CLINICAL STUDY PROTOCOL

Study Title:	A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Efficacy and Safety of Idelalisib (GS-1101) in Combination with Bendamustine and Rituximab for Previously Treated Chronic Lymphocytic Leukemia	
Sponsor:	333 Lakeside Drive Foster City, CA 94404 USA	
IND Number:	101254	
EudraCT Number:	2011-006292-20	
Indication:	Chronic Lymphocytic Leukemia	
Gilead Protocol ID:	GS-US-312-0115	
Gilead Sciences Medical Monitor:	Name: Office Telephone: Mobile Telephone: E-mail:	PPD PPD PPD PPD
Protocol Version/Date:	Version 1.0 (Original) Version 2.0 (Amendment 1) Version 3.0 (Amendment 2) Version 4.0 (Amendment 3) Version 5.0 (Amendment 4) Version 6.0 (Amendment 5) Version 7.0 (Amendment 6) Version 8.0 (Amendment 7) Version 9.0 (Amendment 8) Version 10.0 (Amendment 9) Version 11.0 (Amendment 10)	16 March 2012 19 December 2012 01 May 2013 06 November 2013 25 April 2014 10 October 2014 15 December 2015 25 March 2016 03 August 2016 24 October 2016 21 September 2017

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

PROTOCOL SYNOPSIS

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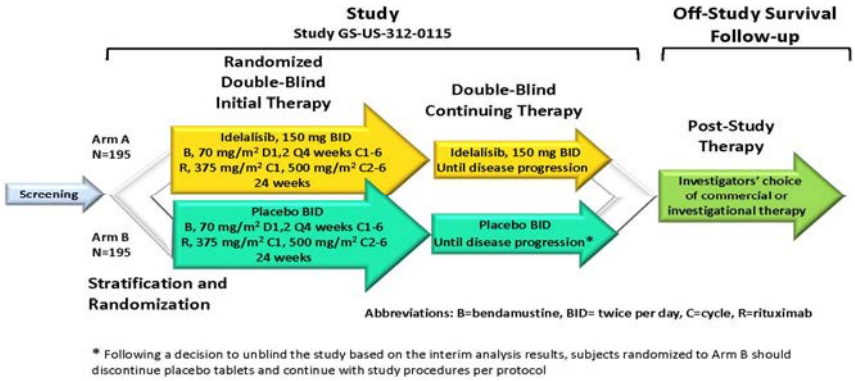
Study Title:	A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Efficacy and Safety of Idelalisib (GS-1101) in Combination with Bendamustine and Rituximab for Previously Treated Chronic Lymphocytic Leukemia
Study Centers Planned:	Approximately 180 centers in North America, South America, Australia Pacific and in Europe
IND Number: **EudraCT Number:**	101254 2011-006292-20
Primary Objective:	• To evaluate the effect of the addition of idelalisib (formerly GS-1101) to bendamustine/rituximab on progression-free survival (PFS) in subjects with previously treated chronic lymphocytic leukemia (CLL)
Secondary Objectives:	• To evaluate the effect of the addition of idelalisib to bendamustine/rituximab on the onset, magnitude, and duration of tumor control • To assess the effect of the addition of idelalisib to bendamustine/rituximab on measures of subject well-being, including overall survival (OS), health-related quality of life (HRQL), and performance status • To assess the effects of the addition of idelalisib to bendamustine/rituximab on disease-associated biomarkers and to evaluate potential mechanisms of resistance to idelalisib • To characterize the effect of bendamustine/rituximab on idelalisib exposure through evaluations of idelalisib plasma concentrations over time • To describe the safety profile observed with the addition of idelalisib to bendamustine/rituximab • To estimate health resource utilization associated with the addition of idelalisib to bendamustine/rituximab

Study Design: Study GS-US-312-0115 is a Phase 3, multicenter, 2-arm, randomized, double-blind, placebo-controlled, parallel-group clinical trial.

Study Schema

Subjects are randomized to double-blind treatment with idelalisib + bendamustine/rituximab or placebo + bendamustine/rituximab for 24 weeks, and then receive double-blind continuing therapy with idelalisib or placebo until disease progression. Following a decision to unblind the study based on the interim analysis results and DMC recommendation, subjects randomized to Arm A (idelalisib + bendamustine/rituximab) may continue study treatment with idelalisib, whereas subjects randomized to Arm B (placebo + bendamustine/rituximab) should discontinue placebo tablets.



Treatment Groups

- Arm A: Idelalisib + bendamustine/rituximab
- Arm B: Placebo + bendamustine/rituximab

Randomization and Stratification

- 1:1 allocation to Arm A vs Arm B with implementation through an interactive web response system (IWRS)
- Fixed-block centralized randomization with allocation of subjects within the 8 strata as defined by the intersection of 3 binary stratification factors:
  - 17p deletion and/or p53 mutation in CLL cells: either vs neither (or indeterminate)
  - Immunoglobulin heavy chain variable region (IgHV) mutation: unmutated (or IgHV3-21) vs mutated (or indeterminate)
  - Disease status: refractory (CLL progression <6 months from completion of prior therapy) vs relapsed (CLL progression ≥6 months from completion of prior therapy)

Number of Subjects Planned:	Total of ~390 subjects (~195 subjects per treatment arm)
Target Population:	Adult subjects with previously treated recurrent CLL who have measurable lymphadenopathy; require therapy for CLL; have received prior therapy containing a purine analog or bendamustine and an anti-CD20 monoclonal antibody; are not refractory to bendamustine; have experienced CLL progression <36 months since the completion of the last prior therapy; and are currently sufficiently fit to receive cytotoxic therapy.
Duration of Treatment:	Study drug (idelalisib/placebo) will be taken continuously until the earliest of subject withdrawal from study drug, definitive progression of CLL, intolerable study drug-related toxicity, pregnancy, substantial noncompliance with study procedures, or study discontinuation. Subjects who are tolerating study drug (idelalisib/placebo) should continue study drug even if bendamustine or rituximab must be discontinued due to bendamustine- or rituximab-related toxicities. Idelalisib administration should be continued in subjects without disease progression and in those with a positive benefit-risk profile assessment as per the investigator. Rituximab will be administered until the earliest of a maximum of 6 infusions, subject withdrawal from study, definitive progression of CLL, intolerable rituximab-related toxicity, pregnancy, substantial noncompliance with study procedures, or study discontinuation. Bendamustine will be administered until the earliest of a maximum of 12 infusions, subject withdrawal from study, definitive progression of CLL, intolerable bendamustine-related toxicity, pregnancy, substantial noncompliance with study procedures, or study discontinuation. Following a decision to unblind the study based on the interim analysis results and DMC recommendation, treatment assignments will be unblinded. Subjects randomized to Arm A (idelalisib +bendamustine/rituximab) may continue study treatment with idelalisib, whereas subjects randomized to Arm B (placebo + bendamustine/rituximab) should discontinue placebo tablets and continue with study procedures per protocol.
Diagnosis and Main Eligibility Criteria:	<u>Inclusion Criteria</u> 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 International Workshop on Chronic Lymphocytic Leukemia (IWCLL) criteria and documented within medical records.

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/μL), or
   e) Autoimmune anemia and/or thrombocytopenia that is poorly responsive to corticosteroids or other standard therapy, or
   f) Constitutional symptoms, defined as any one 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) Presence of measurable lymphadenopathy (defined as the presence of ≥1 nodal lesion that measures ≥2.0 cm in the longest diameter [LD] and ≥1.0 cm in the longest perpendicular diameter [LPD] as assessed by computed tomography [CT] or magnetic resonance imaging [MRI]).
5) Prior treatment for CLL comprising:
   a) ≥2 cycles of a regimen containing a purine analog (eg, fludarabine, pentostatin, cladribine) or bendamustine, and
   b) ≥2 doses with a regimen containing an anti-CD20 monoclonal antibody (eg, rituximab, ofatumumab, GA-101) ***Note: Prior cytotoxic drugs or anti-CD20 antibodies may have been administered as single agents or as components of combination therapies. Subjects may also have received other commercially available therapies (eg, alemtuzumab, lenalidomide, corticosteroids, or others) or non-excluded investigational therapies. Each repeated but separated therapeutic application of the same single-agent or combination is considered an independent regimen.***

6) Documentation of CLL progression <36 months since the completion of the last prior therapy for CLL.
7) Discontinuation of all therapy (including radiotherapy, chemotherapy, immunotherapy, or investigational therapy) for the treatment of CLL ≥3 weeks before randomization. ***Note: Subjects may receive corticosteroids to manage CLL manifestations.***
8) All acute toxic effects of any prior antitumor therapy resolved to Grade ≤1 before randomization (with the exception of alopecia [Grade 1 or 2 permitted], neurotoxicity [Grade 1 or 2 permitted], or bone marrow parameters [Grades 1 or 2 permitted]).
9) Karnofsky performance score of ≥60.
10) Required baseline laboratory data (within 4 weeks prior to randomization) as shown in the following table. ***Note: Confirmation should be considered for out-of-range values to determine if the abnormality is real or artifactual. Values should be obtained within the screening period and should generally be the most recent measurement obtained.***

Required Screening Laboratory Values

Organ System	Parameter	Required Value
Hematopoietic	ANC	≥1.5 x 10^9/L[a]
	Platelets	≥75 x 10^9/L[a]
	Hemoglobin	≥100 g/L (10.0 g/dL or 6.2 mmol/L)[a]
Hepatic	Serum total bilirubin	≤1.5 x ULN (unless elevated due to Gilbert's syndrome or hemolysis)
	Serum ALT	≤2.5 x ULN
	Serum AST	
Renal	eC_{Cr}[b]	≥40 ml/min
Pregnancy	β-HCG[c]	Negative
Infection	HIV	Negative HIV antibody
	HBV	Negative HBsAg and negative HBc antibody or positive HBc and negative for HBV DNA by quantative PCR
	HCV	Negative viral RNA (if HCV antibody is positive)

a Grade ≥2 neutropenia, thrombocytopenia, or anemia is permitted if abnormality is related to bone marrow involvement with CLL (as documented by bone marrow biopsy/aspirate obtained since the last prior therapy).
b As calculated by the Cockcroft-Gault formula {Cockcroft 1976}
c For women of child-bearing potential only; serum β-HCG must be negative during screening and serum β-HCG or urine dipstick pregnancy test must be negative at randomization (Visit 2)

Abbreviations: β-HCG=beta human chorionic gonadotropin, ALT=alanine aminotransferase, ANC=absolute neutrophil count, AST=aspartate aminotransferase, DNA=deoxyribonucleic acid, eC_{Cr}=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

11) For female subjects of childbearing 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 study drug or >12 months from the last dose of rituximab (whichever is later). ***Note: A female subject is considered to be of childbearing potential unless she has had a hysterectomy, bilateral tubal ligation, or bilateral oophorectomy; has medically documented ovarian failure (with serum estradiol and follicle-stimulating hormone [FSH] levels within the institutional postmenopausal range and a negative serum or urine βHCG); or is menopausal (*****defined as age ≥54*** *with amenorrhea for >12 months or amenorrhea for >6 months with serum estradiol and FSH levels within the institutional postmenopausal range).***

12) For male subjects of childbearing potential having intercourse with females of childbearing potential, willingness to use a protocol-recommended method of contraception from the randomization visit (Visit 2) throughout the study and until ≥6 months following the last dose of bendamustine or ≥90 days following the last dose of study drug (whichever is later) and to refrain from sperm donation from randomization (Visit 2) throughout the study and until ≥6 months following the last dose of bendamustine or ≥90 days following the last dose of study drug (whichever is later). ***Note: A male subject is considered able to father a child unless he has had a bilateral vasectomy with documented aspermia or a bilateral orchiectomy, or has ongoing testicular suppression with a depot luteinizing hormone-releasing hormone (LH-RH) agonist (eg, goserelin acetate [Zoladex®]), leuprolide acetate [Lupron®]), or triptorelin pamoate [Trelstar®]).***

13) In the judgment of the investigator, participation in the protocol offers an acceptable benefit-to-risk ratio when considering current CLL disease status, prior treatment history, medical condition, and the potential benefits and risks of alternative treatments for CLL. ***Note: Investigators should consider whether a study subject is an appropriate candidate for bendamustine-containing therapy based on the number and severity of comorbid conditions; subjects with a baseline Cumulative Illness Rating Scale (CIRS) score of ≤6 may be particularly appropriate candidates for this trial.***

14) Willingness and ability to comply with scheduled visits, drug administration plan, imaging studies, laboratory tests, other study procedures, and study restrictions. ***Note: Psychological, social, familial, or geographical factors that might preclude adequate study participation should be considered***.

15) 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). ***Note: Biopsy documentation of the absence or presence of transformation is not required.***
2) Known presence of intermediate- or high-grade myelodysplastic syndrome (ie, subjects are excluded who have ≥5% bone marrow blasts; karotypic abnormalities other than normal, Y deletion, 5q deletion, or 20q deletion; or ≥2 lineages of cytopenias due to myelodysplasia).
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 randomization, other adequately treated Stage 1 or 2 cancer currently in complete remission, or any other cancer that has been in complete remission for ≥5 years.
4) Evidence of ongoing systemic bacterial, fungal, or viral infection at the time of randomization (Visit 2). ***Note: Subjects with localized fungal infections of skin or nails are eligible. Subjects may be receiving prophylactic antiviral or antibacterial therapies at the discretion of the investigator. For subjects who are at substantial risk of an infection (eg, influenza) that may be prevented by immunization, consideration should be given to providing the vaccine prior to initiation of protocol therapy.***
5) 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.
6) Ongoing drug-induced pneumonitis.
7) Ongoing inflammatory bowel disease.

8) Ongoing alcohol or drug addiction.
9) Pregnancy or breastfeeding.
10) History of prior allogeneic bone marrow progenitor cell or solid organ transplantation.
11) Ongoing immunosuppressive therapy other than corticosteroids.
Note: Subjects may use topical, enteric, inhaled, or systemic corticosteroids as therapy for manifestations of CLL, comorbid conditions, or autoimmune anemia and/or thrombocytopenia. During study participation, subjects may receive systemic or other corticosteroids as pretreatment for rituximab infusions or as needed for treatment-emergent comorbid conditions.
12) In a subject with a history of prior bendamustine therapy, a time interval from the last dose of bendamustine to the subsequent CLL progression of <6 months.
13) History of prior therapy with any inhibitor of AKT, Bruton tyrosine kinase (BTK), Janus kinase (JAK), mammalian target of rapamycin (mTOR), phosphatidylinositol 3-kinase (PI3K) (including idelalisib), or spleen tyrosine kinase (SYK).
14) History of anaphylaxis in association with previous administration of monoclonal antibodies.
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:

Subjects will be randomized with a 1:1 ratio into 1 of the 2 treatment arms. Idelalisib or placebo will be taken orally, BID continuously. After study-wide unblinding, placebo will no longer be administered.

Subjects will be administered rituximab in the clinic on Day 1 of each 28-day cycle through Cycle 6. Subjects will be administered bendamustine on Days 1 and 2 of each 28-day cycle through Cycle 6.

Clinic/laboratory visits will occur every 2 weeks through Week 24 and every 6 weeks between Weeks 24 and 48. Subjects who continue on study drug past Week 48 will have clinic visits every 12 weeks (as well as CMV testing approximately every 4 weeks). Subjects will be assessed for safety at each clinic visit. Subjects will be assessed for CLL disease status by physical and laboratory examinations at each clinic visit and by CT or MRI at Weeks 12, 24, 36, and 48 and every 12 weeks thereafter. As of Amendment 10, Version 11, CT/MRI assessments will no longer be performed at the every 12 week scheduled visits, and will only be performed at the time of clinically-suspected disease progression or at study discontinuation.

Test Therapy, Dose, and Mode of Administration:	• Idelalisib: 150 mg/dose or placebo taken orally BID starting on Day 1 and administered continuously thereafter. After study-wide unblinding, placebo will no longer be administered.
Reference Therapy, Dose, and Mode of Administration:	• Rituximab: 375 mg/m^2 intravenously on Day 1 of the first 28-day cycle of treatment; followed by 500 mg/m^2 intravenously on Day 1 of each of 5 further 28-day cycles of treatment (up to 6 total cycles as tolerated) • Bendamustine: 70 mg/m^2/dose intravenously on Day 1 and Day 2 of each 28-day cycle (up to 6 total cycles as tolerated)
Criteria for Evaluation:	Primary Endpoint • 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; definitive disease progression is CLL progression based on standard criteria, other than lymphocytosis alone. Secondary and Tertiary Endpoints Four endpoints are designated as secondary endpoints for which sequential testing will be performed to control Type 1 error rate. Secondary endpoints will be ORR, lymph node response rate, OS, and CR rate. All other endpoints will be considered tertiary. *Tumor Control* • Overall response rate (ORR) – defined as the proportion of subjects who achieve a complete response (CR) or partial response (PR) • Lymph node response rate – defined as the proportion of subjects who achieve a ≥50% decrease from baseline in the sum of the products of the greatest perpendicular diameters (SPD) of index lesions • CR rate – defined as the proportion of subjects who achieve a CR CCI

Patient Well-Being

- Overall survival (OS) – defined as the interval from randomization to death from any cause

Statistical Methods:

Analysis Methods

Appropriate data analysis sets will be defined. The intent-to-treat (ITT) analysis set will be used in the analyses of the primary efficacy endpoint, PFS. The ITT analysis set will include data from all subjects who are randomized with study drug (idelalisib/placebo) assignment designated according to initial randomization. A safety analysis set will comprise data from subjects who receive ≥1 dose of study drug. Other analysis sets [per-protocol and pharmacodynamic/pharmacokinetic data analysis] will be used for certain analyses as well.

Subject characteristics and study results will be described and summarized by treatment arm and assessment for the relevant analysis sets. Descriptive summaries will be prepared to show sample size, mean, standard deviation, 95% confidence intervals (CIs) 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 analyses of PFS and other tumor control endpoints.

For the primary efficacy analysis, the difference in PFS between the treatment arms will be assessed in the ITT analysis set using Kaplan-Meier methods and the stratified log-rank test. Medians, ranges, the proportion of subjects who are progression-free at 24 and 48 weeks from randomization (based on Kaplan-Meier estimates), hazard ratios, and the corresponding 95% confidence intervals (CIs) (as calculated using a Cox proportional hazards regression model) will be presented.

Secondary endpoints will be ORR, lymph node response rate, CR rate, and OS. The primary efficacy hypothesis relating to PFS must be rejected at the 2-sided 0.05 significance level before the efficacy hypotheses for these secondary efficacy endpoints are tested. These 4 secondary endpoints will be tested at the 2-sided 0.032 significance level in the order listed. If a null hypothesis is not rejected, formal sequential testing will be stopped and only nominal significance will be cited for the remaining secondary endpoints.

For secondary or tertiary endpoints relating to tumor control, patient well-being, and biomarkers, analyses will be done based on the ITT, PP, or pharmacodynamic data sets, as appropriate. Time-to-event efficacy endpoints will be analyzed in a similar manner as PFS.

