system. Prior to database lock (or any interim time points as described in the clinical data management plan), the investigator will use his/her log in credentials to confirm that the forms have been reviewed, and that the entries accurately reflect the information in the

source documents. The eCRF capture the data required per the protocol schedule of events and procedures. System-generated or manual queries will be issued to the investigative site staff as data discrepancies are identified by the monitor or internal Gilead staff, who routinely review the data for completeness, correctness, and consistency. The site coordinator is responsible for responding to the queries in a timely manner, within the system, either by confirming the data as correct or updating the original entry, and providing the reason for the update (e.g. data entry error). At the conclusion of the trial, Gilead will provide the site with a read-only archive copy of the data entered by that site. This archive must be stored in accordance with the records retention requirements outlined in Section 9.1.5.

9.1.7. Investigational Medicinal Product Accountability and Return

The study monitor will evaluate each study center's IMP disposal procedures and provide appropriate instruction for destruction of unused IMP supplies. If the site has an appropriate standard operating procedure (SOP) for drug destruction as determined by Gilead QA, the site may destroy used (empty or partially empty) and unused IMP supplies in accordance with that site's approved SOP. A copy of the site's approved SOP will be obtained for central files.

If IMP is destroyed on site, the investigator must maintain accurate records for all IMP destroyed. Records must show the identification and quantity of each unit destroyed, the method of destruction, and the person who disposed of the IMP. Upon study completion, copies of the IMP accountability records must be filed at the site. Another copy will be returned to Gilead.

The study monitor will review IMP supplies and associated records at periodic intervals.

9.1.8. Inspections

The investigator will make available all source documents and other records for this trial to Gilead's appointed study monitors, to IRB/IEC, or to regulatory authority or health authority inspectors.

9.1.9. Protocol Compliance

The investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol.

9.2. Sponsor Responsibilities

9.2.1. Protocol Modifications

Protocol modifications, except those intended to reduce immediate risk to study subjects, may be made only by Gilead. The investigator must submit all protocol modifications to the IRB/IEC in accordance with local requirements and receive documented IRB/IEC approval before modifications can be implemented.

9.2.2. Study Report and Publications

A clinical study report (CSR) will be prepared and provided to the regulatory agency(ies). Gilead will ensure that the report meets the standards set out in the ICH Guideline for Structure and Content of Clinical Study Reports (ICH E3). Note that an abbreviated report may be prepared in certain cases.

Investigators in this study may communicate, orally present, or publish in scientific journals or other scholarly media only after the following conditions have been met:

- The results of the study in their entirety have been publicly disclosed by or with the consent of Gilead in an abstract, manuscript, or presentation form or the study has been completed at all study sites for at least 2 years.
- The investigator will submit to Gilead any proposed publication or presentation along with the respective scientific journal or presentation forum at least 30 days before submission of the publication or presentation.
- No such communication, presentation, or publication will include Gilead's confidential information (see Section 9.1.4).
- The investigator will comply with Gilead's request to delete references to its confidential information (other than the study results) in any paper or presentation and agrees to withhold publication or presentation for an additional 60 days in order to obtain patent protection if deemed necessary.

9.3. Joint Investigator/Sponsor Responsibilities

9.3.1. Payment Reporting

Investigators and their study staff may be asked to provide services performed under this protocol, e.g. attendance at Investigator's Meetings. If required under the applicable statutory and regulatory requirements, Gilead will capture and disclose to Federal and State agencies any expenses paid or reimbursed for such services, including any clinical trial payments, meal, travel expenses or reimbursements, consulting fees, and any other transfer of value.

9.3.2. Access to Information for Monitoring

In accordance with regulations and guidelines, the study monitor must have direct access to the investigator's source documentation in order to verify the accuracy of the data recorded in the eCRF.

The monitor is responsible for routine review of the eCRF at regular intervals throughout the study to verify adherence to the protocol and the completeness, consistency, and accuracy of the data being entered on them. The monitor should have access to any subject records needed to verify the entries on the eCRF. The investigator agrees to cooperate with the monitor to ensure that any problems detected through any type of monitoring (central, on site) are resolved.

9.3.3. Access to Information for Auditing or Inspections

Representatives of regulatory authorities or of Gilead may conduct inspections or audits of the clinical study. If the investigator is notified of an inspection by a regulatory authority the investigator agrees to notify the Gilead medical monitor immediately. The investigator agrees to provide to representatives of a regulatory agency or Gilead access to records, facilities, and personnel for the effective conduct of any inspection or audit.

9.3.4. Study Discontinuation

Both the sponsor and the investigator reserve the right to terminate the study at any time. Should this be necessary, both parties will arrange discontinuation procedures and notify the appropriate regulatory authority(ies), IRBs, and IECs. In terminating the study, Gilead and the investigator will assure that adequate consideration is given to the protection of the subjects' interests.

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11. APPENDICES

Appendix 1. Investigator Signature Page

GILEAD SCIENCES, INC.
333 LAKESIDE DRIVE
FOSTER CITY, CA 94404

STUDY ACKNOWLEDGEMENT

Phase 1b/2 Study of Idelalisib in Combination with BI 836826 in Subjects with Chronic Lymphocytic Leukemia

GS-US-312-1579, Amendment 4, 15 June 2017

This protocol has been approved by Gilead Sciences, Inc. The following signature documents this approval.

PPD

PPD

15 June 2017
Date

INVESTIGATOR STATEMENT

I have read the protocol, including all appendices, and I agree that it contains all necessary details for me and my staff to conduct this study as described. I will conduct this study as outlined herein and will make a reasonable effort to complete the study within the time designated.

I will provide all study personnel under my supervision copies of the protocol and access to all information provided by Gilead Sciences, Inc. I will discuss this material with them to ensure that they are fully informed about the drugs and the study.

Principal Investigator Name (Printed) _____ Signature _____

Date _____ Site Number _____

Appendix 2. Study Procedures Tables

Appendix Table 1. Study Procedures Table *(part 1, Screening through Week 18)*

Shaded columns indicate laboratory draws only occur on these days

Visit	Screen	Idelalisib Run-in and Combination Treatment through Week 18															
Week	**-4**	**1**	**2**	**2**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**12**	**14**	**16**	**18**
Study Day	**-28**	**1**	**8**	**9**		**15**	**22**		**36**		**50**		**64**	**78**	**92**	**106**	**120**
Visit Window		**NA**				**± 1 day**					**± 3 days**						
Informed Consent	X																
Medical History	X																
Medication History	X																
Physical Examination	X	X	X	X		X	X		X		X		X	X	X	X	X
Vital Signs	X	X	X	X		X	X		X		X		X	X	X	X	X
ECOG Performance Status	X																
12-lead ECG	X																
Chemistry & Hematology [1]	X	X	X	X	XXX	X	X	X	X	X	X	X	X	X	X	X	X
Coagulation	X																
Urinalysis	X								X								
HBV, CMV, HCV, HIV Screening	X																
CMV monitoring [2]	X						X				X			X		X	X
β 2 microglobulin		X															
Immune monitoring (CD4)[3]		X					X							X			
ADA testing [4]			X						X				X		X		X
CCI																	
Investigator Assessment	X														X		
Idelalisib & PJP Prophylaxis Dispensing		X					X				X			X		X	X
Idelalisib Accountability							X				X			X		X	
Idelalisib Administration [6]		→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→
BI 836826 Administration [7]			10 mg	50%		50%	100%		X		X		X	X	X	X	X
Adverse Events		X	X	X		X	X		X		X		X	X	X	X	X
Concomitant Medication	X	X	X	X		X	X		X		X		X	X	X	X	X

ALL FOOTNOTES APPEAR AT END OF PART 2

Study Procedures Table (part 2, Week 20 through 30-Day Follow-up/End of Study)

Shaded columns indicate laboratory draws only occur on these days

Visit	Combination Treatment and Post- Combination Treatment									30-Day Follow-up End of Study[8]
Week	**20**	**22**	**24**	**26**	**30**	**34**	**38**	**42**	**46**	
Study Day	**134**	**148**	**162**	**176**	**204**	**232**	**260**	**288**	**316**	
Visit Window	**± 3 days**									**±7 days**
Informed Consent										
Medical History										
Medication History										
Physical Examination		X		X	X	X	X	X	X	X
Vital Signs		X		X	X	X	X	X	X	X
ECOG Performance Status										X
12-lead ECG				X						X
Chemistry & Hematology [1]	X	X	X	X	X	X	X	X	X	X
Coagulation										
Urinalysis				X						X
CMV monitoring [2]		X		X	X	X	X	X	X	X
β 2 microglobulin										
Immune monitoring (CD4) [3]		X					X		X	X
ADA testing [4]				X		X		X		X
CCI										
Investigator Assessment				X			X			X
Idelalisib & PJP Prophylaxis Dispensing		X		X	X	X	X	X	X	
Idelalisib Accountability		X		X	X	X	X	X	X	
Idelalisib Administration [6]		→		→	→	→	→	→	→	
BI 836826 Administration [7]		X		X	X	X	X	X	X	
Adverse Events		X		X	X	X	X	X	X	X
Concomitant Medication		X		X	X	X	X	X	X	X

1 Chemistry & hematology will be obtained a minimum of 3 times in the first week following completion of the first 50% dose of BI 836826 on Day 9; and once after the first full dose of BI 836826 on Day 22, then a minimum of weekly x 6 weeks, then prior to each BI 836826 infusion. All subjects should have blood counts monitored at least every two weeks for the first 6 months of idelalisib treatment. For subjects who develop ANC 0.5 to < 1.0 Gi/L, blood counts should be monitored at least weekly

2 CMV surveillance for active disease must be conducted approximately every 4 weeks throughout the course of idelalisib treatment.

3 Samples for immune monitoring were drawn at Baseline prior to the first dose of idelalisib. With the implementation of Amendment 4, only CD4 will be collected at the time points specified.

4 With the implementation of Amendment 4, PK and biomarker samples are no longer being collected and subjects are past Week 16. Samples for BI 836826 anti-drug antibody testing will be drawn at the time points indicated. For additional information see Appendix Table 2 PK and Anti-Drug Antibody Sampling and the Laboratory Manual.

[redacted]

6 Idelalisib is taken BID; on BI 836826 dose days the morning dose is taken in the clinic approximately 60 minutes prior to starting the BI 836826 infusion

7 BI 836826 given via IV infusion at the indicated time points, beginning with 10 mg and ramping up through 50% to 100% of the intended dose over 4 weeks

8 The 30-day Follow-up assessment will be done following last dose of BI 836826 (no later than Week 50).

Appendix Table 2. PK and Anti-Drug Antibody Sampling

With the implementation of Amendment 4, PK samples are no longer being collected and subjects are past Week 16.

Study Day	Study Week	BI 836826 PK	ADA analysis	Idelalisib PK
8	2	Before start of BI 836826 drug infusion	Before start of BI 836826 drug infusion	Within 30 min prior to idelalisib dose
		Shortly before end of infusion		1.5 hr after idelalisib dose
9	2	Before start of BI 836826 drug infusion		
		Shortly before end of infusion		
15	3	Before start of BI 836826 drug infusion		
		Shortly before end of infusion		
22	4	Before start of BI 836826 drug infusion		Within 30 min prior to idelalisib dose
		Shortly before end of infusion		1.5 hr after idelalisib dose
		8-10 hr after start of drug infusion		
23		23-25 hr after start of drug infusion		
[25-27]		72-120 hr after start of drug infusion		
36 to 106	6 through 16	Before start of BI 836826 drug infusion	Weeks 6, 10, and 14 Before start of BI 836826 drug infusion	Weeks 6 and 14: within 30 min prior to, and 1.5 hr after idelalisib dose
		Shortly before end of infusion (Weeks 6, 10, and 14 only)		
120	18		Before start of BI 836826 drug infusion	
176 to 316	26 through 46		Weeks 26, 34, and 42 Before start of BI 836826 drug infusion	
344	30d follow up/EOS		At any time during the visit	

Appendix 3. ECOG Performance Status Scoring System

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and 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

Appendix 4. Modified International Workshop on Chronic Lymphocytic Leukemia Criteria for Response Assessment

The determination of CLL response and progression will be based on standardized International Workshop on CLL (IWCLL) criteria {Hallek 2008}, as specifically modified for this study to reflect current recommendations which consider the study design and mechanism of action of idelalisib and similar drugs {Cheson 2012}.