Categorical variables will be compared using the Cochran-Mantel-Haenszel test adjusted for stratification factors. Continuous endpoints will be assessed using analysis of covariance (ANCOVA) with baseline values and stratification factors as covariates. Changes from baseline in HRQL parameters and in performance status will be compared between the treatment groups using the Wilcoxon rank-sum test.

Information from the safety analysis set regarding study drug administration, study drug compliance, safety variables, and post-study therapies will be described and summarized. Using data from the pharmacokinetic analysis set, idelalisib plasma concentrations will also be described and summarized.

Sample Size Calculation

Based on data from prior studies, it is reasonable to assume that administration of bendamustine/rituximab to subjects with previously treated CLL in Arm B of this trial will result in a median PFS of ~15 months. An improvement in median PFS from 15 months to 22.5 months due to the addition of idelalisib to bendamustine/rituximab in Arm A of the study would correspond to a benefit ratio of 1.5 (hazard ratio 0.67).

It is assumed that PFS times are exponentially distributed in each of the 2 arms. With a hazard ratio equal to 1 under the null hypothesis of no difference between the 2 treatment arms and a hazard ratio of 0.67 under the

alternative hypothesis of superiority of the idelalisib-containing combination, 260 events (definitive CLL progressions or deaths) are required to achieve a power of 0.90 based on a stratified log-rank test with a 2-sided significance level of 0.05. Further assuming a planned accrual period of 18 months (with approximately half of the subjects enrolled during the initial 60% of the accrual period, and the remaining half of the subjects enrolled during the last 40% of the accrual period), a minimum follow-up period of 24 months, and an expectation that 15% of subjects will be lost to follow-up (7% during the accrual period and 8% during the follow-up period), ~195 subjects per treatment arm (~390 total) are to be enrolled in order to achieve the expected number of events by the end of the planned minimum 24-month follow-up period.

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

β-HCG	Beta human chorionic gonadotropin
ABCG2	adenosine triphosphate-binding cassette sub-family G member 2 (see also BCRP)
AKT	AKT (a serine/threonine protein kinase)
ALC	absolute lymphocyte count
ALL	acute lymphocytic leukemia
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
ATC	Anatomical-Therapeutic-Chemical classification system for drugs
BCRP	breast cancer resistance protein (see also ABCG2)
BID	twice per day
BTK	Bruton tyrosine kinase
CCL	chemokine (C-C motif) ligand
CFR	Code of Federal Regulations
CI	confidence interval
CIRS	Cumulative Illness Rating Scale
CLL	chronic lymphocytic leukemia
cGMP	current Good Manufacturing Practice
C_{max}	maximum concentration
CMV	cytomegalovirus
CR	complete response
CRO	contract research organization
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
C_{trough}	trough concentration
CXCL	chemokine (C-X-C motif) ligand
CYP	cytochrome P450 enzyme
DLCO	diffusing capacity of the lung for carbon monoxide
DMC	data monitoring committee
DNA	deoxyribonucleic acid
DOR	duration of response
DSPH	Gilead Drug Safety and Public Health
ECG	electrocardiogram
eC_{Cr}	estimated creatinine clearance

eCRF	electronic case report form
EDC	electronic data capture
ELISA	enzyme-linked immunosorbent assay
EQ-5D	EuroQoL Five-Dimension utility measure
FACT-Leu	Functional Assessment of Cancer Therapy: Leukemia questionnaire
FCεRI	high-affinity IgE receptor
FDA	United States Food and Drug Administration
FDAMA	Food and Drug Modernization Act
FDG	fluorodeoxyglucose (18F)
FISH	fluorescence in-situ hybridization,
FSH	follicle-stimulating hormone
G-CSF	granulocyte colony-stimulating factor
GGT	gamma-glutamyltransferase
GLP	Good Laboratory Practice
GM-CSF	granulocyte-macrophage colony-stimulating factor
HBc antibody	anti-hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
hERG	human ether-à-go-go-related gene
HL	Hodgkin lymphoma
HIV	human immunodeficiency virus
HRQL	health-related quality of life
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
idelalisib	Formerly CAL-101 and GS-1101
IEC	independent ethics committee
Ig	immunoglobulin (including subtypes A, E, G, and M)
IgHV	immunoglobulin heavy chain variable region
IND	Investigational New Drug (application)
iNHL	indolent non-Hodgkin lymphoma
INR	international normalized ratio
IRB	institutional review board
IRC	independent review committee
ITT	intention to treat
IUD	intrauterine device
IWCLL	International Workshop on CLL
IWRS	interactive web response system
JAK	Janus kinase
K_2-EDTA	potassium-ethylenediaminetetraacetic acid

LD	longest diameter
LDH	lactate dehydrogenase
LH-RH	luteinizing hormone-releasing hormone
LLN	lower limit of normal
LPD	longest perpendicular diameter
LVD	longest vertical dimension
MTD	maximum tolerated dose
MCL	mantle cell lymphoma
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
mTOR	mammalian target of rapamycin
ND	no disease
NHL	non-Hodgkin lymphoma
NOAEL	no-observed-adverse effect level
NOEL	no-observed-effect level
OCT	organic cation transporter
ORR	overall response rate
OS	overall survival
pAKT	phosphorylated AKT
PCR	polymerase chain reaction
PD	progressive disease
PET	positron-emission tomography
PI3K	phosphatidylinositol 3-kinase
PI3Kδ	phosphatidylinositol 3-kinase p110δ isoform
PFS	progression-free survival
PJP	*Pneumocystis jirovecii* pneumonia
PML	progressive multifocal leukoencephalopathy
PP	per-protocol
PPD	product of the perpendicular diameters
PRO	patient-reported outcome
PR	partial response
PT	prothrombin time
PVA	polyvinyl alcohol
QD	once per day
QT (interval)	measure of time between start of Q wave and end of T wave in electrical cycle of heart
RNA	ribonucleic acid
SADR	serious adverse drug reaction
SD	stable disease
SJS	Steven's- Johnson Syndrome
SPD	sum of the products of the perpendicular diameters of measured lymph nodes

SSC	Study Steering Committee
SUSAR	suspected, unexpected, serious adverse reaction
SYK	spleen tyrosine kinase
$t_{1/2}$	half-life
T_{max}	time of maximum concentration
TEN	toxic epidermal necrolysis
TTR	time to response
UGT	uridine 5'-diphospho-glucuronosyltransferase
ULN	upper limit of normal
US	United States
WHODRUG	World Health Organization Drug Dictionary
ZAP=70	zeta-associated protein 70

1. INTRODUCTION

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}. CLL constitutes the most commonly occurring leukemia in the United States (US) and Europe {Sant 2010, Surveillance Epidemiology and End Results (SEER) Program 2011}. While some patients never require treatment, many will need therapy for disfiguring or obstructing lymphadenopathy, debilitating constitutional B symptoms (fevers, night sweats, fatigue, weight loss) {Redaelli 2004}, or recurrent cytopenias and infections {Keating 2002b, Perkins 2002}. 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}.

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 eventually relapse and further intervention is required to obtain and maintain tumor control. If the interval from prior therapy to disease progression has been long (≥24 to 36 months), retreatment with the previous regimen is advocated {Eichhorst 2010, Zelenetz 2011}. However, if the interval from prior therapy has been shorter (<24 to 36 months), it is presumed that resistance to the previously administered cytotoxic agent is likely and that a change in therapy is warranted.

Bendamustine is an alkylating agent with a unique chemical structure that has seen increasing use in the therapy of lymphoid malignancies {Kalaycio 2009}. The drug was approved for the treatment of CLL in Europe and in the US based on positive results of randomized Phase 3 trial showing substantially improved tumor control with bendamustine alone compared with chlorambucil alone in previously untreated patients {Knauf 2009}. However, the pharmacological profile of bendamustine suggested that it might also be useful in patients with disease that had become resistant to other cytotoxic agents {Jamshed 2009}. Preclinical data indicated that bendamustine has distinctive activity in cell lines resistant to other alkylators {Kalaycio 2009} and clinical findings showing substantial activity in patients with indolent non-Hodgkin lymphoma (iNHL) refractory to alkylating agents or purine analogs {Friedberg 2008}.

Application of bendamustine in patients with previously treated CLL was explored in a Phase 1 dose-ranging study that included patients who had received prior fludarabine {Lissitchkov 2006}. The starting dose regimen of 100 mg/m^2 on Days 1 and 2 of each 4-week treatment cycle was the same as had been employed in the Phase 3 registration trial in previously untreated patients {Knauf 2009}. In the Phase 1 study in previously treated patients it was found that the planned starting dose of 100 mg/m^2 was intolerable due to myelotoxicity and infection.

Sequential dose-de-escalation was performed in 10-mg/m^2 decrements (with dose levels including 100, 90, 80, and 70 mg/m^2). The data confirmed a maximum tolerated dose (MTD) of 70 mg/m^2 but showed that this starting dose level was still associated with antitumor activity in the majority of patients.

These findings led to efforts to combine bendamustine with rituximab as therapy for previously treated CLL. In a prospective Phase 2 study of the German CLL Study Group, 78 patients received bendamustine 70 mg/m^2 on Day1 and 2 in 6 planned 4-week cycles. Study participants also received rituximab at the beginning of each cycle, with planned doses of 375 mg/m^2 in the first cycle and 500 mg/m^2 in the 5 subsequent cycles {Fischer 2011}. The overall response rate (ORR) was 59% and progression-free survival (PFS) was 15.2 months. The best positive predictors of improved tumor control were absence of a 17p deletion and mutated immunoglobulin heavy chain variable region (IgHV) in malignant cells. The clinical data from this trial were supported by an Italian retrospective analysis of 109 patients with previously treated CLL receiving bendamustine/rituximab (N=87) or bendamustine monotherapy (N=22) {Iannitto 2011}. Among those administered bendamustine/rituximab, 63% ORR was observed. Median PFS was reported at 16 months. The results indicated that patients with relapsed disease had substantially better outcomes than those with refractory CLL. Myelotoxicity was the major reported adverse event reported in both series and was more prominent among patients with comorbidities such as renal dysfunction {Fischer 2011}.

These data have supported adoption of bendamustine/rituximab therapy in current treatment guidelines as a standard of care for previously treated patients who are sufficiently fit to receive cytotoxic therapy {Eichhorst 2010, Zelenetz 2011}. Based on the deliberations of an international panel of expert hematologists, a bendamustine starting dose of 70 mg/m^2 has been considered appropriate when the drug is coadministered with rituximab in patients who had received prior therapy {Cheson 2010}

However, while the bendamustine/rituximab combination offers benefit, tumor response is not universal and progressive disease eventually develops in all patients. New non-myelosuppressive, well-tolerated, and convenient therapies that can be successfully combined with bendamustine/rituximab are needed in order to enhance and prolong tumor control.

1.2. Phosphatidylinositol 3-Kinase in Lymphoid Malignancies

Phosphatidylinositol 3-kinases (PI3Ks) are enzymes that regulate several cellular functions including motility, proliferation, and survival {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. While potentially important in multiple cell types, 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, and live a normal life span without an increased susceptibility to infections {Okkenhaug 2003a}. However, the B-lymphocyte population in these animals shows a decrease in maturation, diminished receptor-induced proliferation, and increased susceptibility to apoptotic cell death. 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 {Cuni 2004, Herman 2010, Lannutti 2011}.

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

1.3. Idelalisib (formerly GS-1101)

1.3.1. General Information

Idelalisib was approved in the US on July 23, 2014 and in the European Union on September 18, 2014. Refer to local labeling for the approved indication statements and dosing recommendations.

Gilead Sciences, Inc. has developed novel drugs that can suppress tumor growth through targeting of PI3Kδ activity. High-throughput screening was the basis for the discovery of novel agents that selectively inhibit PI3Kδ function but spare other PI3K isoforms and other kinases. Chemical optimization, pharmacological characterization, and toxicological evaluation have led to identification of idelalisib, a 415-dalton, orally bioavailable, new chemical entity with potential clinical utility in the treatment of cancers.

In primary tumor samples and in cell lines derived from patients with CLL, indolent non-Hodgkin lymphoma (iNHL), mantle cell lymphoma (MCL), B-cell acute lymphocytic leukemia (ALL), or Hodgkin lymphoma (HL), idelalisib induces dose-dependent reductions in AKT phosphorylation {Herman 2010, Lannutti 2011, Meadows 2010}. In addition, idelalisib disrupts the PI3Kδ activation and supportive intercellular signaling observed when CLL or HL cells are cocultured with stromal cells {Hoellenriegel 2011, Meadows 2010}. These effects have therapeutic consequences. In multiple lymphoid primary tumors and malignant cell lines, idelalisib enhances apoptosis and concentration-dependent cell killing when applied as a single agent and increases the therapeutic efficacy of other antineoplastic agents when given in combination {Hoellenriegel 2011, Meadows 2011}. In preclinical systems, coadministration of idelalisib with rituximab has not impaired rituximab-mediated activity {Herman 2010}.

1.3.2. Safety Pharmacology

In vitro and in vivo safety pharmacology studies with idelalisib have demonstrated a favorable non-clinical safety profile. These studies indicate that the drug may minimally slow bone marrow progenitor proliferation and differentiation and that it has expected inhibitory effects on B-cell response to antigen challenge. However, the data indicate that idelalisib is unlikely to cause serious off-target effects or adverse effects on critical organ systems. Idelalisib has no meaningful effect on the human ether-à-go-go-related gene (hERG) channel, indicating that idelalisib would not be expected to induce clinical QT prolongation.

The drug has also proved well tolerated in standard in vivo Good Laboratory Practice (GLP) studies of pharmacological safety. A functional observation battery in rats revealed no adverse effects on behavior or on autonomic, neuromuscular, or sensorimotor function. In a cardiopulmonary function study in awake, telemeterized male beagle dogs, single doses of idelalisib induced no meaningful abnormalities in pulmonary, cardiovascular, arterial blood gas, or electrocardiographic (ECG) (including QT interval) parameters. In an assessment of bacterial challenge in rats, idelalisib enhanced, rather than impaired, the phagocytic host clearance of staphylococcal bacteria.

1.3.3. Nonclinical Pharmacology and Metabolism

Consistent with the moderate to high bioavailability seen in nonclinical species, idelalisib shows high permeability across human Caco-2 cell monolayers. At lower concentrations, the reverse permeability at low concentration exceeds forward permeability, indicating efflux driven by transporters (for eg, human P-glycoprotein MDR1 and breast cancer resistance protein (BCRP)); idelalisib is a substrate for the efflux transporters MDR1 and BCRP; however, the permeability increases in a concentration-dependent manner, resulting in a lower efflux ratio at higher, clinically relevant concentrations of idelalisib.

Idelalisib exhibits moderately high plasma protein binding in mouse, rat, dog, and human. In dog and human plasma, the protein binding is concentration-independent between 1 and 20 μM. Protein binding in human plasma is slightly higher than in mouse, rat, and dog plasma, which have comparable free fractions. In human plasma, idelalisib and GS-563117 (a metabolite of idelalisib) have an average free fraction of ~16% and ~12%, respectively.

After oral administration of [^{14}C] idelalisib to rats and dogs, radioactivity is widely distributed, but relatively excluded from bone, brain, spinal cord, and eye lens in rats and from brain and eyes in dogs. In rats, the radioactivity declines steadily and most tissues have undetectable levels by 72 hours post dose. In bile duct-cannulated rats and dogs, ≥ 69% of radioactivity is recovered in bile and urine, indicating high absorption of idelalisib in vivo.

In hepatic tissues from nonclinical species, idelalisib is primarily metabolized by aldehyde oxidase, CYP3A, and UGT1A4. In vitro metabolism in dog and human yields 3 primary oxidative metabolites and 5 primary glucuronides. Of these, the oxidative product GS-563117 is the predominant metabolite in vitro and in vivo. In preclinical species, plasma levels of GS-563117 are below those of idelalisib. In humans GS-563117 (the only circulating metabolite, formed via aldehyde oxidase) plasma levels significantly exceed those of idelalisib. After oral administration of [^{14}C] idelalisib to rats and dogs, biliary excretion appears to be the major route of elimination of idelalisib and its metabolites as the majority of radioactivity is found in feces or bile and little in urine.

Idelalisib is not a substrate for the renal transporters OCT2, OAT1, and OAT3 or the hepatic uptake transporters OATP1B1 and OATP1B3. GS-563117 is not a substrate for OATP1B1 and OATP1B3.

Idelalisib is not an inhibitor of CYP1A, CYP2B6, CYP2C9, and CYP2D6, and at concentrations above those observed clinically, is an inhibitor of CYP2C8 (IC_{50} = 13 µM), CYP2C19 (IC_{50} = 76 µM), and CYP3A (IC_{50} = 44 µM). GS-563117 is not an inhibitor of CYP1A, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP2D6, and a competitive and time dependent inhibitor of CYP3A (IC_{50} = 3.1 µM), (K_I = 0.18 µM, k_{inact} = 0.033 min^{-1} with midazolam as the probe substrate).

In vitro, idelalisib is not an inhibitor of the transporters BCRP, OCT2, OAT1, and OAT3, and is an inhibitor of MDR1 (IC_{50} = 7.7 µM), OATP1B1 (IC_{50} = 10.1 µM), OATP1B3 (IC_{50} = 7.0 µM), and, at concentrations above those observed clinically, of glucuronosyltransferase UGT1A1 (IC_{50} = 42.0 µM). GS-563117 is not an inhibitor of MDR1, BCRP, OATP1B1, OATP1B3, OAT1, OAT3, and OCT2, and at concentrations above those observed clinically, an inhibitor of UGT1A1 (IC_{50} = 16.8 µM).

Idelalisib does not activate human AhR or induce CYP1A2 [messenger RNA (mRNA) or activity] at clinically relevant concentrations. Idelalisib is a weak activator of human PXR (EC_{50} = 18 µM) and shows similarly weak potency as an inducer of CYP3A4, CYP2C8, CYP2C9, UGT1A1, and MDR1 (by mRNA). Approximately 2-fold weaker induction of CYP2B6 activity and mRNA suggests weak activation of CAR. GS-563117 shows no induction of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP3A, UGT1A1, UGT1A4, MDR1, and aldehyde oxidase at clinically relevant concentrations.

Any potential clinical implications of these metabolism studies are being evaluated in a formal drug-drug interaction study (GS-US-313-0130) which is evaluating the effect of idelalisib on cytochrome P450 3A and the drug transporters P-gp, OATP1B1, and OATP1B3. Study GS-US-313-0130 will also evaluate the impact of an inducer of metabolizing enzymes and transporters (rifampin) on the PK of idelalisib in healthy human subjects. Preliminary findings from this study are presented in Section 1.3.5.1.