1.1. Identification and Follow-up of Lesions and Organomegaly

CT/MRI scans are no longer required as of Amendment 4. The following guidelines are recommendations for local imaging studies, if done.

1.1.1. Index Lesions

For subjects entering the study with lymphadenopathy, up to 6 lymph nodes should be selected as index lesions that will be used to quantitate the status of the disease during study treatment. Ideally, the index lesions should be located in disparate regions of the body. Only peripheral nodes need be selected as index lesions, however, it is optimal if mediastinal and retroperitoneal areas of disease are assessed whenever these sites are involved.

Index lesions will be measured and recorded at baseline and at the stipulated intervals. The cross-sectional dimensions (the largest cross-sectional diameter, ie, the longest diameter (LD) × the longest perpendicular diameter (LPD) will be recorded for each index lesion. The product of the perpendicular diameters (PPD) for each index lesion and the shortest perpendicular diameter (SPD) for all index lesions will be calculated and recorded. The baseline SPD will be used as references by which objective disease response will be characterized during treatment. The nadir LD of individual lesions and the nadir SPD will be used as references by which CLL progression will be characterized. All LD and LPD diameters will be reported in cm and all PPDs and SPDs will be reported in cm^2.

A nodal mass may be selected as a nodal index lesion if it is both abnormal and measurable at baseline. A lymph node lesion is considered abnormal if it has a single diameter that is > 1.5 cm and is considered measurable if it has 2 perpendicular diameters that can be accurately measured in cross section with the LD being ≥1.0 cm and the LPD also being ≥1.0 cm.

At follow-up time points, the LDs for individual lesions and the SPD of all nodal index lesions will be considered. Because nodal index lesions that have 1 or both diameters > 0 cm and < 1.0 cm cannot be reliably measured, a default value of 1.0 cm will be assigned for each diameter that meets these criteria and the resulting PPD will be used in SPD calculations.

A new node that measures > 1.5 cm in the LD and > 1.0 cm in the LPD will be considered PD.

In cases in which a large lymph node mass has split into multiple components, all subcomponents regardless of size will be used in calculating the SPD. Progression of the lesion will be based on the SPD of sub-components. Lesion sub-components will have the true PPDs calculated. Similarly, lesion sub-components that are visible but neither abnormal nor measurable will have the default PPD of 1.0 cm^2 (1.0 cm × 1.0 cm) used in calculating the SPD.

If lesions merge, a boundary between the lesions may be established so the LD of each individual lesion can continue to be measured. If the lesions have merged in a way that they can no longer be separated by this boundary, the newly merged lesion will be measured bi-dimensionally.

1.1.2. Spleen and Liver

Both the spleen and liver will be assessed by CT/MRI scan at baseline and at the stipulated intervals during the study. The baseline and nadir values for the longest vertical dimension (LVD) of each organ will be used as reference to further characterize the objective tumor response of the measurable dimensions of the CLL during the study.

The spleen will be considered enlarged if it is > 12 cm in LVD {Asghar 2011, Bezerra 2005}, with the LVD being obtained by multiplying the number of sections on which the spleen is visualized by the thickness of the sections (eg, if the spleen is seen in 14 contiguous cross-sectional images with 0.5-cm thickness, the LVD is recorded as 7 cm). The amount of enlargement of a spleen with LVD > 12 cm is equal to the LVD minus 12 cm. For subjects with splenomegaly at baseline evaluations of the spleen will consider only changes relative to the amount of enlargement at baseline. Splenic progression will be based on increase from the nadir measurement, or 12 cm if the nadir is ≤ 12 cm.

A 50% decrease (minimum 2 cm decrease) from baseline in the enlargement of the spleen or decrease in LVD to ≤ 12 cm by imaging is required for declaration of a splenomegaly response. Conversely, an increase in splenic enlargement by ≥ 50% from nadir (minimum increase of 2 cm) is required for declaration of splenic progression; the spleen must be at least 14 cm in LVD to assess splenic progression.

The liver will be considered enlarged if it is > 18 cm in LVD {Erturk 2006}, with the LVD being obtained by multiplying the number of sections on which the liver is visualized by the thickness of the sections (eg, if the liver is seen in 36 contiguous cross-sectional images with 0.5-cm thickness, the LVD is recorded as 18 cm). The amount of enlargement of a liver with LVD > 18 cm is equal to the LVD minus 18 cm.

A 50% decrease (minimum 2 cm decrease) from baseline in the enlargement of the liver or decrease in LVD to ≤ 18 cm by imaging is required for declaration of a hepatomegaly response. Conversely, an increase in liver enlargement by ≥ 50% from nadir (minimum increase of 2 cm) is required for declaration of hepatic progression; the liver must be at least 20 cm in LVD to assess hepatic progression.

1.1.3. Non-Index Lesions

Any other measurable and abnormal nodal lesions not selected for quantitation as index lesions may be considered non-index lesions. In addition, non-measurable evidence of CLL such as nodal lesions with both diameters < 1.0 cm, extra-nodal lesions, bone lesions, leptomeningeal disease, ascites, pleural or pericardial effusions, lymphangitis of the skin or lung, abdominal masses that are not confirmed and followed by imaging techniques, cystic lesions, previously irradiated lesions, lesions with artifacts may be considered as non-index disease.

The presence or absence of non-index disease should be recorded at baseline and at the stipulated intervals during the study. If present at baseline, up to 6 non-index lesions should be recorded. The non-index disease at baseline will be used as a general reference to further characterize regression or progression of CLL during assessments of the objective disease response during treatment. Measurements are not required and these lesions should be followed as "present", "progressed" or "absent".

1.2. Definitions of Disease Response and Progression

Responses will be categorized by the IRC as CR, CR with incomplete marrow recovery (CRi), PR, SD, or PD. In addition, a response category of not evaluable (NE) is provided for situations in which there is inadequate information to otherwise categorize response status. A response category of no disease (ND) is included for situations in which there is no evidence of tumor either at baseline or on the study.

The best OR will be determined. The best OR is the best response recorded from the start of treatment until progressive disease/recurrence (taking as reference for PD the smallest measurements recorded since treatment started). Subjects with NE or ND will be included in the denominator in the analyses of disease response.

1.2.1. Complete Response

To satisfy criteria for a CR, all of the following criteria must be met:

- No evidence of new disease
- ALC in peripheral blood of $<4 \times 10^9$/L
- Regression of all index nodal masses to normal size ≤ 1.5 cm in the LD
- Normal spleen and liver size
- Regression to normal of all nodal non-index disease and disappearance of all detectable non-nodal, non-index disease
- Morphologically negative bone marrow defined as <30% of nucleated cells being lymphoid cells and no lymphoid nodules in a bone marrow sample that is normocellular for age
- Peripheral blood counts meeting all of the following criteria:
  - ANC > 1.5×10^9/L without need for exogenous growth factors (eg, G-CSF)
  - Platelet count ≥ 100×10^9/L without need for exogenous growth factors or transfusions
  - Hemoglobin ≥ 110 g/L (11.0 g/dL) without red blood cell transfusions or need for exogenous growth factors (eg, erythropoietin)

1.2.2 Partial Response

Subjects who fulfill all the criteria for a CR (including bone marrow criteria) but who have a persistent anemia, thrombocytopenia, or neutropenia or a hypocellular bone marrow that is related to prior or ongoing drug toxicity (and not to CLL) will be considered a CRi.1.2.2. Partial Response

To satisfy criteria for a PR, all of the following criteria must be met:

- No evidence of new disease
- No index, splenic, liver, or non-index disease with worsening that meets the criteria for definitive PD
- Peripheral blood counts meeting ≥ 1 of the following criteria:

  a) ANC > 1.5×10^9/L or ≥ 50% increase over baseline without need for exogenous growth factors (eg, G-CSF)

  b) Platelet count ≥ 100 x 10^9/L or ≥ 50% increase over baseline without need for exogenous growth factors or transfusions

  c) Hemoglobin ≥ 110 g/L (11.0 g/dL) or ≥ 50% increase over baseline without red blood cell transfusions or need for exogenous growth factors (eg, erythropoietin)

- Change in disease status meeting the following criteria:

Phase 1b:

- Subjects entering the study with baseline lymphocytosis, but without lymphadenopathy, hepatomegaly, or splenomegaly:

  — A decrease in peripheral blood ALC by ≥ 50% from baseline or a decrease to < 4×10^9/L.

- Subjects entering the study with baseline lymphocytosis AND ONLY ONE of the following additional abnormal baseline findings: baseline lymphadenopathy OR baseline hepatomegaly OR baseline splenomegaly:

  — In a subject with baseline lymphadenopathy, decrease by ≥ 50% from the baseline in the SPD of the index nodal lesions

  — In a subject with enlargement of the spleen at baseline, a splenomegaly response as defined in Appendix 4 Section 1.1.2

  — In a subject with enlargement of the liver at baseline, a hepatomegaly response as defined in Appendix 4 Section 1.1.2

  — WITH OR WITHOUT a decrease in peripheral blood ALC by ≥ 50% from baseline or a decrease to < 4×10^9/L.

- Subjects entering the study with baseline lymphocytosis and AT LEAST TWO of the following additional abnormal baseline findings: baseline lymphadenopathy OR baseline hepatomegaly OR baseline splenomegaly:

  — Response demonstrated in AT LEAST TWO of the same additional abnormal baseline findings

  — OR response demonstrated in ONE of the same additional abnormal baseline findings AND a decrease in peripheral blood ALC by ≥ 50% from baseline or a decrease to $< 4 \times 10^9$/L

Phase 2:

- Subjects entering the study with at least one lymph node with LD ≥20 mm and LPD of ≥10 mm at baseline:

  — Change in disease status meeting ≥ 2 of the following criteria, with 2 exceptions in which only 1 criterion is needed: (1) Only lymphadenopathy is present at baseline; (2) Only lymphadenopathy and lymphocytosis are present at baseline. In these 2 cases, only lymphadenopathy must improve to the extent specified below:

    ■ In a subject with baseline lymphocytosis (ALC $\geq 4 \times 10^9$/L), a decrease in peripheral blood ALC by ≥ 50% from baseline or a decrease to $< 4 \times 10^9$/L

    ■ A decrease by ≥ 50% from the baseline in the SPD of the index nodal lesions

    ■ In a subject with enlargement of the spleen at baseline, a splenomegaly response as defined in Appendix 4 Section 1.1.2.

    ■ In a subject with enlargement of the liver at baseline, a hepatomegaly response as defined in Appendix 4 Section 1.1.2

    ■ A decrease by ≥ 50% from baseline in the CLL marrow infiltrate or in B-lymphoid nodules

- Subjects entering the study without lymphadenopathy but with quantifiable CLL in bone marrow at baseline:

  — Change in disease status meeting ≥2 of the following criteria, with 2 exceptions in which only 1 criterion is needed: (1) Only quantifiable CLL in bone marrow is present at baseline; (2) Only quantifiable CLL in bone marrow and lymphocytosis are present at baseline. In these 2 cases, only quantifiable CLL in bone marrow must improve to the extent specified below:

    ■ In a subject with baseline lymphocytosis (ALC $\geq 4 \times 10^9$/L), a decrease in peripheral blood ALC by ≥ 50% from baseline or a decrease to $< 4 \times 10^9$/L

    ■ In a subject with enlargement of the spleen at baseline, a splenomegaly response as defined in Appendix 4 Section 1.1.2.