1.3.4. Toxicology

The toxicological profile of idelalisib was well characterized through the conduct of single dose, repeat dose, developmental and reproductive and genetic toxicology and local tolerance studies. The primary target organ toxicities following repeated dosing include the lymphoid, hepatic, male reproductive systems in rats and dogs, and gastrointestinal system in dogs. Adverse effects in the lymphoid system were primarily the result of on target pharmacology resulting in decreased lymphocytes in multiple lymphoid organs, primarily involving B-cell regions. Liver effects were transient and reversible with continued dosing and did not result in chronic liver injury. Reduction in sperm numbers in males were reversible and did not impact fertility or reproductive performance. Gastrointestinal effects in dogs were minor, superficial, and considered secondary to effects on lymphocytes in Peyer's Patches. Idelalisib was shown to be teratogenic and associated with embryo-fetal lethality. Effects on the reproductive system have been reported for inhibitors which target other isoforms of PI3K. The dose-dependence and potential of idelalisib to selectively inhibit additional PI3K isoforms may be responsible for the off-target toxicity. Additionally, the drug may have the potential to produce phototoxic reactions in humans. These findings represent toxicities that can be monitored, are considered clinically manageable, or are considered acceptable risks in the intended patient population.

Further details on the toxicology of idelalisib can be found in the Idelalisib Investigator's Brochure (IB).

1.3.5. Idelalisib Clinical Studies

1.3.5.1. Phase 1 Studies in Healthy Subjects and in Patients with Allergic Rhinitis

Various studies in healthy subjects have evaluated safety, pharmacokinetics, food effect, and the potential for drug interactions of idelalisib with CYP3A4 inhibitors {Webb 2010}. Safety results from these studies indicated that idelalisib was well tolerated when administered to healthy subjects at single doses through 400 mg (the highest dose level tested) and was also generally well tolerated when administered to healthy subjects over 7 days at dose levels through 200 mg/dose BID (the highest dose level tested). Dosing with 200 mg/dose BID for 7 days resulted in a skin rash in 3 out of 6 subjects; histological findings were consistent with a delayed-type hypersensitivity maculopapular exanthema. Rashes have sometimes occurred in patients with hematological malignancies receiving idelalisib, but have not typically proved dose- or treatment-limiting. In placebo-controlled single-dose and multiple-dose trials, repeated ECG evaluations performed in tandem with pharmacokinetic monitoring showed no evidence of drug-, dose-, or exposure-dependent effects on cardiac rhythm or cardiac intervals (eg, QT interval).

Pharmacokinetic results indicated that idelalisib appeared rapidly in plasma with a median T_{max} of 1 to 1.5 hours. Cmax and AUC increased in a less-than-dose-proportional manner and mean $t_{1/2}$ values across the dose range were 6.5 to 9.8 hours.

Idelalisib dosing after a high-fat, high-calorie meal delayed median time of maximum concentration (T_{max}) from 0.75 hours to 3 hours; mean C_{max} was unaffected and mean AUC was ~40% higher. These changes in idelalisib exposures are considered modest/clinically non-relevant; thus, idelalisib may be given with or without food.

Idelalisib is primarily metabolized in humans by aldehyde oxidase, with some involvement of CYP3A4 and UGT1A4. Accordingly, when idelalisib was administered following 4 days of daily dosing with ketoconazole (a potent inhibitor of CYP3A4), modest/moderate increases in mean idelalisib C_{max} and AUC values of ~30% and ~80%-higher, respectively, were observed, indicating that idelalisib is not a sensitive substrate for CYP3A4. Thus, coadministration of CYP3A4 inhibitors and idelalisib is not contraindicated and does not require special monitoring. GS-563117 is formed from idelalisib primarily via aldehyde oxidase.

The ^{14}C-labeled idelalisib human mass balance results showed that the drug has moderate to high oral bioavailability. Idelalisib is eliminated mainly via hepatic metabolism and biliary excretion in the feces (~78% of dose); recovery in urine was < 15%. GS-563117, was the primary/only circulating metabolite observed in human plasma, and was also observed in urine and feces.

Results from the drug interaction/probe Study GS-US-313-0130 indicate that idelalisib does not affect the pharmacokinetics of substrates of Pgp, BCRP, OATP1B1, or OATP1B3 transporters. Idelalisib is not expected to affect the exposures of coadministered agents via transporter mediated interactions.

The exposures (AUC) of probe CYP3A substrate, midazolam, increased ~5-fold upon coadministration with idelalisib, driven by competitive and time-dependent CYP3A inhibition by GS-563117, the only circulating metabolite of idelalisib. Coadministration of the highly potent CYP3A inducer rifampin resulted in a ~75% reduction in idelalisib systemic exposures, likely driven by a higher relative contribution to CYP3A to overall idelalisib clearance under the induced state.

Pharmacodynamic results showed that a idelalisib dose of 200 mg inhibited ex vivo basophil activation via the PI3Kδ-specific, high-affinity immunoglobulin (Ig)E receptor (anti-FCεR1) in basophils collected from healthy volunteers. The findings were confirmed when the drug was assessed over 7 days in a Phase 1b study in subjects with allergic rhinitis. In this study, idelalisib at a dose level of 100 mg/dose BID showed clinical and pharmacodynamic activity (attenuating adverse responses to allergenic challenge and decreasing markers of inflammation) and was well tolerated.

1.3.5.2. Phase 1 Studies in Patients with Hematological Malignancies

1.3.5.2.1. Phase 1 Monotherapy Study in Patients with Hematological Malignancies (Study 101-02)

A Phase 1 dose-ranging study (Study 101-02) of single-agent idelalisib extended safety and pharmacokinetic observations; documented the clinical and pharmacodynamic activity of idelalisib in subjects with iNHL, MCL, and CLL; and provided dosing information in support of further development {Brown 2011, Coutre 2011, Kahl 2011}. In this study, idelalisib was administered in cohorts of subjects across a range of dose levels from 50 mg/dose BID to 350 mg/dose BID. Idelalisib administration was continued as long as individual subjects were safely benefitting from therapy. Subjects were evaluated in 4-week cycles; response and progression assessments were based on standard criteria {Hallek 2008}.

A total of 191 subjects were enrolled to the study at dose levels of 50 mg BID (n=17), 150 mg QD (n=16), 100 mg BID (n=25), 150 mg BID (n=45), 200 mg BID (n=35), 350 mg BID (n=17), and 300 mg QD (n=19). An additional cohort was also enrolled to receive idelalisib 150 mg BID in 28 day cycles (21 days on idelalisib/7 days off [n=17]), Patients characteristics were as follows: males/females n=139 (73%)/52 (27%) with median age of 64.5 (range 32-91) years. Diagnoses included: CLL, n=54 (28%); iNHL, n=64 (34%); aggressive NHL (MCL and DLBCL), n=49 (26%); AML, n=12 (6%); and MM, n=12 (6%). Categorization of disease by response to the last prior therapy included: refractory, n=111 (58%); relapsed, n=79 (42%); and unknown, n=1 (1%). The median (range) number of prior therapies was 5 (1-14). Among subjects with iNHL and CLL, the majority had received prior rituximab and prior alkylating agent therapy.

Adverse events were usually mild to moderate and not clearly idelalisib-related. Among Grade ≥3 adverse events, pneumonias and diarrhea were notable. Pneumonia was observed in 23 (12%) subjects, primarily in subjects with CLL. In most instances, these findings were considered bacterial in origin, based either on culture results or on response to conventional antibiotics. Grade ≥3 adverse events of diarrhea were seen in 11 subjects (5.8%).

Other Grade ≥3 events included rash in 3 (1.6%) subjects. The relative contributions of disease-related factors, toxicity from prior therapies or ongoing supportive care, and idelalisib to these events was not clear.

Grade ≥3 hematological laboratory abnormalities have included neutropenia, n=46 (24%); thrombocytopenia, n=27, (14%), anemia, n=14 (7.3%), and lymphopenia 13 (6.8%); with 12 subjects (6.3%) having febrile neutropenia. The occurrence of these events was greater in subjects with leukemia, particularly in those with pre-existing hematological abnormalities due to disease or prior therapy, commonly making attribution of these events to idelalisib uncertain.

Consistent with the observations in the 28-day dog toxicology study, reversible Grade ≥3 ALT/AST elevations occurred in 28 (15%) subjects and have been attributed to idelalisib. Onset generally occurred between 2 to 16 weeks after idelalisib initiation and resolution was usually seen 2 to 6 weeks after idelalisib interruption. After resolution of ALT/AST increases, 14 subjects were rechallenged at the same or a reduced dose of idelalisib and 9 (64%) of these subjects were able to resume treatment without recurrence of transaminase elevations. Two (1.0%) subjects had ≥ 2 ULN elevations in bilirubin in the context of Grade ≥ 3 elevated AST/ALT, both of whom had confounding factors (recent history of biliary obstruction or concomitant use of potentially hepatotoxic medications) so that a definitive causal relationship to idelalisib could not be established.

Pharmacokinetic parameters computed from plasma samples collected on Days 1 and 28 demonstrated that there was no appreciable accumulation or loss of exposure with repeated dosing. At both Days 1 and 28, the increase in C_{max} and $AUC_{0\text{-}6h}$ with dose was less than dose-proportional, with minimal incremental increases above the dose level of 150 mg BID.

Pharmacodynamic data supported drug activity. In subjects with NHL, plasma concentrations of chemokines CCL22 and CCL17 were elevated at baseline and showed significant decreases within 1 cycle of idelalisib treatment ($p<0.001$ for both comparisons). Flow cytometry of CLL cells from subjects showed that idelalisib reduced constitutive expression of phosphorylated AKT to background levels when measured after 1 week of treatment ($p<0.0001$), demonstrating pharmacodynamic inhibition of activated PI3K signaling. Plasma concentrations of chemokines CCL3, CCL4, and CXCL13 were elevated in CLL subjects at baseline and decreased significantly within 1 cycle of idelalisib administration ($p<0.001$ for all comparisons).

Tumor reductions meeting antitumor response criteria were not observed in subjects with AML or MM. One of 11 subjects with DLBCL achieved PR. In 104 subjects with iNHL and MCL, idelalisib induced PRs at all dose levels, with respective ORRs in enrolled subjects of 29/64 (45%) for iNHL and 16/40 (40%) for MCL. CCI [redacted]

In subjects with CLL, idelalisib reduced lymphadenopathy in the majority of 54 subjects with ≥1 post-treatment tumor assessment; 44/54 (81.5%) achieved a lymph node response (≥50% reduction in target nodal lesions). An initial increase in peripheral absolute lymphocyte counts of >50% from baseline was observed some subjects; increases were maximal during the

first 2 cycles and decreased thereafter; the pattern suggested drug-mediated lymphocyte redistribution. The ORR was 53.7% (all PR). CCI [redacted]

1.3.5.2.2. Phase 1 Combination Study in Patients with Hematological Malignancies

A separate Phase 1 trial (Study 101-07) has evaluated the safety and preliminary activity of idelalisib given in combination with bendamustine or bendamustine-rituximab to subjects with recurrent iNHL or CLL {de Vos 2011, Sharman 2011}.

In this study, 28 patients with CLL received idelalisib with bendamustine alone (n=14) or with bendamustine/rituximab (n=14). Bendamustine doses were 70 or 90 mg/m^2 on Days 1 and 2 of each of 6 planned 4-week cycles. Rituximab was infused at a dose of 375 mg/m^2 on Day 1 of each of the 6 planned 4-week cycles. Idelalisib was first evaluated at a dose level of 100 mg/dose BID (n=4) and then at a dose level of 150 mg/dose BID (n=24) and was administered continuously for as long as individual subjects were safely benefiting from therapy. Subjects were evaluated in 4-week cycles; response and progression assessments were based on standard criteria {Hallek 2008}.

Among the subjects with CLL, the median age was 65 and ranged to 86 years. Bulky tumors (≥1 lymph node ≥5 cm in diameter) were present in 64% of the subjects. The median number of prior therapies 3 and ranged up to 9 prior treatments. The substantial majority (>90%) had received prior purine analogs, alkylating agents, and rituximab and 36% had received prior bendamustine. Approximately half of subjects had CLL that was refractory to the last prior therapy. At the time of data cut-off, therapy had been administered for a median of 6 cycles, ranging up to 17 cycles (ie, 68 weeks).

No idelalisib-related dose-limiting toxicities were observed within the tested subject cohorts. Grade ≥3 neutropenia was observed in 11 (40%) of patients and only 1 (4%) patient had febrile neutropenia. Grade 3-4 non-myelosuppressive adverse events largely comprised background events resulting from pre-existing disease- or treatment-related conditions or from intercurrent illness. Among these subjects with CLL, 4 (15%) developed pneumonia. For subjects receiving idelalisib together with bendamustine or bendamustine/rituximab, Grade 3-4 elevations in ALT/AST were observed in 3 (11%) of subjects.

When idelalisib was coadministered with bendamustine or bendamustine/rituximab, combination therapy showed a high level of antitumor activity. The intention-to-treat (ITT) ORR was 11/14 (79%) for the idelalisib plus bendamustine regimen and 12/14 (86%) among patients receiving idelalisib with bendamustine/rituximab. Concomitant administration of bendamustine appeared to largely eliminate the redistribution lymphocytosis that is associated with idelalisib monotherapy. At the time of the data analysis, overall PFS through 48 weeks was >80% and a median PFS had not yet been observed.

Collectively, the emerging data from this study support further evaluation of idelalisib together with bendamustine/rituximab in subjects with CLL and indicate that co-administration of idelalisib with bendamustine/rituximab is tolerable when using idelalisib at full dose, ie, at a starting dose level of 150 mg/dose BID.

For additional or updated information, please refer to the current version of the IB.

1.4. Summary and Justification for the Current Study

Gilead Sciences is conducting this Phase 3 study to evaluate the efficacy and safety of adding idelalisib to bendamustine/rituximab in patients with previously treated, recurrent CLL.

The design and conduct of this study is supported by knowledge of the demographics of patients with CLL, the natural history and current therapies for the disease, and the nonclinical and clinical information regarding idelalisib. The collective data support the following conclusions:

- CLL is a serious, disabling, and potentially life-threatening disorder that requires sequential treatment with agents that provide alternative mechanisms of tumor control. Bendamustine/rituximab can offer disease palliation in fit patients with previously treated CLL but tumor control is not lasting. Development of a combination therapy of idelalisib with bendamustine/rituximab that can address disease pathogenesis with a new mechanism of action and might offer complementary nodal and peripheral blood activity would address a persistent unmet medical need.

- PI3Kδ over-expression plays an important role in CLL biology. Further evaluation of idelalisib as a potential treatment for CLL has sound scientific rationale founded on knowledge of the actions of the drug to selectively abrogate PI3Kδ activity and to inhibit malignant cell growth and stromal cell signaling in nonclinical models of CLL. These data are supported by clinical documentation of idelalisib inhibition of PI3Kδ signaling in patients with CLL.

- The potential for clinical efficacy of idelalisib plus bendamustine/rituximab in patients with relapsed or refractory CLL is supported by the observed antitumor activity of idelalisib - given alone or in combination with bendamustine-containing therapy – in patients with heavily pretreated CLL and iNHL.

- The safety of advancing development of the regimen of idelalisib plus bendamustine/rituximab in this Phase 3 study is well supported by safety pharmacology and toxicology studies and by Phase 1 single-agent and combination safety data obtained in healthy volunteers and in subjects with lymphoid cancers.

- Dose-safety, dose-exposure, and dose-activity relationships identified in Phase 1 studies support the dosing regimen and dose modification provisions in this study.

- Observations relating to patterns of CLL response among subjects receiving idelalisib alone or in combination with bendamustine/rituximab in Phase 1 trials provide the foundation for efficacy monitoring in this trial. Of particular note is that idelalisib mobilizes CLL cells from tissues into the peripheral blood. This characteristic pharmacological action is prominent early in therapy but can persist over time and should not be confused with disease progression in patients who have persistent control of other CLL-related signs and symptoms. For this reason, in this Phase 3 study, subjects will be continued on therapy until the occurrence of definitive disease progression, ie, disease progression that is manifest by worsening CLL-related signs other than lymphocytosis alone.

- Thorough nonclinical and clinical characterization of the type, severity, manifestations, and expected timing of adverse events establish the safety monitoring plan in this trial.

- The scientific correlative work performed in prior preclinical and clinical studies provides strong scientific underpinnings for the companion laboratory studies to be performed as a component of this clinical trial.

- Given the seriousness of previously treated CLL in patients with substantial comorbidity, and the aggregate potential benefits considered in the context of potential risks, further development of idelalisib in this Phase 3 clinical trial is justified.

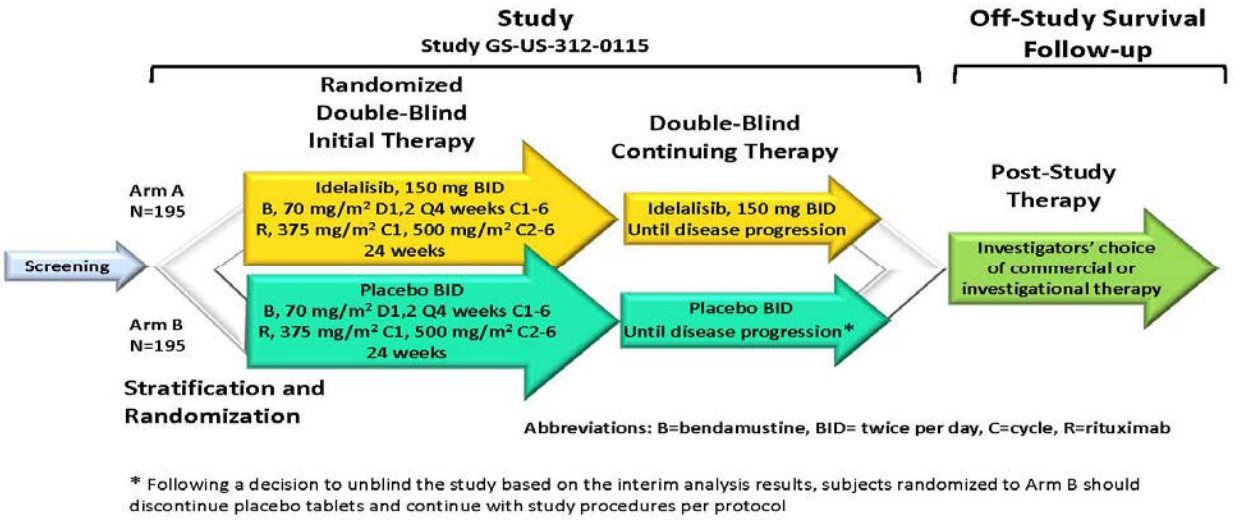
The rationale for specific design features is provided in relevant sections of the protocol, including Section 3.5 (Endpoint Selection Rationale), Section 2.2 (Design Rationale), Section 4.3 (Enrollment Criteria Rationale), Section 5.10 (Study Treatment Rationale), and Section 6.5 (Study Procedure Rationale).

2. STUDY DESIGN

2.1. Design Overview and Study Schema

Study GS-US-312-0115 is a Phase 3, multicenter, 2-arm, randomized, double-blind, placebo-controlled, parallel-group clinical trial (see Figure 2-1) that will be conducted at centers in the United States, Canada, Australia, New Zealand, Russia, Turkey, and in Europe.

Figure 2-1. Study Design



Study candidates will be adults with previously treated recurrent CLL who have measurable lymphadenopathy (as confirmed by the IRC); require therapy for CLL; have received prior therapy containing a purine analog or bendamustine and an anti-CD20 monoclonal antibody; are not refractory to bendamustine; have experienced CLL progression <36 months since the completion of the last prior therapy; and are currently sufficiently fit to receive cytotoxic therapy.

Subjects will be stratified based on 17p deletion and/or a p53 mutation status (either vs neither), immunoglobulin heavy chain variable region (IgHV) mutation status (unmutated vs mutated), and disease status (refractory vs relapsed) and randomized in a 1:1 ratio to receive 1 of the 2 treatment arms.

All subjects will receive rituximab with a planned dosing regimen of 375 mg/m^2 intravenously on Day 1 in the first cycle and 500 mg/m^2 intravenously on Day 1 of each of the subsequent 5 cycles (6 cycles total). All subjects will also be administered bendamustine intravenously at a starting dose of 70 mg/m^2/infusion; bendamustine will be given on Days 1 and 2 of each of the 6 planned 4-week treatment cycles. Bendamustine and rituximab will be administered until the earliest of subject withdrawal from study, definitive progression of CLL, intolerable

bendamustine-or rituximab-related toxicity, pregnancy, substantial noncompliance with study procedures, study discontinuation, or a maximum of 6 cycles. Bendamustine or rituximab may be continued even if the other agent is discontinued due to drug-specific toxicity.

Study drug (idelalisib/placebo) will be taken orally, BID continuously. Subjects will continue whichever study drug (idelalisib/placebo or rituximab or bendamustine) continues to be tolerated, even if one or both the other drugs must be discontinued due to toxicity. After study-wide unblinding, placebo will no longer be administered.

If permanent discontinuation of study drug occurs prior to definitive progression of CLL, subjects shall remain on study until definitive progression of CLL or withdrawal from the study for reasons specified in Section 5.7.

Clinic/laboratory visits will occur every 2 weeks through Week 24 and every 6 weeks between Weeks 24 and 48. Subjects who continue on study treatment past Week 48 will have clinic visits every 12 weeks. Subjects will be assessed for safety at each clinic visit. Subjects will be assessed for CLL disease status by physical and laboratory examinations at each clinic visit and by CT or MRI at Weeks 12, 24, 36, and 48 and every 12 weeks thereafter. As of Amendment 10, Version 11, CT/MRI assessments will no longer be performed at the every 12 week scheduled visits, and will only be performed at the time of clinically-suspected disease progression or at study discontinuation.

The primary objective of Study GS-US-312-0115 will be to evaluate the effect of the addition of idelalisib to bendamustine/rituximab on PFS. Secondary and tertiary objectives will focus on determining the effect of the addition of idelalisib to bendamustine/rituximab on the onset, magnitude, and duration of tumor control; overall survival (OS); health-related quality of life (HRQL); changes in subject performance status; disease-associated biomarkers and potential mechanisms of resistance; treatment administration; safety; and health resource utilization.

2.2. Design Rationale

The randomized, add-on design for GS-US-312-0115 is customary in the comparative evaluation of new therapies for cancer. While this design provides idelalisib efficacy and safety information only in the context of administration of companion antineoplastic agents, it is appropriate because it documents the incremental benefit and toxicity of the investigational therapy in the context of a controlled clinical trial while ensuring that all participants receive potentially active treatment.

Randomization is an accepted means to reduce bias and allows for the highest standard of evidence in documenting a treatment effect. Given the 2-arm, 3-stratification-factor design, a standard block randomization should be sufficient to preclude site personnel from making inferences regarding treatment assignments based on known block sizes. A 1:1 randomization of idelalisib: placebo is planned in order to avoid the loss of statistical power associated with an unbalanced randomization. The randomization process will be established and performed through an IWRS; the intent is to maximize the integrity and security of the randomization and ensure appropriate access and convenience-of-use by the investigational sites.

Stratification will be used to balance allocation by potentially important parameters. The selected stratification factors are those that are likely to have a substantial influence on prognosis based on historical information regarding the therapy of CLL {Cramer 2011, Gonzalez 2011}, considering published data regarding use of bendamustine/rituximab in patients with CLL {Fischer 2011, Iannitto 2011}, or based on information derived from the Phase 1 experience involving the idelalisib treatment of CLL {Coutre 2011}. Available data suggest that each of the selected stratification factors may divide the population relatively evenly, with >30% of the subjects have each of the levels of the strata. Further stratification factors could be considered, but it is problematic to overstratify a trial of this size given the potential loss of statistical power associated with expenditure of further degrees of freedom in the analysis.

Double blinding is included to provide protection against biased interpretations of efficacy and safety data by subjects, caregivers, investigators, Gilead Sciences personnel, or others involved in study conduct.

3. OBJECTIVES AND ENDPOINTS

3.1. Primary Objective

- To evaluate the effect of the addition of idelalisib to bendamustine/rituximab on PFS in subjects with previously treated CLL

3.2. Secondary Objectives

- To evaluate the effect of the addition of idelalisib to bendamustine/rituximab on the onset, magnitude, and duration of tumor control
- To assess the effect of the addition of idelalisib to bendamustine/rituximab on measures of subject well-being, including OS, HRQL, and performance status
- To assess the effects of the addition of idelalisib to bendamustine/rituximab on disease associated biomarkers and to evaluate potential mechanisms of resistance to idelalisib
- To characterize the effect of bendamustine/rituximab on idelalisib exposure through evaluations of idelalisib plasma concentrations over time
- To describe the safety profile observed with the addition of idelalisib to bendamustine/rituximab
- To estimate health resource utilization associated with the addition of idelalisib to bendamustine/rituximab

3.3. Primary Endpoint

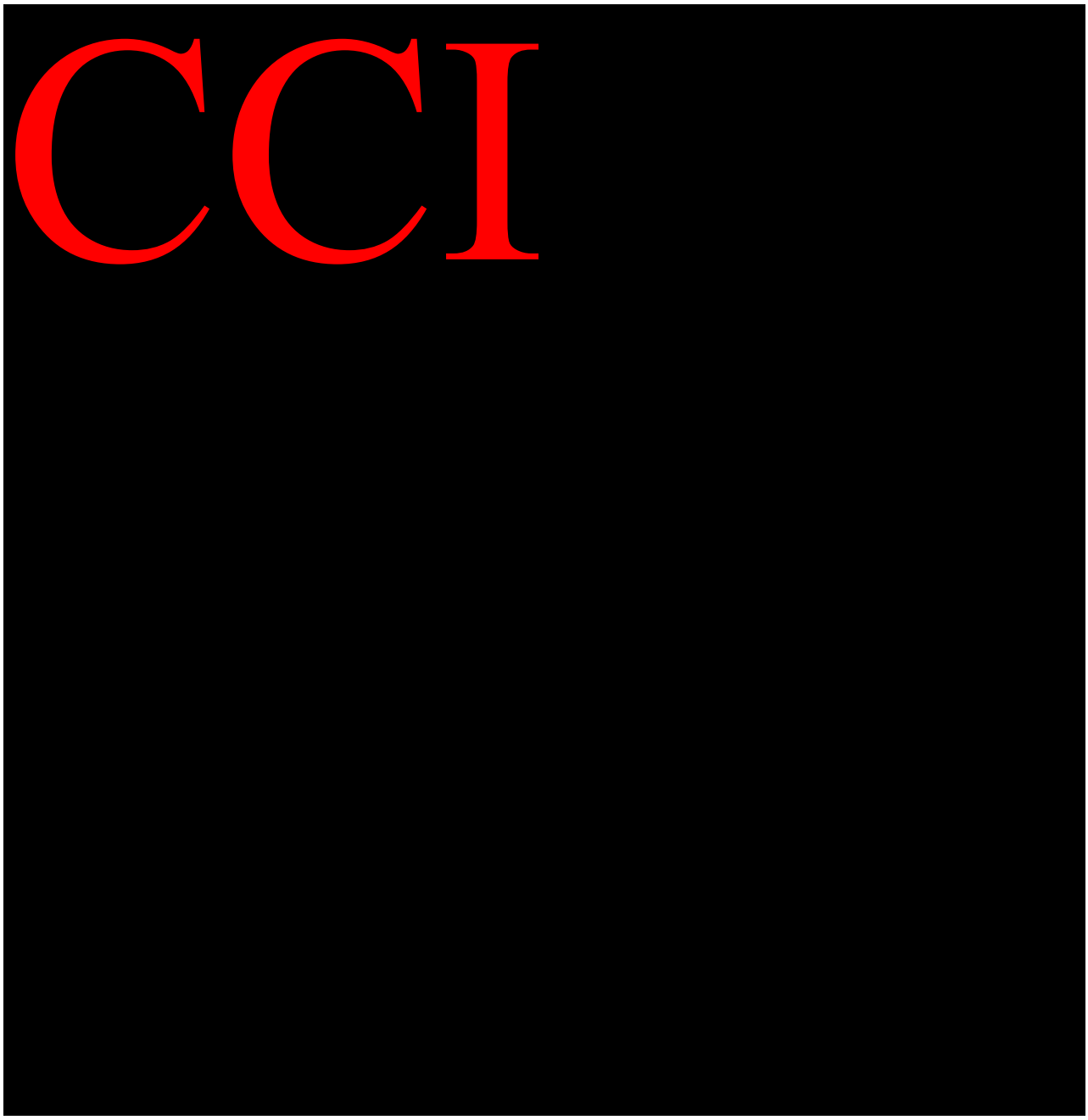
- Progression-free survival (PFS) – defined as the interval from randomization to the earlier of the first documentation of definitive disease progression or death from any cause; definitive disease progression is CLL progression based on standard criteria other than lymphocytosis alone.

3.4. Secondary and Tertiary Endpoints

The following secondary and tertiary endpoints will be defined and analyzed in this study. Four endpoints are designated as secondary endpoints for which sequential testing will be performed to control Type 1 error (see Section 9.3.4.6). Secondary endpoints will be overall response rate (ORR), lymph node response rate, complete response (CR) rate, and OS. All other endpoints will be considered tertiary.

3.4.1. Tumor Control

- ORR – defined as the proportion of subjects who achieve a CR or partial response (PR)
- Lymph node response rate – defined as the proportion of subjects who achieve a ≥50% decrease from baseline in the SPD of index lesions
- CR rate – defined as the proportion of subjects who achieve a CR



3.4.2. Patient Well-Being

- Overall survival (OS) – defined as the interval from randomization to death from any cause

3.4.3. Pharmacodynamic Markers of Drug Activity and Resistance

3.4.4. Exposure

3.4.5. Safety

3.4.6. Pharmacoeconomics

3.5. Endpoint Selection Rationale

The proposed endpoints have been chosen based on relevance to the pathophysiology and clinical manifestations of CLL, the known pharmacology of idelalisib, and the goals of the study in documenting idelalisib benefit-to-risk ratio. These types of endpoints have been employed in prior studies in CLL and can be evaluated with acceptable reliability and accuracy.

3.5.1. Tumor Control Endpoints

Assessments of the magnitude and duration of changes in tumor size are routinely employed in registration-directed oncology clinical studies to determine therapeutic effect. Unlike OS, these endpoints directly assess the ability of the drug to control the malignancy. Such assessments are also integral to treatment decisions; because subjects are being treated until disease progression, repeated tumor assessment must be performed in order to define the proper duration of treatment for each study participant. Standard response and progression criteria have been established by the International Workshop on CLL (IWCLL) {Hallek 2008}; the assessments of treatment effects in this study will be based on these criteria, taking into account the specific pharmacology of idelalisib.

In CLL, disease-related nodal enlargement is a major cause of patient discomfort and can cause organ dysfunction {Dighiero 2008}. Extensive lymphadenopathy constitutes a reason to treat CLL and controlling the size of pathologically enlarged lymph nodes is an important therapeutic goal for improving patient well-being and relieving obstructive symptoms {Hallek 2008}. Given that the natural history of recurrent CLL is inexorable nodal growth, enhancing tumor shrinkage and prolonging tumor control provides strong evidence of pharmacological activity. In assessing PFS as the primary outcome measure, this study builds on a past precedent in randomized, pivotal trials supporting the approval of rituximab or bendamustine in CLL {Hallek 2010, Knauf 2009, Robak 2010}. PFS offers a well-established primary outcome measure that directly measures treatment effect, conveys important longitudinal information regarding tumor control, can be characterized in all subjects using ITT principles, and is readily analyzed using statistical methods such as Kaplan-Meier techniques, log-rank tests, and Cox regression models.

Other endpoints of overall tumor control as evaluated in this trial are customarily assessed and reported in studies of new therapies in patients with cancer. In CLL, ORR provides an integrated assessment of the magnitude and extent of changes in lymphadenopathy, organomegaly, bone marrow infiltration, and bone marrow function that conveniently categorizes and describes treatment effects. CCI [redacted] Beyond providing descriptions on overall response assessment using ORR, this protocol will also seek to characterize the individual components of response that are important in assessment of CLL {Hallek 2008}. CCI [redacted]

Because idelalisib mobilizes CLL cells from tissues into the peripheral blood as part of its pharmacological effect, there is a risk of falsely declaring a subject to have experienced disease progression if lymphocyte count is considered as the sole basis for potential CLL worsening. To account for this potential problem, changes in lymphocyte count will not be considered in determining whether a subject has progressive disease, ie, subjects will only be declared to have progressive CLL if they meet any of the IWCLL criteria for progressive disease other than lymphocytosis alone. Thus, subjects with worsening lymphadenopathy, organomegaly, bone marrow involvement, worsening post-chemotherapy cytopenias, appearance of new disease, or transformation to a more aggressive lymphoid malignancy histology (eg, Richter syndrome) will be considered to have progressed. Subjects with lymphocytosis without any of these other events will not be considered to have progressed. Given that lymphocytosis has no prognostic significance in patients with relapsed/refractory disease {Silverman 2002, Tsimberidou 2007} and is not generally considered a reason to treat in patients with CLL {Eichhorst 2010, Hallek 2008, Zelenetz 2011}, this approach does not jeopardize subject safety or subsequent therapy. Furthermore, it will allow complete collection of all response and progression data (both considering lymphocytosis and ignoring lymphocytosis) with the intent of providing complete information for regulatory authority review.

The current IWCLL guidelines indicate that physical examination is generally sufficient to evaluate nodal response and progression in patients with CLL {Hallek 2008} but that radiographic assessments may be appropriate in clinical trials. Computed tomography (CT) is considered the preferred imaging method unless patients have contraindications that require use of magnetic resonance imaging (MRI). Given the low fluorodeoxyglucose (FDG) avidity of CLL, positron- emission tomography (PET) does not have a role in evaluation of this disease. The incremental benefits of using radiographic imaging is limited in patients undergoing long-term follow-up following first-line therapy {Blum 2007, Eichhorst 2011}. However, in the patients with advanced CLL and bulky adenopathy such as those who will be enrolled to this trial, it is known that CT scans commonly detect bulky intra-abdominal lymphadenopathy and splenomegaly that would be missed by palpation alone and that the presence of large-volume, intra-abdominal disease of the nodes and spleen is associated with a poor prognosis {Norin 2010}. Thus, while use of CT confers greater radiation exposure, subjects have the chance to benefit from radiographic imaging because it will offer more accurate information regarding their response to protocol therapy and the appropriate duration of protocol treatment. Having this information is particularly important in this trial because PI3Kδ inhibition precludes use of lymphocyte counts as evidence for disease progression. Based on published data {Fischer 2011, Iannitto 2011}, median OS for patients with comparably advanced CLL is ~1.5 to 3 years, so the long-term secondary malignancy risk from CT-related radiation exposure is very low. Finally, in the context of a registration-directed pivotal trial of a new drug with a new mechanism of action, radiographic imaging is critically important to provide reassurance regarding subject safety and trial validity. In this regard, CT evaluations of the lung can be used retrospectively to compare the treatment arms for radiographic evidence of drug-induced lung changes {Maroto 2011, White 2010}. Furthermore, CT measurements have greater accuracy and reproducibility than palpation, are subject to independent expert review, and can be audited against electronic case report form (eCRF) information.

The timing of radiographic tumor assessments has been carefully considered. Among subjects receiving idelalisib in Phase 1b/2 studies who experienced a nodal response (≥50% regression in tumor area), such responses were observed with the first 24 week of therapy {Coutre 2011, Sharman 2011}; the planned timing of tumor assessments (at Weeks 12, 24, 36, and 48 and every 12 weeks thereafter) in this study fits with this known timing of changes in lymph node size during idelalisib therapy. Scans at 12-week intervals during the first 24 weeks allow efficient documentation of response. During this period, early documentation of disease progression allows subjects who are not benefiting from study therapy to move rapidly to alternative treatments. After 24 weeks on study, the frequency of CT scans (at 12-week intervals) reduces the overall protocol burden for subjects while still allowing detection of the incremental ≥7.5-month improvement in PFS (from a median of 15 months to 22.5 months) that is targeted in this comparative trial. As outlined in Section 7.2, iodine-containing or gadolinium contrast material may be omitted in subjects for whom use of a contrast agent would be medically contraindicated.

3.5.2. Measures of Patient Well-Being

3.5.2.1. Overall Survival

While OS provides an ultimate measure of patient well-being, it has not routinely been used as the primary endpoint in CLL clinical trials. Unlike PFS, it does not specifically measure drug-mediated tumor control, and thus provides only an indirect assessment of treatment effect. Depending upon the treatment setting, long OS times in patients with CLL can preclude use of this endpoint as an efficient method for understanding drug benefits. In both the front-line and recurrent disease settings, post-study treatments can influence OS in unpredictable ways, potentially confounding differences between treatment groups.

However, given the life-threatening nature of systemic malignancy, documentation of OS is customary in oncology therapeutic clinical trials, including those evaluating subjects with recurrent CLL {Fischer 2011, Iannitto 2011, Keating 2002a, Wierda 2010}. Evaluation of OS in this study has the potential to ensure that no unexpected, early adverse effect on the likelihood of death occurs as a consequence of the addition of idelalisib to rituximab and bendamustine.

3.5.2.2. Health-Related Quality of Life

Direct patient reporting of outcomes using standardized methods has become an increasingly important component of therapeutic assessment. Evaluation of patient-reported outcomes (PROs) is particularly relevant in patients who cannot be cured of disease {Reeve 2007}. PRO questionnaires have been previously used in CLL to understand how patients differ from the general population in terms of health concerns {Eichhorst 2007, Else 2008, Holzner 2004, Shanafelt 2007}, to understand differences in perceptions of well-being in younger vs older patients {Else 2008, Levin 2007}, to determine how treatment affects HRQL {Catovsky 2007, Efficace 2008, Eichhorst 2007}, and to assess the pharmacoeconomic cost of improvements in HRQL {Stephens 2005}.