- In a subject with enlargement of the liver at baseline, a hepatomegaly response as defined in Appendix 4 Section 1.1.2
- A decrease by ≥ 50% from baseline in the CLL marrow infiltrate or in B-lymphoid nodules

1.2.3. Stable Disease

To satisfy criteria for SD, the following criteria must be met:

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

1.2.4. Definitive Progressive Disease

The occurrence of any of the following events indicates definitive PD:

- Evidence of any new disease:
  a) A new node that measures >1.5 cm in the LD and >1.0 cm in the LPD
  b) New or recurrent splenomegaly, with a minimum LVD of 14 cm
  c) New or recurrent hepatomegaly, with a minimum LVD of 20 cm
  d) Unequivocal reappearance of an extra-nodal lesion that had resolved
  e) A new unequivocal extra-nodal lesion of any size
  f) New non-index disease (eg, effusions, ascites, or other organ abnormalities related to CLL)

Isolated new effusions, ascites, or other organ abnormalities are not sufficient evidence alone of PD unless histologically confirmed. Thus, a declaration of PD should not be made if this is the only manifestation of apparently new disease.

- Evidence of worsening of index lesions, spleen or liver, or non-index disease:
  a) Increase from the nadir by ≥50% in the SPD of index lesions
  b) Increase from the nadir by ≥50% in the LD if an individual node that now has an LD of >1.5 cm and an LPD of > 1.0 cm
  c) Splenic progression defined as an increase in splenic enlargement by ≥50% from nadir (with a minimum 2 cm increase and a minimum LVD of 14 cm)
  d) Hepatic progression defined as an increase in hepatic enlargement by ≥50% from nadir (with a minimum 2 cm increase and minimum LVD of 20 cm)

e) Unequivocal increase in the size of non-index disease (eg, effusions, ascites, or other organ abnormalities related to CLL)

f) Transformation to a more aggressive histology (eg, Richter syndrome) as established by lymph node biopsy or other tissue biopsy, or fluid cytology (with the biopsy or fluid cytology date being considered the date of CLL progression if the subject has no earlier objective documentation of CLL progression).

- Decrease in platelet count or hemoglobin that is attributable to CLL, is not attributable to an autoimmune phenomenon, and is confirmed by bone marrow biopsy showing an infiltrate of clonal CLL cells:

  a) The current platelet count is $< 100 \times 10^9$/L and there has been a decrease by > 50% from the highest on-study platelet count

  b) The current hemoglobin is < 110 g/L (11.0 g/dL) and there has been a decrease by > 20 g/L (2 g/dL) from the highest on-study hemoglobin

- At any time greater than 4 weeks after the discontinuation of idelalisib: an increase in the number of blood lymphocytes by 50% or more with at least 5000 B lymphocytes per microliter as measured from the nadir during that time period.

1.2.5. Non-Evaluable and No Disease

In a subject who does not have evidence of PD, the occurrence of any of the following conditions indicates a response status of NE:

- There are no images or inadequate or missing images.
- Images of the liver and/or spleen are missing at that time point (with the exception that absence of splenic images will not result in an NE designation in a subject known to have undergone splenectomy).

A time-point will be considered to have a response of NE if any index lesion is missing. PD may be assigned at any time point regardless of the extent of missing index or non-index lesions. Missing non-index lesions will not impact the ability to assess for response or disease progression.

No Disease Subjects have a status of ND if all of the following conditions occur:

- No index disease noted at baseline or on-the study
- No non-index disease noted at baseline or on-the study
- No enlargement of the liver or spleen at baseline or on-the study
- No abnormalities of peripheral blood counts (elevated ALC or abnormally low ANC, platelet count, or hemoglobin) and no evidence of CLL in bone marrow (if available) at baseline or on the study

1.3. Lymphocytosis During Therapy

Idelalisib can mobilize CLL cells from tissues into the peripheral blood. This characteristic pharmacological action can be prominent early in therapy but can persist over time and should not be confused with disease progression in subjects who have persistent control of other CLL-related signs and symptoms.

In the absence of other objective evidence of disease progression, the occurrence of lymphocytosis will not preclude subjects from meeting the criteria for a PR if other criteria for PR are met and will not be considered evidence of CLL progression if occurring in isolation.

Subjects with lymphocytosis should be continued on study drug until the occurrence of definitive disease progression (ie, disease progression that is manifest by worsening CLL-related signs other than lymphocytosis alone), or the occurrence of another reason to discontinue study treatment as described in Protocol Section 6.

Appendix 5. Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Requirements

1) Definitions

a. Definition of Childbearing Potential

For the purposes of this study, a female born subject is considered of childbearing potential following the initiation of puberty (Tanner stage 2) until becoming post-menopausal, unless permanently sterile or with medically documented ovarian failure.

Women are considered to be in a postmenopausal state when they are ≥ 54 years of age with cessation of previously occurring menses for ≥ 12 months without an alternative cause. In addition, women of any age with amenorrhea of ≥ 12 months may also be considered postmenopausal if their follicle stimulating hormone (FSH) level is in the postmenopausal range and they are not using hormonal contraception or hormonal replacement therapy.

Permanent sterilization includes hysterectomy, bilateral oophorectomy, or bilateral salpingectomy in a female subject of any age.

b. Definition of Male Fertility

For the purposes of this study, a male born subject is considered of fertile after the initiation of puberty unless permanently sterile by bilateral orchidectomy or medical documentation.