Patients with CLL have overtly impaired well-being relative to comparable controls {Eichhorst 2007, Else 2008, Holzner 2004, Shanafelt 2007}. Fatigue is cited as a common complaint, being present in the substantial majority of patients. Impairment of HRQL prior to any treatment is apparent in those with B symptoms or in patients with anemia, supporting the concept of initiating treatment when patients experience symptomatic disease. Factors associated with lower overall HRQL have included older age, greater fatigue, severity of co-morbid health conditions, advanced stage, and ongoing treatment for CLL {Shanafelt 2007}. Younger patients appear to have worse emotional and social well-being but older patients experience worse physical HRQL {Levin 2007}. In comparative evaluation of chemotherapy-containing regimens, differences in HRQL between therapies (eg, fludarabine vs fludarabine-cyclophosphamide vs chlorambucil) reflected differences in toxicity while improved HRQL was associated with greater efficacy {Catovsky 2007, Eichhorst 2007}.

In this Phase 3 study of idelalisib plus bendamustine/rituximab, it is postulated that incremental idelalisib-mediated tumor control will be correlated with greater positive changes in HRQL and that assessments of the drug's safety profile will be supported by HRQL evaluations. The FACT-Leu (see Appendix 2) has been selected to evaluate such outcomes for the study. The FACT-Leu comprises a general HRQL measure for patients receiving cancer treatment that yields a total score and subscales for physical, functional, social/family and emotional well-being {Cella 1993} and a diagnosis-specific measure for patients with leukemia {Webster 2002}. The FACT-Leu was developed to assess symptoms (eg, fevers, chills, night sweats, nodal swelling, fatigue) specifically relevant to patients with leukemia. FACT instruments have documented psychometric properties {Brucker 2005, Cella 2005, Cella 1993, Victorson 2008, Webster 2002}.

The FACT-Leu instrument is available in appropriate languages for this study. FACT-Leu data will be obtained at baseline and during each investigational clinic visit during treatment. Having FACT-Leu data concurrent with tumor response information will allow an evaluation of the potential relationship between tumor response and symptomatic changes as reported by patients. To avoid biasing HRQL results, the FACT-Leu will be administered at each visit before other procedures are performed and before any study information is conveyed to the subject.

3.5.2.3. Changes in Performance Status

Performance status evaluation provides an integrated assessment of patient well-being before, during, and after treatment and, ideally, may indicate how drug efficacy and toxicity affect patient functioning. In patients with CLL performance status can be predictive of PFS or OS {Hallek 1996, Sorensen 1997, Youngson 1995}.

In this study, it is hypothesized that idelalisib-mediated tumor control will be correlated with changes in performance status and that assessments of the drug's safety profile might be supported by performance status evaluations. The well-established, reliable, and validated Karnofsky performance score {Karnofsky 1949, Schag 1984, Yates 1980} (see Appendix 3) will be employed in the trial for characterization of the subject population and repeated assessment of performance status.

3.5.3. Pharmacodynamic Markers of Drug Activity and Resistance

In CLL, disease-related perturbations in inflammatory status can be clinically overt; patients often develop bothersome B symptoms (fevers, night sweats, and weight loss) that are characteristic of excessive systemic inflammation {Redaelli 2004}. Consistent with such disease manifestations, the PI3Kδ/AKT/mTOR pathway is constitutively overactive in circulating CLL cells {Coutre 2011}. In addition, chemokines and cytokines that are markers of aberrant B-cell trafficking or perturbations in inflammation are overexpressed by CLL tissues or by stromal cells and circulate in plasma {Burger 2010, Coutre 2011}. In Phase 1 studies of idelalisib it has been confirmed that idelalisib largely normalizes AKT phosphorylation and induces dose-dependent reductions in plasma concentrations of circulating chemokines and cytokines in patients with CLL {Coutre 2011}.

In this study, it is hypothesized that incremental changes in these biomarkers provide direct evidence of mechanism-specific idelalisib effects on PI3Kδ activity or indirectly document drug effects on overall tumor cell volume. In either case, improvements in these pharmacodynamic measures provide corroborative evidence in support of idelalisib pharmacological activity; conversely, worsening of these biomarkers may indicate acquisition of resistance to idelalisib. In addition, it is possible that disease-or inflammation-related biomarkers may provide corollary information relating to the adverse effects of idelalisib on the liver; such data might allow better prediction of which subjects might be most susceptible to ALT/AST elevations during idelalisib treatment. Finally, it can also be postulated that genetic, protein, or metabolic changes in CLL cells could provide signatures that would correlate with drug sensitivity and resistance.

Based on these considerations, this study will evaluate PI3K/AKT/mTOR pathway activation status in CLL cells. For this purpose, blood will be evaluated by flow cytometry {Hoellenriegel 2011}. CLL cells will be identified using anti-CD5 and anti-CD19 antibodies. AKT activation will be determined by quantifying phosphorylation at the Ser473 and Thr308 AKT sites using specific anti-pAKT Thr308 and anti-pAKT Ser473 antibodies. Additional assessments of PI3K/AKT/mTOR pathway signaling (eg, evaluating phosphorylation state for other downstream enzymes) may also be explored.

Plasma will be collected for assessment of circulating concentrations of relevant chemokines and cytokines with a particular focus on CCL2, CCL3, CCL4, CXCL12, CXCL13, CCL17, CCL19, CCL21, CCL22, sCD40 ligand, tumor necrosis factor-α, and C-reactive protein. In addition serum markers of iron metabolism (eg, hepcidin, iron, ferritin, transferrin) that might provide markers linking disease-related inflammation with perturbations of liver iron and sensitivity to liver injury will be evaluated {Ferrucci 2010, Nemeth 2003}. Circulating concentrations of chemokines and cytokines will be measured at baseline and during the course of idelalisib therapy.

CLL cell deoxyribonucleic acid (DNA), ribonucleic acid (RNA), and protein will be collected at baseline and at the conclusion of a subject's treatment on study. DNA and RNA samples will be analyzed using gene array technologies to evaluate for changes in DNA mutations or in RNA expression patterns that might be associated with intrinsic or acquired resistance to study

treatments. Similarly, protein will be evaluated for state-specific changes in protein phosphorylation to evaluate for differences in pathway activation at baseline or during therapy that might be associated with differences in response or in acquisition of resistance to therapy.

3.5.4. Assessments of Exposure

3.5.4.1. Study Drug Administration and Compliance

Evaluation of study drug administration and compliance provides context for assessments of safety, pharmacokinetics, and pharmacological activity. Evaluations of treatment administration and modifications from planned therapy document the influence of treatment-emergent adverse events on prescribing practice. Compliance assessment offers a general indication of patients' acceptance of therapy, integrating factors of tolerability, palatability, and convenience.

In this study, information regarding planned treatment and modification from planned treatment (eg, dose reductions and interruptions) will be collected. The compliance of the subject will be verified by accounting for used and unused drug.

3.5.4.2. Pharmacokinetics

Given the intent of this protocol to assess longer-term dosing, collection of plasma for idelalisib concentrations is important for evaluating exposures over time. These data may allow correlations of exposure with measures of efficacy, toxicity, and resistance. Because the idelalisib pharmacokinetic profile has been well characterized in Phase 1 studies, limited plasma sampling will be performed in this study. Samples will be collected pre-dose and 1.5 hours post-dose relative to the morning administration of idelalisib. Based on discussions with investigators, collecting more than 2 samples in the morning is not considered reasonable given the need to minimize time requirements for study participants and to avoid substantial inconvenience for clinic staff.

Evaluation of idelalisib plasma concentrations will be performed using liquid chromatography with tandem mass spectrometry. The method has been fully validated in the context of prior Phase 1 studies {Webb 2010}. Plasma samples will be retained for potential later analyses of idelalisib metabolites.

3.5.5. Evaluations of Safety

In defining the therapeutic relevance of a drug in a particular clinical setting, it is imperative that its safety profile be fully characterized. As is conventional in all clinical studies, proper description of each adverse event or laboratory abnormality requires an understanding of the type, incidence, timing, severity, and relatedness to study drug. While information on all reported adverse events will be collected, listed, and summarized, particular focus will be placed on monitoring and reporting adverse events and laboratory abnormalities that were encountered in the prior toxicology studies and clinical experience with idelalisib.Safety parameters of specific interest in reporting study results will include those relating to bone marrow function, dermatological events, gastrointestinal inflammation, infection, pulmonary events

(eg, pneumonia/pneumonitis), and liver injury. Additional scrutiny will be applied to Grade 3-4 adverse events, to adverse events causing interruption or discontinuation of the therapeutic agents, and to serious adverse events.

Rituximab commonly causes infusion reactions that are mediated via release of cytokines or are induced by activation of mast cells or basophils; such reactions are most common during the first two infusions of the monoclonal antibody and are commonly managed by slowing the rate of infusion {Chung 2008}. Because idelalisib reduces cytokine release by B-cells and decreases mast cell and basophil activation, it is possible that idelalisib pretreatment may have a modulating effect on rituximab-induced infusion reactions and may permit more rapid administration of rituximab. To evaluate this hypothesis, the maximum severity of rituximab infusion reactions and the duration of the rituximab infusion will be recorded during rituximab infusions.

In addition, the protocol may evaluate for potential adverse idelalisib effects on laboratory parameters of immune function including: circulating cells (CD4+, CD5+, CD8+, CD16/CD56+, CD19+, and CD20+ cells), a lymphocyte subset panel using flow cytometry (immunophenotyping), quantitative immunoglobulins IgG, IgM, IgA, and serum CH50 level.

For consistency of interpretation, adverse events will be coded using the standard Medical Dictionary for Regulatory Activities (MedDRA), and the severity adverse events and laboratory abnormalities will be graded using the well-defined Common Terminology Criteria for Adverse Events (CTCAE), Version 4.03. Standard definitions for seriousness will be applied (see Section 8.1.2).

3.5.6. Pharmacoeconomic Measures

It is increasingly important to understand the potential cost implications of introducing a new medication into patient care for CLL {Hornberger 2012, Main 2010}. In order to analyze the pharmacoeconomic consequences of adding idelalisib to bendamustine/rituximab, data will be collected regarding the health status of subjects and regarding health care resource utilization.

Heath status information will be obtained with the EQ-5D, which is a self-administered, generic, indirect utility measure {The EuroQol Group 1990} (see Appendix 4). The EQ-5D consists of a visual analogue scale on which subjects are asked to rate their current overall health status and 5 single-item dimensions which ask subjects to rate their health in terms of mobility, self-care, usual activities, pain/discomfort and anxiety/depression. For each of the 5 items patients must choose between 3 levels of difficulty in accomplishing tasks in that dimension. The visual analog scale is then used in combination with the dimension scores to generate a health utility score that can be incorporated into analyses of cost effectiveness. The EQ-5D has been successfully used in the evaluation of patients with B-cell and other cancers {Doorduijn 2005, Witzens-Harig 2009, Yang 2010}.

The EQ-5D instrument is available in appropriate languages for this study. EQ-5D data will be obtained at baseline and during each investigational clinic visit during treatment. The EQ-5D will be administered immediately after administration of the FACT-Leu instrument, before other procedures are performed and before any study information is conveyed to the subject. The EQ-5D instrument takes only 5 minutes to complete.

Health care resource utilization data collection will be based on information provided in the eCRFs and will be focused on the most relevant direct medical resource utilization such as physician visits, laboratory tests, medications (including dose and route), medical procedures, interventions (eg, transfusions), and hospitalizations.

The basic approach will be to combine the resource utilization data from the trial with data on unit prices (collected separately) to estimate total costs in preparation for a full-cost analysis. Based on the degree to which the addition of idelalisib to rituximab increases costs overall, the incremental costs will be compared relative to the health care gains as measured by duration of tumor control, the symptom-free survival period, and/or utility gains or some other appropriate measure of clinical benefits.

4. SUBJECT POPULATION

4.1. Number of Subjects

The planned sample size is ~390 subjects (~195 subjects per treatment arm). However, as many as 420 subjects may be enrolled in order to permit study participation by eligible subjects who have already signed the informed consent document and entered screening at the time that study enrollment is closed. The total accrual may be increased if a blinded analysis of the event rate indicates that an upward sample size adjustment is warranted (see Section 9.4.2).

4.2. Subject Selection Criteria

This clinical trial can fulfill its objectives only if appropriate participants are enrolled. The following eligibility criteria are designed to select subjects for whom study participation is considered appropriate. All relevant medical and non-medical conditions should be taken into consideration when deciding whether this protocol is suitable for a particular subject. Eligibility criteria may not be waived by the investigator and conformance to the eligibility criteria is subject to review in the case of a Good Clinical Practice (GCP) or a regulatory authority audit. Any questions regarding a subject's eligibility should be discussed with the study sponsor medical monitor prior to enrollment.

4.2.1. 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 IWCLL criteria and documented within medical records.

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/µL), or

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

f) Constitutional symptoms, defined as any one 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) Presence of measurable lymphadenopathy (defined as the presence of ≥1 nodal lesion that measures ≥2.0 cm in the longest diameter [LD] and ≥1.0 cm in the longest perpendicular diameter [LPD] as assessed by CT or MRI).

5) Prior treatment for CLL comprising:

a) ≥2 cycles of a regimen containing a purine analog (eg, fludarabine, pentostatin, cladribine) or bendamustine, and

b) ≥2 doses with a regimen containing an anti-CD20 monoclonal antibody (eg, rituximab, ofatumumab, GA-101) ***Note: Prior cytotoxic drugs or anti-CD20 antibodies may have been administered as single agents or as components of combination therapies. Subjects may also have received other commercially available therapies (eg, alemtuzumab, lenalidomide, corticosteroids, or others) or non-excluded investigational therapies. Each repeated but separated therapeutic application of the same single-agent or combination is considered an independent regimen.***

6) Documentation of CLL progression <36 months since the completion of the last prior therapy for CLL.

7) Discontinuation of all therapy (including radiotherapy, chemotherapy, immunotherapy, or investigational therapy) for the treatment of CLL ≥3 weeks before randomization. ***Note: Subjects may receive corticosteroids to manage CLL manifestations.***

8) All acute toxic effects of any prior antitumor therapy resolved to Grade ≤1 before randomization (with the exception of alopecia [Grade 1 or 2 permitted], neurotoxicity [Grade 1 or 2 permitted], or bone marrow parameters [Grades 1 or 2 permitted]).

9) Karnofsky performance score of ≥60 (see Appendix 3).

10) Required baseline laboratory data (within 4 weeks prior to randomization) as shown in the following table. ***Note: Confirmation should be considered for out-of-range values to determine if the abnormality is real or artifactual. Values should be obtained within the screening period and should generally be the most recent measurement obtained.***

Table 4-1. Required Screening Laboratory Values

Organ System	Parameter	Required Value
Hematopoietic	ANC	≥1.5 x 10^9/L[a]
	Platelets	≥75 x 10^9/L[a]
	Hemoglobin	≥100 g/L (10.0 g/dL or 6.2 mmol/L)[a]
Hepatic	Serum total bilirubin	≤1.5 x ULN (unless elevated due to Gilbert's syndrome or hemolysis)
	Serum ALT	≤2.5 x ULN
	Serum AST	
Renal	eC_{Cr}[b]	≥40 ml/min
Pregnancy	β-HCG[c]	Negative
Infection	HIV	Negative HIV antibody
	HBV	Negative HBsAg and negative HBc antibody or positive HBc and negative for HBV DNA by quantitative PCR
	HCV	Negative viral RNA (if HCV antibody is positive)

a Grade ≥2 neutropenia, thrombocytopenia, or anemia is permitted if abnormality is related to bone marrow involvement with CLL (as documented by bone marrow biopsy/aspirate obtained since the last prior therapy).
b As calculated by the Cockcroft-Gault formula (see Appendix 5) {Cockcroft 1976}
c For women of child-bearing potential only; serum β-HCG must be negative during screening and serum β-HCG or urine dipstick pregnancy test must be negative at randomization (Visit 2)

Abbreviations: β-HCG=beta human chorionic gonadotropin, ALT=alanine aminotransferase, ANC=absolute neutrophil count, AST=aspartate aminotransferase, DNA=deoxyribonucleic acid, eC_{Cr}=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

11) For female subjects of childbearing 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 study drug or >12 months from the last dose of rituximab (whichever is later). ***Note: A female subject is considered to be of childbearing potential unless she has had a hysterectomy, bilateral tubal ligation, or bilateral oophorectomy; has medically documented ovarian failure (with serum estradiol and follicle-stimulating hormone [FSH] levels within the institutional postmenopausal range and a negative serum or urine βHCG); or is menopausal (*****defined as age ≥54*** ***with amenorrhea for >12 months or amenorrhea for >6 months with serum estradiol and FSH levels within the institutional postmenopausal range).***

12) For male subjects of childbearing potential having intercourse with females of childbearing potential, willingness to use a protocol-recommended method of contraception from the randomization visit (Visit 2) throughout the study treatment period and until ≥6 months following the last dose of bendamustine or ≥ 90 days following the last dose of study drug (whichever is later) and to refrain from sperm donation from randomization (Visit 2) throughout the study treatment period and until ≥6 months following the last dose of bendamustine or ≥90 days following the last dose of study drug (whichever is later).

Note: A male subject is considered able to father a child unless he has had a bilateral vasectomy with documented aspermia or a bilateral orchiectomy, or has ongoing testicular suppression with a depot luteinizing hormone- releasing hormone (LH RH) agonist (eg, goserelin acetate [Zoladex®]), leuprolide acetate [Lupron®]), or triptorelin pamoate [Trelstar®]).

13) In the judgment of the investigator, participation in the protocol offers an acceptable benefit-to-risk ratio when considering current CLL disease status, prior treatment history, medical condition, and the potential benefits and risks of alternative treatments for CLL. ***Note: Investigators should consider whether a study subject is an appropriate candidate for bendamustine-containing therapy based on the number and severity of comorbid conditions; subjects with a baseline Cumulative Illness Rating Scale (CIRS) score of ≤6 (see Appendix 6) may be particularly appropriate candidates for this trial.***

14) Willingness and ability to comply with scheduled visits, drug administration plan, imaging studies, laboratory tests, other study procedures, and study restrictions. ***Note: Psychological, social, familial, or geographical factors that might preclude adequate study participation should be considered.***

15) 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.

4.2.2. 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). ***Note: Biopsy documentation of the absence or presence of transformation is not required.***

2) Known presence of intermediate- or high-grade myelodysplastic syndrome (ie, subjects are excluded who have ≥5% bone marrow blasts; karotypic abnormalities other than normal, Y deletion, 5q deletion, or 20q deletion; or ≥2 lineages of cytopenias due to myelodysplasia).

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 randomization, other adequately treated Stage 1 or 2 cancer currently in complete remission, or any other cancer that has been in complete remission for ≥5 years.

4) Evidence of ongoing systemic bacterial, fungal, or viral infection at the time of randomization (Visit 2). ***Note: Subjects with localized fungal infections of skin or nails are eligible. Subjects may be receiving prophylactic antiviral or antibacterial therapies at the discretion of the investigator. For subjects who are at substantial risk of an infection (eg, influenza) that may be prevented by immunization, consideration should be given to providing the vaccine prior to initiation of protocol therapy.***

5) 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.

6) Ongoing drug-induced pneumonitis.

7) Ongoing inflammatory bowel disease.

8) Ongoing alcohol or drug addiction.

9) Pregnancy or breastfeeding.

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

11) Ongoing immunosuppressive therapy other than corticosteroids ***Note: Subjects may use topical, enteric, inhaled, or systemic corticosteroids as therapy for manifestations of CLL, comorbid conditions, or autoimmune anemia and/or thrombocytopenia during study participation, subjects may receive systemic or other corticosteroids as pretreatment for rituximab infusions or as needed for treatment-emergent comorbid conditions.***

12) In a subject with a history of prior bendamustine therapy, a time interval from the last dose of bendamustine to the subsequent CLL progression of <6 months.

13) History of prior therapy with any inhibitor of AKT, Bruton tyrosine kinase (BTK), Janus kinase (JAK), mammalian target of rapamycin (mTOR), phosphatidylinositol 3 kinase (PI3K) (including idelalisib), or spleen tyrosine kinase (SYK).

14) History of anaphylaxis in association with previous administration of monoclonal antibodies.

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.

4.3. Enrollment Criteria Rationale

In general, the eligibility criteria are designed to limit enrollment to subjects who clearly have CLL, are able to tolerate study procedures, and will provide interpretable results.

To maximize the likelihood that therapeutic intervention is appropriately matched to disease risk, subjects must have CLL that is sufficiently severe to justify therapy as determined by accepted criteria {Hallek 2008}. The requirement of measurable lymphadenopathy ensures that subjects have disease that can adequately be assessed for evidence of drug activity. Prior therapy provisions are intended to identify subjects who have already received appropriate therapies with well-defined activity. Exclusion of patients who have experienced CLL progression within 6 months of prior bendamustine therapy avoids treating those with disease known to be refractory to this agent. Ensuring participation of only patients who are <36 months from prior therapy limits enrollment to subjects who might benefit from a change in therapy (including the addition of study drug) based on current guidelines {Eichhorst 2010, Zelenetz 2011}. Extending this interval to as long as 36 months acknowledges that patients who had received and tolerated bendamustine-based therapy in the past and have now relapsed after a protracted period (eg, after 18-36 months) might wish to consider bendamustine-based therapy again.

This protocol focuses on establishing a combination chemoimmunotherapy that will be suitable for patients who are likely to tolerate a regimen containing a potently myelosuppressive cytotoxic agent. Thus, while any degree of cytopenias are permitted if due to CLL, the trial requires that study candidates not have Grade ≥3 neutropenia, thrombocytopenia, or anemia attributable to cumulative myelotoxicity. Given that bendamustine-related myelotoxicity is substantially more likely in patients with severe renal dysfunction {Fischer 2011}, subjects must have a baseline eC_{Cr} value ≥40 mL/minute.

To ensure that subjects are able to perform basic self-care functions and are not so ill from life-threatening comorbidities that they require hospitalization and stabilization, subjects with Karnofsky performance scores <60 will not be enrolled. To preserve subject safety and trial integrity, subjects must not have other serious prior or concomitant conditions or therapies that would compromise safety, compliance, or evaluation. Severe comorbid conditions (eg, myelodysplasia, other cancers {Luciani 2009}, active hepatitis, hepatic dysfunction, ongoing of drug-induced pneumonitis) may mask, exacerbate, or confound the interpretation of adverse effects or efficacy of idelalisib and therefore subjects with such medical disorders are excluded.

Pregnancy testing and restrictions on eligibility relating to reproduction, pregnancy, and nursing are important. Rituximab is known to have effects on the immune system in the developing fetuses of drug-exposed female animals and humans; such effects can persist in infants for several months following in utero exposure. Bendamustine is known to be embryotoxic and teratogenic in laboratory animals {Cephalon 2012}. Idelalisib is a new chemical entity and it is unknown if it may have adverse effects on conception, on fetal development, or on the health of a breast-feeding child.

To minimize missing data and premature discontinuations, subjects should have sufficient psychological and social resources to comply with study procedures and restrictions. Consistent with GCP guidelines, subjects must provide informed consent before initiation of any study procedures.

While it will not be used to determine eligibility in this trial, the general health status of study subjects will be characterized at baseline using the Cumulative Illness Rating Scale (CIRS) instrument (see Appendix 6). The CIRS has a well-established history as a clinical tool for classifying patient comorbidities {Linn 1968}. Its utility is based on its validation as a predictor of clinical outcomes in older patient populations {Boulos 2006, Castle 2005, Conwell 1993, de Groot 2003, Extermann 2000, Extermann 1998, Miller 1992, Parmelee 1995, Salvi 2008, Zekry 2010}; its utility in predicting prognosis, appropriate patient selection, and treatment tolerability in patients with cancer {Firat 2006, Monfardini 2005, Ngeow 2010, Wedding 2007a, Wedding 2007b}, and its increasing use to categorize treatable fit ("GO-GO") vs treatable frail ("SLOW-GO") patients with CLL {Eichhorst 2009, Hallek 2010}.

5. TREATMENT OF SUBJECTS

5.1. Randomization and Blinding

5.1.1. Interactive Web Response System

An IWRS will be employed to manage the conduct of the trial. The IWRS will be used to maintain a central log documenting screening, to implement stratification and 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.

5.1.2. Randomization and Stratification

After a subject has completed the necessary screening assessments and has been confirmed to be eligible, the subject can be randomized into the study. In order to obtain a treatment arm assignment for a subject, a site representative will access the IWRS and supply the system with the required information.

Subjects will be randomized in a 1:1 ratio to either of the following treatment assignments:

- Arm A: Idelalisib + bendamustine/rituximab
- Arm B: Placebo + bendamustine/rituximab

In order to balance treatment allocation by potentially important predictive factors, a fixed-block centralized randomization will allocate subjects within the 8 strata as defined by the intersection of the following 3 binary stratification factors:

- 17p deletion and/or p53 mutation in CLL cells: either vs neither (or indeterminate)
- Immunoglobulin heavy chain variable region (IgHV) mutation: unmutated (or IgHV3-21) vs mutated (or indeterminate)
- Disease status: refractory (CLL progression <6 months from completion of prior therapy) vs relapsed (CLL progression ≥6 months from completion of prior therapy)

The IWRS will assign bottle numbers and instructions for dispensing of blinded study drug (idelalisib or placebo). It is anticipated that subjects will usually begin study drug immediately after randomization at Visit 2 of the study. In case of administrative delays, every attempt should be made to initiate study drug as soon as possible, but no more than 7 days from randomization.

5.1.3. Blinding

The identity of the treatments will be concealed by central blinding of study drug assignments. Blinding will be accomplished through use of a placebo that is well-matched to the active drug in appearance, packaging, labeling, and schedule of administration (see Section 5.2.1.1). During the study, subjects, caregivers, investigational site personnel, Gilead Sciences study team members, and all other study personnel will remain blinded to the identity of the treatment assignments;

these assignments will be available only to the IWRS, the data monitoring committee (DMC) for the study, an independent bioanalytical group that supports the DMC, and drug safety personnel who are not part of the study team. Unblinding an individual subject's treatment assignment during the study will only occur in the case of subject emergencies (see Section 5.5). Where required by local regulation, expedited reporting of serious adverse events to specific regulatory authorities will include information regarding the study drug treatment assignment (idelalisib or placebo); this will be done in such a way that subjects, investigational site personnel, institutional review board/independent ethics committees (IRB/IEC), and study team members remain blinded as to the treatment assignment for the subject described in the adverse event report.

The final unblinded analysis of the study will only be performed when the database is completed and locked, unless the DMC recommends unblinding the study following an interim analysis of unblinded data. While bioanalytical assays to determine idelalisib concentrations may be performed prior to unblinding, pharmacokinetic data that would allow identification of treatment assignments for individual subjects will not be available to the study team until after the blind is broken and the primary analysis has occurred. Except for emergency unblinding, individual subjects, caregivers, and site personnel will not be informed of the randomized treatment assignments until the implications of revealing such data for the overall idelalisib study program have been determined by the clinical project leader for the idelalisib development program.

In the event that treatment is unblinded, subjects randomized to Arm A will be informed of their treatment assignment, and continue to receive idelalisib and be followed for progression free survival. Subjects randomized to Arm B should continue with study procedures per protocol, but must discontinue from placebo. Subjects should remain on study until definitive progression of CLL or discontinuation from the study for reasons specified in Section 5.9.

5.2. Investigational and Reference Study Drugs

5.2.1. Investigational Study Drug (Idelalisib/Placebo)

5.2.1.1. Description

For subjects allocated to Arm A of the study, idelalisib will be provided in tablets intended for oral administration. Each tablet contains 150 mg or 100 mg of active idelalisib. The 150-mg tablets will be used for initial therapy; the 100-mg tablets are provided for use by those subjects who require a dose reduction (see Section 5.3.3). The 150-mg tablets are either pink, oval-shaped, film-coated tablets with "GSI" on one side and "150" on the other side or plain faced tablets, and include the following inactive excipients: microcrystalline cellulose, hydroxypropyl cellulose, croscarmellose sodium, sodium starch glycolate, magnesium stearate, red iron oxide, polyethylene glycol, talc, polyvinyl alcohol (PVA), and titanium dioxide. The 100-mg tablets are either orange, oval-shaped, film-coated, tablets with "GSI" on one side and "100" on the other side or plain-faced tablets, 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, polyethylene glycol, talc, PVA, and titanium dioxide.

For subjects allocated to Arm B of the study, an inactive placebo formulation will be provided in tablets intended for oral administration. The placebo tablets match the active idelalisib formulations in appearance. The placebo tablets matching the 150-mg tablets are pink, film-coated, and include the following inactive ingredients: silicified microcrystalline cellulose, sodium starch glycolate, magnesium stearate, red iron oxide, polyethylene glycol, talc, PVA, and titanium dioxide. The placebo tablets matching the 100-mg tablets are orange, film-coated, and include the following inactive ingredients: silicified microcrystalline cellulose, sodium starch glycolate, magnesium stearate, FD&C Yellow #6/Sunset Yellow FCF Aluminum Lake, polyethylene glycol, talc, PVA and titanium dioxide.

5.2.1.2. Source

Both active idelalisib and placebo will be supplied free of charge by Gilead Sciences.

5.2.1.3. Packaging and Labeling

Study drug (idelalisib/placebo) will be provided in bottles. Each bottle contains 60 tablets (4-week supply plus a modest overage) of one of the relevant dose strengths (150 mg, 100 mg, or matching placebos) and a polyester packing material. Bottles are white and are made of high-density polyethylene. Each bottle is closed with a white, continuous-thread, child-resistant, polypropylene screw cap fitted with an induction-sealed, aluminum-faced liner.

Each bottle will have a unique number. Labeling for active idelalisib (GS-1101) and placebo will be identical, and may include either idelalisib or GS-1101. All labels for study drugs to be distributed to centers in the US and other countries will meet all applicable requirements of the United States Food and Drug Administration (FDA), Annex 13 of Current Good Manufacturing Practice (cGMP) (Manufacture of Investigational Medicinal Products, July 2010), and/or other local regulations as applicable.

5.2.1.4. Storage and Handling

Bottles containing tablets of study drug (idelalisib/placebo) 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 the study drugs are dispensed to the subjects, all bottles should be stored in a securely locked area, accessible only to authorized site personnel.

To ensure stability and proper identification, study drug(s) should not be stored in a container other than the container in which they were supplied. Consideration should be given to handling, preparation, and disposal through measures that minimize drug contact with the body. Appropriate precautions should be followed to avoid direct eye contact or exposure when handling idelalisib.

5.2.1.5. Dispensing

The clinic staff (eg, pharmacist or other qualified person) will be responsible for dispensing study drug (idelalisib/placebo) according to the IWRS directions. It is planned that drug will be dispensed at 12-week intervals Multiple bottles will be dispensed at a single visit. Tablets should be dispensed in the original bottles provided.

At the time of randomization, the IWRS will provide the clinic staff with the bottle numbers designating the bottles to be dispensed. The clinic staff (eg, pharmacist or other qualified person) will write the subject number on each bottle that is dispensed. Immediately before dispensing, the clinic staff will write the bottle number for each dispensed bottle in the study drug administration record corresponding to the subject number.

5.2.1.6. Return

The study drug (idelalisib/placebo) should be retrieved from each subject at the end of each dispensing interval. The quantity of study drug and the date returned by the subject should be recorded in the study drug accountability records. All study drug returned by the subject should be retained for review by the study site monitor prior to return to Gilead Sciences or destruction.

5.2.1.7. Accountability

The disposition of all study drug (idelalisib/placebo) should be documented from the time of receipt at the site through subject dispensing and return.

Study personnel must ensure that all study drug is kept in a secure locked area with access limited to authorized personnel. The study drug must not be used outside the context of this protocol. Under no circumstances should the investigator or site personnel supply study drug to other investigators or clinics, or allow the study drug to be used other than as directed by this protocol.

The investigator and/or the responsible site personnel must maintain accurate records of the receipt of all study drug shipped by Gilead Sciences or its designee, including, but not limited to, the date received, lot number, amount received, and the disposition of all study drug. Upon receipt of a drug shipment, the shipment must be logged into the IWRS. Study drug accountability records must also be maintained that include the subject number to whom the study drug was dispensed and the date, quantity and lot number of the study drug dispensed.

Depending upon the decision of Gilead Sciences, remaining unused study drug supply will be returned to Gilead Sciences or its designee after the study is completed or will be discarded or destroyed at the clinical site. If the study drug is discarded or destroyed at the clinical site, standard institutional policy should be followed. Records documenting the date of study drug shipping or destruction, relevant lot numbers, and amount shipped or destroyed should be maintained.

5.2.1.8. Overdose Precautions

In Phase 1 studies, an MTD for idelalisib was not reached when administering the drug continuously at dose levels of 350 mg/dose BID (700 mg per day) {Coutre 2011, Kahl 2011}. However, in this protocol, an overdose is defined as administration of more than the prescribed daily dose (ie, >300 mg in a single day).

In a subject who experiences an overdose, consideration should be given as to whether idelalisib administration should be temporarily interrupted. If the overdose ingestion is recent and substantial, and if there are no medical contraindications, use of gastric lavage or induction of emesis may be considered. Observation for any symptomatic side effects should be instituted, and biochemical and hematological parameters should be followed closely (consistent with the protocol or more frequently, as needed). Appropriate supportive management to mitigate adverse effects should be initiated.

The Gilead Sciences medical monitor should be contacted if a study drug overdose occurs. Cases of study drug (idelalisib/placebo) overdose will result in specific reporting requirements (see Section 8.8).

5.2.1.9. Inadvertent Exposure and Spill Precautions

Based on available data from nonclinical studies, idelalisib does not appear to be acutely toxic, genotoxic, or irritative at levels that are likely to result from inadvertent exposure to the contents of broken tablets. However, personnel handling the drug should use reasonable precautions to avoid eye contact, skin contact, inhalation, or ingestion of the study drug product. For further information regarding inadvertent exposure and spill precautions, please consult the idelalisib investigator brochure.

5.2.2. Reference Drug (Rituximab)

5.2.2.1. Description

Rituximab (Rituxan®) is a genetically engineered chimeric murine/human monoclonal IgG1 kappa antibody directed against the CD20 antigen found on pre-B and mature B cells {Genentech Inc 2011}. Rituximab is produced by mammalian Chinese hamster ovary cells. The protein has an approximate molecular weight of 145 kD.

The drug is provided as a clear, colorless, preservative-free liquid concentrate containing 10 mg/mL of rituximab. The product is formulated in 9 mg/mL sodium chloride, 7.35 mg/mL sodium citrate dihydrate, 0.7 mg/mL polysorbate 80, and water for injection with a pH of 6.5.

5.2.2.2. Packaging

Rituximab is supplied in 100-mg (10-mL) or 500-mg (50-mL) single-use vials.

5.2.2.3. Source – Commercial Supply

Unless otherwise instructed by the sponsor, the rituximab to be used in this study may be obtained from available commercial supplies. As applicable for a specific subject, costs for rituximab should be submitted for insurance reimbursement; if such costs are not covered by the medical insurance for the subject, these expenses can be submitted to Gilead Sciences for reimbursement.

5.2.2.4. Source – Non-Commercial Supply

If rituximab is obtained from a source other than available commercial source, the disposition of all rituximab should be documented from the time of receipt at the site through subject dispensing and infusion.

Study personnel must ensure that all rituximab is kept in a secure locked area with access limited to authorized personnel. Rituximab must not be used outside the context of this protocol.

The investigator and/or the responsible site personnel must maintain accurate records of the receipt of all study drug shipped by Gilead Sciences or its designee, including, but not limited to, the date received, lot number, amount received, and the disposition of all rituximab. Rituximab accountability records must also be maintained that include the subject number to whom the study drug was dispensed and the date, quantity, and lot number of the rituximab dispensed.

Depending upon the decision of Gilead Sciences, remaining unused rituximab supply will be returned to Gilead Sciences or its designee after the study is completed or will be discarded or destroyed at the clinical site. If the rituximab is discarded or destroyed at the clinical site, standard institutional policy should be followed and be readily available for review by Gilead Sciences and/or its designee. Records documenting the date of rituximab shipping or destruction, relevant lot numbers, and amount shipped or destroyed should be maintained.

5.2.2.5. Storage and Stability

Rituximab vials are stable at 2 °C–8 °C (36 °F–46 °F). Vials should be protected from direct sunlight and should not be frozen or shaken.

Diluted rituximab solutions for infusion may be stored at 2 °C–8 °C (36 °F–46 °F) for 24 hours and are known to be stable for an additional 24 hours at room temperature. However, since rituximab solutions do not contain a preservative, diluted solutions should be stored refrigerated (2 °C-8 °C).

No incompatibilities between rituximab and polyvinylchloride or polyethylene bags have been observed. The storage and stability data is provided as guidelines, local standard practice may also be followed.

5.2.2.6. Solution Preparation and Dispensing

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

Using aseptic technique, the necessary amount of rituximab should be withdrawn from the vial and diluted to a final concentration of 1 to 4 mg/mL in an infusion bag containing either 0.9% Sodium Chloride, USP or 5% Dextrose in Water, USP. The bag should be gently inverted to mix the solution. The infusion solution should not be mixed or diluted with other drugs. Any unused portion of rituximab remaining in the vial should be discarded.

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.

5.2.2.7. Accountability

Acquisition, storage, control, and disposal of rituximab used in the study should be performed according to institutional procedures and policies.