2) Contraception Requirements for Female Subjects

a. Study Drug Effects on Pregnancy and Hormonal Contraception

Idelalisib is contraindicated in pregnancy as a malformation effect has been demonstrated/suspected or is unknown, taking into consideration class effects, genotoxic potential, or a strong suspicion of human teratogenicity/fetotoxicity in early pregnancy based on non-clinical data. Idelalisib has demonstrated/suspected or has insufficient data to exclude the possibility of a clinically relevant interaction with hormonal contraception that results in reduced contraception efficacy. Therefore, contraceptive steroids are not recommended as a contraceptive method either solely or as a part of a contraceptive regimen. Please refer to the latest version of the IB for additional information.

b. Contraception Requirements for Female Subjects of Childbearing Potential

The inclusion of female subjects of childbearing potential requires the use of highly effective contraceptive measures. They must also not rely on hormone-containing contraceptives as a form of birth control during the study. They must have a negative serum pregnancy test at Screening and a negative pregnancy test on the Baseline/Day 1 visit prior to randomization. Pregnancy tests will be performed at monthly intervals thereafter. Female subjects must agree to one of the following from the Screening visit throughout the study, and for 30 days from the last dose of idelalisib or 12 months from the last dose of BI 836826 (whichever is later).

- Complete abstinence from intercourse of reproductive potential. Abstinence is an acceptable method of contraception only when it is in line with the subject's preferred and usual lifestyle.

  Or

- Consistent and correct use of 1 of the following methods of birth control listed below.

  — Intrauterine device (IUD) with a failure rate of <1% per year

  — Tubal sterilization

  — Essure micro-insert system (provided confirmation of success 3 months after procedure)

  — Vasectomy in the male partner (provided that the partner is the sole sexual partner and had confirmation of surgical success 3 months after procedure)

Female subjects must also refrain from egg donation and in vitro fertilization during treatment and for 30 days from the last dose of idelalisib or 12 months from the last dose of BI 836826 (whichever is later).

3) Contraception Requirements for Male Subjects

It is theoretically possible that a relevant systemic concentration may be achieved in a female partner from exposure of the male subject's seminal fluid. Therefore, male subjects with female partners of childbearing potential must use condoms during treatment and until 90 days following the last dose of idelalisib or 12 months from the last dose of BI 836826 (whichever is later). Additional contraception recommendations should also be considered if the female partner is not pregnant.

Male subjects must also refrain from sperm donation during treatment and until at least 90 days following the last dose of idelalisib or 12 months from the last dose of BI 836826 (whichever is later).

Unacceptable Birth Control Methods

Birth control methods that are unacceptable include periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM). Female condom and male condom should not be used together.

4) Procedures to be Followed in the Event of Pregnancy

Subjects will be instructed to notify the investigator if they become pregnant at any time during the study, or if they become pregnant within 30 days for females or 90 days for female partners of male subjects of last study drug dose. Subjects who become pregnant or who suspect that they are pregnant during the study must report the information to the investigator and discontinue study drug immediately. Subjects whose partner has become pregnant or suspects she is pregnant during the study must report the information to the investigator. Instructions for reporting pregnancy, partner pregnancy, and pregnancy outcome are outlined in Section 7.7.2.1.

Appendix 6. Bayesian Logistic Regression Model

Determination of the highRP2D will be based on the posterior probability of DLT estimated by a 5-parameter BLRM with overdose control {Babb 1998, Neuenschwander 2008}.

Let $\pi_1[d_1]$ be the probability of DLT during the first 7 weeks of study therapy at dose level d_1 of idelalisib and $\pi_2[d_2]$ be the probability of DLT at dose level d_2 of BI 836826, under the assumption that there is no drug-drug interaction. Let $\pi_{12}[d_1, d_2]$ denote the probability of DLT when the combination of the 2 drugs are given at dose level of d_1 for idelalisib with dose level of d_2 for BI 836826. Additionally, the d_1^* and d_2^* denote a reference dose of idelalisib and BI 836826, respectively. The statistical model describing dose-toxicity relationship will have the following form:

$$\pi_1[d_1] = \frac{\exp(\log(\alpha_1) + \beta_1 \log(\frac{d_1}{d_1^*}))}{1 + \exp(\log(\alpha_1) + \beta_1 \log(\frac{d_1}{d_1^*}))}$$

$$\pi_2[d_2] = \frac{\exp(\log(\alpha_2) + \beta_2 \log(\frac{d_2}{d_2^*}))}{1 + \exp(\log(\alpha_2) + \beta_2 \log(\frac{d_2}{d_2^*}))}$$

$$\pi_{12}^0[d_1, d_2] = \pi_1[d_1] + \pi_2[d_2] - \pi_1[d_1] \times \pi_2[d_2]$$

$$odds\left(\pi_{12}[d_1, d_2]\right) = \frac{\pi_{12}^o[d_1, d_2]}{1 - \pi_{12}^o[d_1, d_2]} \times \exp\left(\gamma \left[d_1 / d_1^*\right] \times \left[d_2 / d_2^*\right]\right)$$

$$\pi_{12}[d_1, d_2] = \frac{odds\left(\pi_{12}[d_1, d_2]\right)}{1 + odds\left(\pi_{12}[d_1, d_2]\right)}$$

where

$\alpha_1, \beta_1, \alpha_2, \beta_2 > 0$, and $-\infty < \gamma < \infty$

The prior specification of the model parameters is provided in Section 3. The estimate of parameters will be updated as data are accumulated and the toxicity probability at each dose level will be calculated based on the posterior distributions of the model parameters. The estimated posterior probability of DLT at each dose level will be summarized using the following intervals:

Under dosing: [0.00, 0.20)

Targeted toxicity: [0.20, 0.35)

Excessive toxicity: [0.35, 1.00]

The overdose control criterion is set as the posterior probability of excessive toxicity less than 25%. The maximum allowable dose increment for the subsequent cohort will be no more than 100% for each drug. Out of all dose candidates satisfying the overdose control criterion, the dose cohort at which the posterior probability for the target toxicity interval is the maximum will be chosen for the next dose cohort.

Dose search will continue until one of the following incidences occurs:

- Starting dose level is declared to be too toxic.
- Maximum number of subjects (N = 36) is reached.
- More than 6 subjects have been evaluated at this dose level, posterior probability of targeted toxicity exceeds 40% at this dose level, and a minimum of 12 subjects have been treated in total at all dose levels.

1. Planned Dose Levels

The provisional dose levels for idelalisib are 50 mg BID (starting dose), 100 mg BID, and 150 mg BID, and for BI 836826 are 100 mg (starting dose), 200 mg, and 400 mg. However, dose levels for BI 836826 may subsequently be modified to include additional doses through 600 mg, dependent on safety data from this study and from Boehringer Ingelheim study 1270.1.

2. Prior Specification

BLRM model parameters include (α_1, β_1) for idelalisib, (α_2, β_2) for BI 836826, and γ for interaction between idelalisib and BI 836826.

A bivariate normal prior distribution for ($\log(\alpha_1)$, $\log(\beta_1)$) will be specified as follows:

- The estimated DLT rate at the reference dose (100 mg BID) will be set to 10%.
- Doubling the dose level is assumed to double the odds of DLT.
- Variance of $\log(\alpha_1)$ and $\log(\beta_1)$ are set to 2 with correlation of 0 to consider the uncertainty of priors.

A bivariate normal prior distribution for ($\log(\alpha_2)$, $\log(\beta_2)$) corresponding to BI 836826 will be specified similarly as follows:

- The estimated DLT rate at the reference dose (200 mg BID) will be set to 10%.
- Doubling the dose level is assumed to double the odds of DLT.
- Variance of $\log(\alpha_2)$ and $\log(\beta_2)$ are set to 2 with correlation of 0 to consider the uncertainty of priors.

A normal prior will be specified for the interaction parameter γ as follows, in a way that the distribution reflects the uncertainty in safety profile by combining idelalisib with BI 836826.

- No increase/decrease in odds of DLT is expected by interaction of idelalisib and BI 836826.
- Variance of γ is set to 2 to consider the uncertainty of priors.

In summary, the parameters of the prior distributions for BLRM are provided in Appendix Table 3, with the corresponding summaries of prior probability of DLT shown in Appendix Table 4.

Appendix Table 3. Parameters of the prior distributions

Parameter	Means	Variances	Correlation
Priors for idelalisib: ($\log(\alpha_1)$, $\log(\beta_1)$)	(-2.197, 0)	(2, 2)	0
Priors for BI 836826: ($\log(\alpha_2)$, $\log(\beta_2)$)	(-2.197, 0)	(2, 2)	0
Prior for interaction: γ	0	2	N/A

Appendix Table 4. Summary of prior probability of DLT

Dose level		Pr(DLT)	Prior Probability of		
Idelalisib	BI 836826	Median	Excessive [35%, 100%)	Target [20%, 35%)	Under [0%, 20%)
50 mg BID	100 mg	0.111	0.144	0.178	0.678
100 mg BID	100 mg	0.190	0.264	0.217	0.519
150 mg BID	100 mg	0.305	0.460	0.170	0.370
50 mg BID	200 mg	0.181	0.270	0.195	0.535
100 mg BID	200 mg	0.260	0.401	0.174	0.425
150 mg BID	200 mg	0.383	0.527	0.126	0.347
50 mg BID	400 mg	0.346	0.496	0.139	0.365
100 mg BID	400 mg	0.466	0.551	0.092	0.357
150 mg BID	400 mg	0.621	0.592	0.053	0.355

There are safety data available from Study 101-02 in which subjects with previously treated CLL received monotherapy idelalisib (Appendix Table 5) and from ongoing Phase 1 dose-escalation study 1270.1 in which subjects with R/R CLL received BI 836826 (Appendix Table 6. Assuming there is no drug-drug interaction, the predicted DLT probabilities of combination doses are summarized in Appendix Table 7.

The proposed priors have higher probabilities of DLT than the predicted ones using historical data at each combination dose level. The study will use more conservative priors for the combination therapy.

Appendix Table 5. Summary of DLTs* from monotherapy idelalisib study

Dose of idelalisib	No of DLTs/No of evaluable subjects
100 mg BID	3/11
150 mg BID	8/52
200 mg BID	3/10
350 mg BID	3/7

* Number of DLTs is retrospectively re-calculated using the definition of DLT in Study GS-US-312-1579

Appendix Table 6. Summary of DLTs from monotherapy BI 836826 study

Dose of BI 836826	No of DLTs/No of evaluable subjects
1 mg	0/3
3 mg	0/3
9 mg	0/6
25 mg	0/6
50 mg	0/3
100 mg	0/3
200 mg	1/6
400 mg	0/3
800 mg	1/2

Appendix Table 7. Summary of DLTs predicted from monotherapy of Idelalisib and BI 836826

Dose level		Pr(DLT)
Idelalisib	**BI 836826**	**Median**
50 mg BID	100 mg	0.107
100 mg BID	100 mg	0.169
150 mg BID	100 mg	0.222
50 mg BID	200 mg	0.152
100 mg BID	200 mg	0.211
150 mg BID	200 mg	0.261
50 mg BID	400 mg	0.259
100 mg BID	400 mg	0.311
150 mg BID	400 mg	0.355

3. Operating Characteristics

In order to assess operating characteristics, simulation studies were performed under 2 hypothetical scenarios. A total of 1000 trials were simulated under each scenario.

- Scenario 1: Only lowest dose level is safe
- Scenario 2: Only 2 middle dose levels have DLTs in the targeted region

Appendix Table 8. True underlying probabilities of DLT

		BI 836826		
Scenario	**idelalisib**	**100 mg**	**200 mg**	**400 mg**
1	50 mg BID	0.302	*0.436*	*0.525*
	100 mg BID	*0.398*	*0.466*	*0.563*
	150 mg BID	*0.428*	*0.491*	*0.603*
2	50 mg BID	0.092	0.136	0.185
	100 mg BID	0.149	0.257	0.322
	150 mg BID	*0.362*	*0.411*	*0.441*

* Underlined text indicates doses with true probability of DLT within the target toxicity interval [0.20, 0.35)
* Italicized text indicates doses with true probability of DLT within the target toxicity interval [0.35, 1)

Simulation parameters

The metrics evaluated to review operating characteristics are:

I. Proportion of trials that recommend dose levels with true Pr(DLT) in [20%, 35%) as the MTD (correct decision)

II. Proportion of trials that recommend dose levels with true Pr(DLT) ≥ 35% as the MTD (patient risk)

III. Proportion of trials that recommend dose levels with true Pr(DLT) < 20% as the MTD

IV. Proportion of trials which stops early because all dose levels are too toxic

V. Average number of subjects evaluated

Results of simulation study

Appendix Table 9 summarizes the operating characteristics of the model for the 2 simulated scenarios.