The investigator and/or the responsible site personnel must maintain accurate records of the source, dates of administration, quantities of administration, and lot numbers of the rituximab dispensed for this study.

5.2.2.8. Overdose Precautions

Rituximab doses as high as 2000 mg/m^2 have been administered without inducing excessive toxicity {O'Brien 2001}. However, for this protocol, an overdose is defined as infusion of >500 mg/m^2 of rituximab in a single day.

In a subject who experiences an overdose, any further rituximab infusion on that day should be interrupted. Observation for any symptomatic side effects should be instituted, and biochemical and hematological parameters should be followed closely (consistent with the protocol or more frequently, as needed). Appropriate supportive management to mitigate adverse effects should be initiated, as necessary.

The Gilead Sciences medical monitor should be contacted if a rituximab overdose occurs. Cases of rituximab overdose may result in specific reporting requirements (see Section 8.6).

5.2.2.9. Exposure and Spill Precautions

Based on available data, rituximab does not appear to be irritative, acutely toxic, or genotoxic at levels that are likely to result from inadvertent exposure to the drug. No special precautions relating to exposure are required.

5.2.3. Reference Drug (Bendamustine)

5.2.3.1. Description

Bendamustine (Treanda®) is a bifunctional mechlorethamine derivative containing a purine-like benzimidazole ring {Cephalon 2012}. The chemical name of bendamustine hydrochloride is 1H-benzimidazole-2-butanoic acid, 5-[bis(2-chloroethyl)amino]-1 methyl-, monohydrochloride. Its empirical molecular formula is $C_{16}H_{21}Cl_2N_3O_2$ HCl, and its molecular weight is 394.7 daltons.

Mechlorethamine and its derivatives form electrophilic alkyl groups. These groups form covalent bonds with electron-rich nucleophilic moieties, resulting in interstrand DNA crosslinks. The bifunctional covalent linkage can lead to cell death via several pathways. Bendamustine is cytotoxic in both quiescent and dividing cells.

Bendamustine hydrochloride for injection is provided as a sterile non-pyrogenic white to off-white lyophilized powder mixed with mannitol.

5.2.3.2. Packaging

Bendamustine hydrochloride for injection is provided in individual cartons containing amber 8-mL or 20-mL single-use vials. The 8-mL vial contains 25 mg of bendamustine and 42.5 mg of mannitol powder. The 20-mL vial contains 100 mg of bendamustine and 170 mg of mannitol powder.

5.2.3.3. Source – Commercial Supply

Unless otherwise instructed by the sponsor, the bendamustine to be used in this study may be obtained from available commercial supplies. As applicable for a specific subject, costs for bendamustine should be submitted for insurance reimbursement; if such costs are not covered by the medical insurance for the subject, these expenses can be submitted to Gilead Sciences for reimbursement.

5.2.3.4. Source – Non-Commercial Supply

If bendamustine is obtained from a source other than available commercial source, the disposition of all bendamustine should be documented from the time of receipt at the site through subject dispensing and infusion.

Study personnel must ensure that all bendamustine is kept in a secure locked area with access limited to authorized personnel. The study drug must not be used outside the context of this protocol.

The investigator and/or the responsible site personnel must maintain accurate records of the receipt of all study drug shipped by Gilead Sciences or its designee, including, but not limited to, the date received, lot number, amount received, and the disposition of all study drug. Study drug accountability records must also be maintained that include the subject number to whom the study drug was dispensed and the date, quantity and lot number of the study drug dispensed.

Depending upon the decision of Gilead Sciences, remaining unused bendamustine supply will be returned to Gilead Sciences or its designee after the study is completed or will be discarded or destroyed at the clinical site. If the bendamustine is discarded or destroyed at the clinical site, standard institutional policy should be followed and be readily available for review by Gilead Sciences and/or its designee. Records documenting the date of study drug shipping or destruction, relevant lot numbers, and amount shipped or destroyed should be maintained.

5.2.3.5. Storage and Stability

Bendamustine vials are stable when stored at room temperatures up to 25 °C (77 °F). Temperature excursions are permitted up to 30 °C (86 °F). Bendamustine should be stored in the original containers until the time of use in order to protect the drug from light.

Bendamustine contains no antimicrobial preservative. The admixture should be prepared as close as possible to the time of patient administration. Once diluted with either 0.9% Sodium Chloride Injection, USP, or 2.5% Dextrose/0.45% Sodium Chloride Injection, USP, the final admixture is stable for 24 hours when stored refrigerated (2-8 °C or 36-47 °F) or for 3 hours when stored at room temperature (15-30 °C or 59-86 °F) in room light. Drug administration should be completed within the established periods of stability for the admixed solution. The storage and stability data is provided as guidelines, local standard practice may also be followed.

5.2.3.6. Solution Preparation and Dispensing

Bendamustine hydrochloride for injection is intended for intravenous infusion only after reconstitution with Sterile Water for Injection, USP, and after further dilution with either 0.9% Sodium Chloride Injection, USP, or 2.5% Dextrose/0.45% Sodium Chloride Injection, USP. No other diluents have been shown to be compatible.

Vials of bendamustine should be inspected visually for particulate matter and discoloration prior to administration. Vials should be aseptically reconstituted as follows:

- 25 mg bendamustine vial to be mixed with 5 mL of Sterile Water for Injection, USP.
- 100 mg bendamustine vial to be mixed with 20 mL of Sterile Water for Injection, USP.

With shaking, the lyophilized powder should completely dissolve in 5 minutes, yielding a clear, colorless to pale yellow solution with a bendamustine hydrochloride concentration of 5 mg/mL. The pH of the reconstituted solution is 2.5 - 3.5. If particulate matter is observed, the reconstituted product should not be used.

Within 30 minutes of reconstitution, the volume needed for the required dose (based on a 5-mg/mL concentration) should be transferred to a 500-mL infusion bag of 0.9% Sodium Chloride Injection, USP (normal saline) As an alternative to 0.9% Sodium Chloride Injection, USP, a 500-mL infusion bag of 2.5% Dextrose/ 0.45% Sodium Chloride Injection, USP, may be used. After transferring, thoroughly mix the contents of the infusion bag. The resulting admixture should be a clear and colorless to slightly yellow solution with a final concentration of bendamustine hydrochloride in the infusion bag of 0.2-0.6 mg/mL.

5.2.3.7. Accountability

Acquisition, storage, control, and disposal of bendamustine used in the study should be performed according to institutional procedures and policies.

The investigator and/or the responsible site personnel must maintain accurate records of the source, dates of administration, quantities of administration, and lot numbers of the bendamustine dispensed for this study.

5.2.3.8. Overdose Precautions

The intravenous LD_{50} of bendamustine HCl is 240 mg/m^2 in the mouse and rat. Toxicities included sedation, tremor, ataxia, convulsions, and respiratory distress. Across all clinical experience, the reported maximum single dose received was 280 mg/m^2. Three of four patients treated at this dose showed ECG changes considered dose-limiting at 7 and 21 days post-dosing. These changes included QT prolongation (one patient), sinus tachycardia (one patient), ST and T wave deviations (two patients) and left anterior fascicular block (one patient). Cardiac enzymes and ejection fractions remained normal in all patients. In this protocol, an overdose is defined as administration of more than the prescribed dose (ie, >70 mg/m^2 in a single day).

No specific antidote for bendamustine overdose is known. Management of overdosage should include general supportive measures, including monitoring of hematologic parameters and ECGs.

The Gilead Sciences medical monitor should be contacted if a bendamustine overdose occurs. Cases of bendamustine overdose may result in specific reporting requirements (see Section 8.6).

5.2.3.9. Exposure and Spill Precautions

As with other potentially toxic anticancer agents, care should be exercised in the handling and preparation of solutions prepared from bendamustine. The use of gloves and safety glasses is recommended to avoid exposure in case of breakage of the vial or other accidental spillage. If a solution of bendamustine contacts the skin, wash the skin immediately and thoroughly with soap and water. If bendamustine contacts the mucous membranes, flush thoroughly with water.

5.3. Study Drug Administration

5.3.1. Combination Dosing Regimen

Table 5-1 provides information regarding the planned study drug (idelalisib/placebo), bendamustine, and rituximab dosing regimen.

Table 5-1. Planned Dosing Regimen During the Randomized Double-Blind Combination Therapy Portion of the Study

Period	Screen	Combination Therapy[a]																		Further Therapy[a]
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**
Week	**-4**	**0**		**2**	**4**		**6**	**8**		**10**	**12**		**14**	**16**		**18**	**20**		**22**	**24**
Day	**-28**	**1**	**2**	**15**	**29**	**30**	**43**	**57**	**58**	**71**	**85**	**86**	**99**	**113**	**114**	**127**	**141**	**142**	**155**	**169**
Purpose	**Screening**	**Clinic Visits**		**Lab Visit**	**Clinic Visit**		**Lab Visit**	**Clinic Visit**		**Lab Visit**	**Clinic Visit**		**Lab Visit**	**Clinic Visit**		**Lab Visit**	**Clinic Visit**		**Lab Visit**	**Clinic Visit**
Study Drug (idelalisib/placebo)		150 mg/dose BID,[a] taken continuously →																		
Premedication		X	X		X	X		X	X		X	X		X	X		X	X		
Rituximab Dose, mg/m^2		375	-		500	-		500	-		500	-		500	-		500	-		
Bendamustine Dose, mg/m^2		70	70		70	70		70	70		70	70		70	70		70	70		

a Intended dose levels and schedules of administration are shown. However, individual study subjects may require dose modifications or delays in therapy to accommodate drug-related, dose-limiting toxicities (see Section 5.3.5).

Abbreviation: BID=2 times per day

Table 5-2 indicates the planned sequence of drug administration that should be followed on the first day and second day of each treatment cycle. As noted in the table, the sequence of drug administration may be prolonged to 3 days in subjects for whom the investigator believes such an extension is medically warranted.

Table 5-2. Planned Sequence of Drug Administration on Day 1 and Day 2 of Each Cycle

Day	Drug		Sequencing and Instructions
1	Study drug (see also Section 5.3.3)		Morning dose of study drug (idelalisib/placebo) to be administered orally to the subject in the clinic (with recording of the date and actual clock time of the study drug administration).
	Pretreatment (see also Section 5.3.2)		Antipyretic and antihistamine to be administered orally to the subject at the same time as study drug (idelalisib/placebo) and ~30 minutes prior to rituximab infusion. An intravenous corticosteroid may also be administered per local practices as a premedication to minimize rituximab infusion reactions. Antiemetics may be given to minimize bendamustine-related nausea. Prophylaxis for tumor lysis syndrome may be considered per local practices. Prophylaxis for *Pneumocystis (carinii) jiroveci* should also be considered.
	Rituximab (see also Section 5.3.4.1)	Cycle 1 dose (375 mg/m^2)[a]	Rituximab intravenous infusion to be started ~30 minutes after pretreatment administration at initial infusion rate of 50 mg/hr; in the absence of infusion toxicity, the infusion rate can be increased in 50-mg/hr increments every 30 minutes, to a maximum of 400 mg/hr.
		Cycle 2-6 doses (500 mg/m^2)	Rituximab intravenous infusion to be started ~30 minutes after pretreatment administration at initiation infusion rate of 100 mg/hr; in the absence of infusion toxicity, the infusion rate can be increased in 100-mg/hr increments every 30 minutes, to a maximum of 400 mg/hr.
	Bendamustine[b] (Section 5.3.4.2)		Bendamustine intravenous infusion to be started at completion of rituximab; bendamustine to be administered over ~60 minutes.
2	Study drug (see also Section 5.3.3)		Morning dose of study drug (idelalisib/placebo) to be taken orally by the subject at home.
	Pretreatment[c] (see also Section 5.3.2)		Antiemetics may be given to minimize bendamustine-related nausea.
	Bendamustine (see also Section 5.3.4.2)		Bendamustine intravenous infusion to be administered over ~60 minutes.

a For a subject with a greater risk of infusion reactions due to a pretreatment ALC of ≥25 x 10^9/L, the Day 1 rituximab infusion may be limited to 100 mg total drug (ie, 1 vial of rituximab) and the remainder of the planned total rituximab dose may be administered prior to bendamustine on Day 2.

b Bendamustine infusions may be deferred and administered on Days 2 and 3 for subjects in whom a more extended drug administration sequence is warranted (eg, due to the occurrence of a rituximab-related infusion reaction or a protracted rituximab infusion time on Day 1).

c For a subject who appears to be prone to bendamustine-related infusion reactions, premedication with an antipyretic, an antihistamine, and a corticosteroid should also be considered prior to administration of bendamustine on Day 2.

Abbreviations: ALC=absolute lymphocyte count

5.3.2. Premedications

No specific premedication is required for study drug (idelalisib/placebo) administration.

In accordance with rituximab prescribing information {Genentech Inc 2011}, subjects should be premedicated with an antipyretic and an antihistamine to reduce the incidence and severity of infusion reactions. A recommended regimen is diphenhydramine, 25 mg orally, and acetaminophen (paracetamol), 650 mg orally, both given ~30 minutes prior to each rituximab administration. An intravenous corticosteroid may also be administered as a premedication. Local practices and guidelines may be followed.

Bendamustine administration has been associated with nausea and/or vomiting in ~15 to 20% of patients. Investigators may wish to provide prophylactic antiemetics according to local practices.

In the absence of concomitant cytotoxic administration, tumor lysis syndrome is uncommon with either idelalisib or rituximab. Tumor lysis syndrome has occurred in ~5% of patients when idelalisib had been combined with bendamustine or bendamustine/rituximab. Investigators may wish to institute prophylaxis and monitoring for tumor lysis syndrome according to local practices.

5.3.3. Study Drug (Idelalisib/Placebo) Administration

Study drug (idelalisib/placebo) dose levels are shown in Table 5-3 below. The starting dose level will be 150 mg/dose BID. The lower dose level (Dose Level -1) is provided in case a subject requires a study drug dose modification (see Section 5.3.5).

Table 5-3. Study Drug (Idelalisib/Placebo) Dose Levels

Dose Level	Dosing Regimen
Starting	150 mg/dose BID
-1	100 mg/dose BID

Abbreviation: BID=twice per day

The prescribed dose of study drug (idelalisib/placebo) should be taken orally. At each dose administration, the tablet number corresponding to the appropriate dose of study drug is to be swallowed whole with 100 to 200 mL (~ 4 to 8 ounces) of water. In case of breakage of the tablets in the oral cavity, additional water should be taken as a rinse. Study drug may be taken with or without food. There are no known dietary restrictions related to study drug use.

Study drug will be started on a BID schedule beginning ~30 minutes prior to the initial rituximab infusion. At this first treatment visit and at specific follow-up clinic visits, the morning dose of study drug will be administered in the clinic with dosing appropriately timed relative to blood sampling for idelalisib pharmacokinetics. As detailed in Section 6.2, clinic staff should record study drug 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.

Subjects should be instructed to take study drug at approximately the same times each day. Ideally, doses should be taken at ~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 study drug 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.

Vomited doses may be retaken, but only if the tablet is visible in the vomitus.

5.3.4. Reference Drug (Bendamustine/Rituximab) Administration

5.3.4.1. Rituximab

Rituximab dose levels for the initial cycle and subsequent cycles of study treatment are shown in Table 5-4 below. Dosing will be based on mg/m^2 of body surface area. The dose calculation of body surface area will be based on the subject's pretreatment height and actual body weight. The total doses of rituximab throughout therapy should be based on the pretreatment body surface area without consideration of fluctuations in body weight during treatment. Escalations or reductions in rituximab dosing are not planned.

Table 5-4. Reference Drug (Rituximab) Dose Levels

	Cycle 1	Cycles 2-6
Rituximab dose	375 mg/m^2	500 mg/m^2

Rituximab will be administered intravenously in the clinic according to the dosing regimen and administration sequence described in Table 5-1 and Table 5-2. Unless drug-specific toxicities preclude its further administration, rituximab should always be administered at the beginning of each cycle in synchrony with bendamustine. Thus, if bendamustine administration must be delayed due to bendamustine-related toxicities, rituximab should also be delayed. Information regarding delays or discontinuations of rituximab therapy for specific adverse events is provided in Section 5.4.

5.3.4.2. Bendamustine

Bendamustine dose levels are shown in Table 5-5 below. Dosing will be based on mg/m^2 of body surface area. The dose calculation of body surface area will be based on the subject's pretreatment height and actual body weight. The total doses of bendamustine throughout therapy should be based on the pretreatment body surface area without consideration of fluctuations in body weight during treatment. The starting dose level will be 70 mg/m^2. The lower dose levels (Dose Level -1 and Dose Level -2) are provided in case a subject requires a bendamustine dose modification (see Section 5.3.5)

Table 5-5. Reference Drug (Bendamustine) Dose Levels

Dose Level	Dosing Regimen
Starting	70 mg/m^2 on Days 1 and 2
-1	50 mg/m^2 on Days 1 and 2
-2	25 mg/m^2 on Days 1 and 2

Bendamustine will be administered intravenously in the clinic according to the schedule and administration sequence described in Table 5-1 and Table 5-2. Unless drug-specific toxicities preclude its further administration, bendamustine administration must be delayed due to bendamustine-related toxicities. Information regarding delays or discontinuations of bendamustine therapy for specific adverse events is provided in Section 5.4.

5.3.5. Safety Monitoring and Study Treatment Interruption/Dose Modification

Subjects must be monitored closely for adverse events or laboratory abnormalities during the course of the study. Reference should be made to the CTCAE, Version 4.03 for grading the severity of adverse events and laboratory abnormalities.

Modifications of the dosing regimen based on the drug and the type and severity of adverse events or laboratory abnormalities are provided in Table 5-6. The dose modification instructions focus on the types of events most commonly attributed to the study agent(s). The idelalisib modifications in Table 5-6 include both recommended as well as required actions. When a modification is indicated as a recommendation it only serves as a guideline; variations from the recommendation may be warranted based on an investigator's individual judgment in considering potential risks, benefits, and therapeutic alternatives available to each subject.

Consistent with Table 5-6, if a subject experiences an adverse event that is suspected to be related to study drug (idelalisib/placebo) during the course of study treatment, then study drug administration may be held, as necessary, until the adverse event resolves or stabilizes to an acceptable degree (as described in Table 5-6). If permanent discontinuation is not required per Table 5-6, study drug may be reinstituted at either the starting dose level (150 mg/dose BID) or at Dose Level -1 (100 mg/dose BID) consistent with the instructions in Table 5-6. A further attempt at reinitiation of therapy at Dose Level -1 (100 mg/dose BID) may be attempted if the investigator feels that a rechallenge at that dose level is medically appropriate. After a study drug dose reduction, the dose need not be re-escalated, even if there is minimal or no toxicity with the reduced dose. However, if the subject tolerates the lower dose level of study drug for ≥4 weeks then the dose may be increased to 150 mg/dose BID, at the discretion of the investigator. Such re-escalation may be particularly warranted if further evaluation reveals that the adverse event that led to the dose reduction was not study-drug-related. The starting dose level (150 mg/dose BID) should not be exceeded in this study.