Appendix Table 9. Simulation results for operating characteristics

	Metrics				
Scenario	**I**	**II**	**III**	**IV**	**V**
1	14.0%	8.9%	NA	77.1%	9
2	44.0%	12.2%	15.4%	28.4%	19

The probability of recommending a correct dose combination (metric I) shows reasonable performance of BLRM, with 14.0% for Scenario 1 and 44.0% for Scenario 2. The probability of identifying an overly toxic dose combination as MTD (metric II) is low for both scenarios. When most dose combinations are set to overly toxic as in Scenario 1, the chance of stopping the study with identifying the correct MTD or declaring toxicity of all dose levels is high.

In conclusion, the simulations illustrate that the model has reasonable operating characteristics.

4. Simulation Trial Conduction

To help understand the algorithm better, we describe a simulated trial conduct of Scenario 2 with details on DLT observations, posterior distribution, and dose escalation decisions below. Detailed posterior distribution of Pr(DLT) for the candidate combination dose levels are shown for cohort 1 and 2 only to illustrate the algorithm of dose selection. Same algorithm is applied for other cohorts thus not detailed here.

Cohort 1: Three patients were treated at the starting dose of idelalisib 50 mg BID + BI 836826 100 mg (50, 100). None of them experienced a DLT. Let $Pr(DLT)_p$ represent the posterior distribution of Pr(DLT), BLRM provides probabilities of overdose, on target, and underdose for each combination dose level. There are 5 dose levels satisfying overdose control criterion as listed in the table below. The next dose level to be escalated is (100, 200), which has the highest posterior probability for the target toxicity interval out of all the dose candidates.

Dose Level (idelalisib, BI 836826)	**Overdose $Pr(DLT)_p \geq 35\%$**	**On Target $35\% > Pr(DLT)_p \geq 20\%$**	**Under Dose $Pr(DLT)_p < 20\%$**
100, 200	0.161	0.188	0.651
150, 100	0.221	0.170	0.609
100, 100	0.079	0.158	0.763
50, 200	0.106	0.151	0.743
50, 100	0.031	0.085	0.884

Cohort 2: Three patients were treated at dose level (100, 200), and 1 patient experienced a DLT. BLRM finds the following dose levels satisfying the overdose criterion, and recommends next dose level as (50, 200).

Dose Level (idelalisib, BI 836826)	**Overdose $Pr(DLT)_p \geq 35\%$**	**On Target $35\% > Pr(DLT)_p \geq 20\%$**	**Under Dose $Pr(DLT)_p < 20\%$**
50, 200	0.146	0.245	0.609
100, 100	0.182	0.226	0.592
50, 100	0.047	0.123	0.830

Cohort 3: Three more patients were treated at dose level (50, 200), and no patient experienced a DLT. BLRM recommends dose escalation to (100, 200).

Cohort 4: One DLT was observed in 3 patients treated at dose level (100, 200). BLRM recommends staying at dose level (100, 200).

Cohort 5: No patient experienced DLT, and BLRM recommends dose escalation to (150, 200)

Cohort 6: One DLT was observed, and BLRM recommends dose de-escalation to (100, 200).

Cohort 7: Two DLTs were observed. The algorithm stops as it satisfies the stopping rule. The MTD is claimed as (100, 200).

Appendix Table 10. Simulated Trial of Scenario 2

Cohort	Dose Level (idelalisib, BI 836826)	DLT/ Number of Patients
1	50, 100	0/3
2	100, 200	1/3
3	50, 200	0/3
4	100, 200	1/3
5	100, 200	0/3
6	150, 200	1/3
7	100, 200	2/3

There are safety data available from Study 101-02 in which subjects with previously treated CLL received monotherapy idelalisib (Appendix Table 11) and from ongoing Phase 1 dose-escalation study 1270.1 in which subjects with R/R CLL received BI 836826 (Appendix Table 12). Assuming there is no drug-drug interaction, the predicted DLT probabilities of combination doses are summarized in Appendix Table 13.

The proposed priors have higher probabilities of DLT than the predicted ones using historical data at each combination dose level, which means more conservative priors are used for the combination therapy.

Appendix Table 11. Summary of DLTs* from monotherapy idelalisib study

Dose of idelalisib	No of DLTs/No of evaluable subjects
100 mg BID	3/11
150 mg BID	8/52
200 mg BID	3/10
350 mg BID	3/7

* Number of DLTs is retrospectively re-calculated using the definition of DLT in Study GS-US-312-1579

Appendix Table 12. Summary of DLTs from monotherapy BI 836826 study

Dose of BI 836826	No of DLTs/No of evaluable subjects
1 mg	0/3
3 mg	0/3
9 mg	0/6
25 mg	0/6
50 mg	0/3
100 mg	0/3
200 mg	1/6
400 mg	0/3
800 mg	1/2

Appendix Table 13. Summary of DLTs predicted from monotherapy of Idelalisib and BI 836826

Dose level		Pr(DLT)
Idelalisib	BI 836826	Median
50 mg BID	100 mg	0.107
100 mg BID	100 mg	0.169
150 mg BID	100 mg	0.222
50 mg BID	200 mg	0.152
100 mg BID	200 mg	0.211
150 mg BID	200 mg	0.261
50 mg BID	400 mg	0.259
100 mg BID	400 mg	0.311
150 mg BID	400 mg	0.355
50 mg BID	800 mg	0.459
100 mg BID	800 mg	0.497
150 mg BID	800 mg	0.529