Investigators should contact the Gilead Sciences medical monitor with any questions regarding dose modification. To implement either a dose reduction or a dose reescalation, the investigator/study staff member will access the IWRS, enter the subject randomization number, and inform the IWRS of the need for dose titration. The IWRS will provide details regarding the bottles to be dispensed to the subject. The appropriate clinic staff should instruct the subject/caregiver about the change in dose.

Rituximab doses will not be modified during the study. As shown in Table 5-6, the scheduling of rituximab should be synchronized with that for bendamustine.

Bendamustine administration should follow the recommendations in Table 5-6. If a subject experiences an adverse event that is suspected to be bendamustine-related and requires a dose modification during the course of study therapy, then the bendamustine dose should be reduced by 1 dose level. Successive adjustments to progressively lower dose levels can be made. If the patient cannot tolerate bendamustine at Dose Level -2 (25 mg/m^2/dose on Days 1 and 2), then the patient should be discontinued from bendamustine therapy. After a bendamustine dose reduction, the dose need not be re-escalated, even if there is minimal or no toxicity with the reduced dose. However, if the patient tolerates a reduced dose of bendamustine then the bendamustine may be increased to the next higher dose level, at the discretion of the investigator. Such re-escalation may be particularly warranted if further evaluation reveals that the adverse event that led to the dose reduction was not bendamustine-related. Successive adjustments to progressively higher dose levels can be made at 4-week intervals. The starting dose level (70 mg/m^2/dose on Days 1 and 2) should not be intentionally exceeded.

Investigators should contact the Gilead Sciences medical monitor with any questions regarding dose modification.

Table 5-6. Modifications of Study Treatments for Subsequent Cycle Based on Worst Drug-Related Adverse Events Observed in the Prior Cycle

NCI CTCAE Grade[a]	Idelalisib	Rituximab	Bendamustine
HEMATOLOGICAL ADVERSE EVENTS			
Neutropenia			
Grade ≤2	Recommended Action: Maintain current dose level and schedule.	Maintain 500-mg/m^2 dose level and schedule.	Maintain current dose level and schedule.
Grade 3	Required Action: Monitor blood counts at least weekly until ANC ≤ Grade 2. Recommended Action: Maintain current dose level and schedule.	Delay rituximab until Grade ≤2 (ANC ≥1 x 10^9/L); thereafter, resume at 500-mg/m^2 dose level. If delay of rituximab is >4 weeks, discontinue bendamustine.	Delay until Grade ≤2 (ANC ≥1 x 10^9/L); if delay is 2-4 weeks, reduce by 1 dose level and consider G-CSF support. If delay is >4 weeks, discontinue bendamustine.
Grade 4 (or occurrence of neutropenic fever or infection)	**Dosing:** • Required Action: Withhold idelalisib. • Recommended Action: May resume idelalisib at lower dose level when ANC ≤ Grade 3. Required Action: Monitor blood counts at least weekly until ANC ≤ Grade 2. Recommended Action: Neutropenia should be managed according to established clinical guidelines.	Delay rituximab until Grade ≤2 (ANC ≥1 x 10^9/L); thereafter, resume at 500-mg/m^2 dose level. If delay of rituximab is >4 weeks, discontinue bendamustine.	Delay until Grade ≤2 (ANC ≥0.5 x 10^9/L); reduce by 1 dose level and consider G-CSF support. If delay is >4 weeks, discontinue bendamustine.
Thrombocytopenia			
Grade ≤2	Recommended Action: Maintain current dose level and schedule.	Maintain 500-mg/m^2 dose level and schedule	Maintain current dose level and schedule
Grade ≤3	Recommended Action: Maintain current dose level and schedule.	Delay rituximab until Grade ≤1 (platelets ≥75 x 10^9/L); thereafter, resume at 500-mg/m^2 dose level. If delay of rituximab is >4 weeks, discontinue bendamustine.	Delay until Grade ≤1 (platelets ≥75 x 10^9/L); if delay is 2-4 weeks reduce by 1 dose level. If delay is >4 weeks, discontinue bendamustine.

NCI CTCAE Grade[a]	Idelalisib	Rituximab	Bendamustine
Grade 4	Required Action: Withhold idelalisib for bruising or bleeding until ≤ Grade 3. Recommended Action: May resume idelalisib at initial or lower dose level at investigator discretion.	Delay rituximab until Grade ≤1 (platelets ≥75 x 10^9/L); thereafter, resume at 500-mg/m^2 dose level. If delayof rituximab is >4 weeks, discontinue bendamustine.	Delay until Grade ≤1 (platelets ≥75 x 10^9/L); reduce by 1 dose level. If delay is >4 weeks, discontinue bendamustine.
NON-HEMATOLOGICAL ADVERSE EVENT			
Rash			
Grade ≤1	Recommended Action: Maintain current dose level and schedule.	Maintain 500-mg/m^2 dose level and schedule	Maintain current dose level and schedule
Grade 2	Recommended Action: Maintain current dose level and schedule.	Delay bendamustine and rituximab until Grade ≤1; thereafter, resume at 500-mg/m^2 dose level.	Delay bendamustine and rituximab until Grade ≤1. Resume bendamustine at current dose level. If rechallenge at same dose level results in recurrence, may resume bendamustine at next lower dose level.
Grade ≥ 3	Required Action: Withhold idelalisib until Grade ≤1. Recommended Action: Resume at lower dose level or discontinue idelalisib at investigator discretion.	Delay bendamustine and rituximab until Grade ≤1; thereafter, resume at 500-mg/m^2 dose level or discontinue rituximab at investigator discretion.	Delay bendamustine and rituximab until Grade ≤1. Thereafter, resume at next lower dose level or discontinue bendamustine at investigator discretion.
Grade 4	Required Action: Withhold idelalisib until Grade ≤1. Recommended Action: Resume at lower dose level or discontinue idelalisib at investigator discretion.	Discontinue rituximab.	Discontinue bendamustine.
Stevens-Johnson Syndrome (SJS)/Toxic Epidermal Necrolysis (TEN)			
Any Grade	Required Action: Discontinue idelalisib. Interrupt coadministered medications potentially associated with SJS/TEN. Institute treatment per institutional standards.		

NCI CTCAE Grade[a]	Idelalisib	Rituximab	Bendamustine
Gastrointestinal Inflammation/Diarrhea			
Grade ≤1	Required Action: Obtain history of onset and duration of diarrhea, including description of number of stools, stool composition (eg, watery, bloody, nocturnal), travel history, dietary changes and a medication review to identify possible diarrheogenic agents. Required Action: Perform physical examination including assessment for fever, dizziness, abdominal pain/cramping, and weakness (eg, evaluate for sepsis, bowel obstruction, dehydration). Recommended Action: Differentiate between small-bowel and large-bowel diarrhea on a clinical basis[b]. Provide anti-diarrheal (eg, loperamide) and maintain current idelalisib dose level and schedule; ensure good hydration status.	Maintain 500-mg/m^2 dose level and schedule	Maintain current dose level and schedule
Grade 2	Required Action: Obtain history of onset and duration of diarrhea, including description of number of stools, stool composition (eg, watery, bloody, nocturnal), travel history, dietary changes and a medication review to identify possible diarrheogenic agents. Required Action: Perform physical examination including assessment for fever, dizziness, abdominal pain/cramping, and weakness (eg, evaluate for sepsis, bowel obstruction, dehydration). **Dosing:** • For **persistent** Grade 2 Colitis or Diarrhea (without clear etiology): o Required Action: Withhold idelalisib. o Recommended Action: At Grade ≤1 may resume idelalisib at lower dose or discontinue at investigator discretion.	Maintain 500-mg/m^2 dose level and schedule	Maintain current dose level and schedule

NCI CTCAE Grade[a]	Idelalisib	Rituximab	Bendamustine
	• For Grade 2 Colitis or Diarrhea (without clear etiology): ○ Recommended Action: Maintain current idelalisib dose level and schedule. Required Action: For Grade 2 colitis or diarrhea (unless clinical diagnosis is established from medical history and physical examination), perform stool culture for routine pathogens (Salmonella, Shigella, Campylobacter species), testing for Clostridium difficile toxin, Rotavirus, Cytomegalovirus (CMV), Adenovirus, ova and parasites (Cryptosporidium parvum, Isospora belli, Enterocytozoon bieneusi, Septata intestinalis, Strongyloides, Microsporidia, Entamoeba histolytica, Cyclospora), and Giardia antigen. Recommended Action: For **persistent** Grade 2 colitis or diarrhea without clear etiology (eg, clostridium difficile enterocolitis) endoscopy with biopsy is strongly recommended to assess by immunohistochemistry (IHC) and PCR for CMV, Adenovirus. CCI [redacted] Recommended Action: Differentiate between small-bowel and large-bowel diarrhea on a clinical basis[b]. Provide anti-diarrheal (eg, loperamide). Consider addition of anti-inflammatory agent (eg, sulfasalazine, budesonide). Ensure good hydration status.		

NCI CTCAE Grade[a]	Idelalisib	Rituximab	Bendamustine
Grade 3	Required Action: Obtain history of onset and duration of diarrhea, including description of number of stools, stool composition (eg, watery, bloody, nocturnal), travel history, dietary changes and a medication review to identify possible diarrheogenic agents. Required Action: Perform physical examination including assessment for fever, dizziness, abdominal pain/cramping, and weakness (eg, evaluate for sepsis, bowel obstruction, dehydration). **Dosing:** • Required Action: Withhold idelalisib. • Recommended Action: At grade ≤1, may resume at lower dose level or discontinue idelalisib at investigator discretion. Required Action: For Grade 3 colitis or diarrhea (unless clinical diagnosis is established from medical history and physical examination), perform stool culture for routine pathogens (Salmonella, Shigella, Campylobacter species), testing for Clostridium difficile toxin, Rotavirus, Cytomegalovirus (CMV), Adenovirus, ova and parasites (Cryptosporidium parvum, Isospora belli, Enterocytozoon bieneusi, Septata intestinalis, Strongyloides, Microsporidia, Entamoeba histolytica, Cyclospora), and Giardia antigen. Recommended Action: Endoscopy with biopsy is strongly recommended to assess by immunohistochemistry (IHC) and PCR for CMV, Adenovirus. CCI [redacted]	Delay as necessary to ensure subject is sufficiently stable to receive further treatment; maintain 500-mg/m^2 dose level and schedule	Delay as necessary to ensure subject is sufficiently stable to receive further treatment; maintain current dose level and schedule

NCI CTCAE Grade[a]	Idelalisib	Rituximab	Bendamustine
Grade 4	Required Action: Obtain history of onset and duration of diarrhea, including description, number of stools, stool composition (eg, watery, bloody, nocturnal), travel history, dietary changes and a medication review to identify possible diarrheogenic agents. Required Action: Perform physical examination including assessment for fever, dizziness, abdominal pain/cramping, and weakness (eg, evaluate for sepsis, bowel obstruction, dehydration). **Dosing:** • Required Action: Withhold idelalisib. • Recommended Action: At Grade ≤1, may resume at lower dose level or discontinue idelalisib at investigator discretion. Required Action: For Grade 4 colitis or diarrhea (unless clinical diagnosis is established from medical history and physical examination), perform stool culture for routine pathogens (Salmonella, Shigella, Campylobacter species), testing for Clostridium difficile toxin, Rotavirus, Cytomegalovirus (CMV), Adenovirus, ova and parasites (Cryptosporidium parvum, Isospora belli, Enterocytozoon bieneusi, Septata intestinalis, Strongyloides, Microsporidia, Entamoeba histolytica, Cyclospora), and Giardia antigen. Recommended Action: Endoscopy with biopsy is strongly recommended to assess by immunohistochemistry (IHC) and PCR for CMV, Adenovirus. CCI [redacted]	Delay as necessary to ensure subject is sufficiently stable to receive further treatment; maintain 500-mg/m^2 dose level and schedule or discontinue rituximab at investigator discretion.	Delay as necessary to ensure subject is sufficiently stable to receive further treatment; maintain current dose level and schedule

NCI CTCAE Grade[a]	Idelalisib	Rituximab	Bendamustine
Hepatic Adverse Events (elevations in ALT, AST, or bilirubin)			
Grade ≤1 (ALT/AST ≤ 3xULN) (Bilirubin ≤ 1.5xULN)	Recommended Action: Maintain current dose level and schedule.	Maintain 500-mg/m^2 dose level and schedule	Maintain current dose level and schedule
Grade 2 (ALT/AST > 3-5xULN) (Bilirubin > 1.5- ≤ 3xULN)	Recommended Action: Maintain current dose level and schedule. Monitor ALT, AST, ALP, and bilirubin at least 1x per week until all abnormalities are Grade ≤1.	Maintain 500-mg/m^2 dose level and schedule.	Maintain current dose level and schedule.
Grade 3 (ALT/AST>5-20xULN) (Bilirubin > 3-10xULN)	Recommended Action: Withhold idelalisib until ALT, AST, ALP, and bilirubin are Grade ≤1. • If bilirubin abnormality was Grade <3, resume idelalisib at same dose level. • If bilirubin abnormality was Grade ≥3, resume idelalisib at lower dose level. Recommended Action: Monitor ALT, AST, ALP, and bilirubin at least 1x per week until all abnormalities are Grade ≤1.	Delay and monitor ALT, AST, ALP, and bilirubin at least 1x per week until all abnormalities are Grade ≤1; thereafter maintain 500-mg/m^2 dose level.	Delay and monitor ALT, AST, ALP, and bilirubin at least 1x per week until all abnormalities are Grade ≤1. If bilirubin abnormality is Grade <3 may resume study drug at same dose level. If bilirubin abnormality is Grade ≥3, resume at next lower dose level.
Grade 4 (ALT/AST>20xULN) (Bilirubin > 10xULN)	Required Action: Withhold idelalisib until ALT, AST, ALP, and bilirubin are Grade ≤1. • Required Action: If bilirubin abnormality was Grade 4, discontinue idelalisib. • Recommended Action: If bilirubin abnormality was Grade < 4, resume idelalisib at lower dose level. Required Action: Monitor ALT, AST, ALP, and bilirubin at least 1x per week until all abnormalities are Grade ≤1.	Delay and monitor ALT, AST, ALP, and bilirubin at least 1x per week until all abnormalities are Grade ≤1; thereafter maintain 500-mg/m^2 dose level.	Delay and monitor ALT, AST, ALP, and bilirubin at least 1x per week until all abnormalities are Grade ≤1. If bilirubin abnormality is Grade <3 may resume study drug at same dose level. If bilirubin abnormality is Grade ≥3, resume at next lower dose level.

NCI CTCAE Grade[a]	Idelalisib	Rituximab	Bendamustine
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 500- mg/m^2 dose level and schedule.	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.	Grade 2: Maintain 500- mg/m^2 dose level and schedule. Grade 3: Delay as necessary to ensure subject is sufficiently stable to receive further treatment; maintain 500-mg/m^2 dose level and schedule or discontinue rituximab at investigator discretion. Grade 4: Discontinue rituximab.	Grade 2: Maintain current dose level and schedule. Grade 3 and Grade 4: Delay as necessary to ensure subject is sufficiently stable to receive further treatment; maintain current dose level, reduce dose, or discontinue bendamustine at investigator discretion.
Pneumocystis Pneumonia			
Any Grade	Required Action: Discontinue idelalisib permanently.		
Organizing Pneumonia			
Any Grade	Required Action: Discontinue idelalisib permanently.		
Unequivocal CMV infection[c] or Reactivation			
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, consideration should be given to administering pre-emptive CMV therapy.		
Other Nonhematological Adverse Events			
Grade ≤2	Recommended Action: Maintain current dose level and schedule.	Maintain 500- mg/m^2 dose level and schedule	Maintain current dose level and schedule

NCI CTCAE Grade[a]	Idelalisib	Rituximab	Bendamustine
Grade ≥3	Recommended Action: Withhold idelalisib until Grade ≤1. May resume at lower dose level or discontinue idelalisib at investigator discretion.	Delay as necessary to ensure subject is sufficiently stable to receive further treatment; maintain 500-mg/m^2 dose level and schedule or discontinue rituximab at investigator discretion.	Delay as necessary to ensure subject is sufficiently stable to receive further treatment; reduce dose or discontinue bendamustine at investigator discretion.

a CTCAE, Version 4.03.
b Refer to 5.4.2.2 for recommendations if the differentiation between small-bowel and large-bowel diarrhea is unclear
c CMV should be diagnosed using clinical or laboratory criteria per established institutional standard
Abbreviations: ALP=alkaline phosphatase, ALT=alanine aminotransferase, ANC=absolute neutrophil count, AST=aspartate aminotransferase, CMV=cytomegalovirus, CTCAE=Common Terminology Criteria for Adverse Events, G-CSF=granulocyte-colony-stimulating factor, NCI=National Cancer Institute, ULN=upper limit of normal

5.4. Evaluation, Intervention, and Drug Discontinuation for Specific Adverse Events or Conditions

5.4.1. Dermatological Events

5.4.1.1. Dermatological Events (Idelalisib)

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 pruritis 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 until Grade ≤1; idelalisib can then be resumed at a lower dose level or discontinued at the investigator's discretion.

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 and all coadministered medications associated with SJS or TEN should be interrupted and the subject treated accordingly.

Subjects should be monitored for the development of SJS, TEN, or other severe cutaneous reactions, and idelalisib treatment must be discontinued if such events occur.

Severe, including fatal, mucocutaneous reactions can occur in patients receiving rituximab. These reactions include paraneoplastic pemphigus, Stevens-Johnson syndrome, lichenoid dermatitis, vesiculobullous dermatitis, and toxic epidermal necrolysis {Genentech Inc 2011}. The onset of these reactions has varied from 1 to 13 weeks following initiation of rituximab exposure. The safety of readministration of rituximab to patients with severe mucocutaneous reactions has not been determined; thus, for subjects experiencing a severe mucocutaneous reaction, rituximab should be discontinued.

Among patients receiving bendamustine, skin reactions have been reported in clinical trials and post-marketing safety reports {Cephalon 2012}. These events have included rash, toxic skin reactions, bullous exanthema, and purpura {Gavini 2012}. Cases of Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported when bendamustine was administered concomitantly with allopurinol and other medications known to cause these syndromes. There may be an increased risk of skin toxicity in subjects receiving bendamustine together with trimethoprim-sulfamethoxazole. Because of coadministration of other agents, the precise relationship of cutaneous adverse events to bendamustine has often been uncertain. Where skin reactions to bendamustine do occur, they may be progressive and increase in severity with further treatment. Therefore, patients with skin reactions should be monitored closely. If skin reactions are severe or progressive, bendamustine should be discontinued.

5.4.2. 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. Idelalisib must be discontinued in subjects who experience bowel perforation.

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. 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 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.

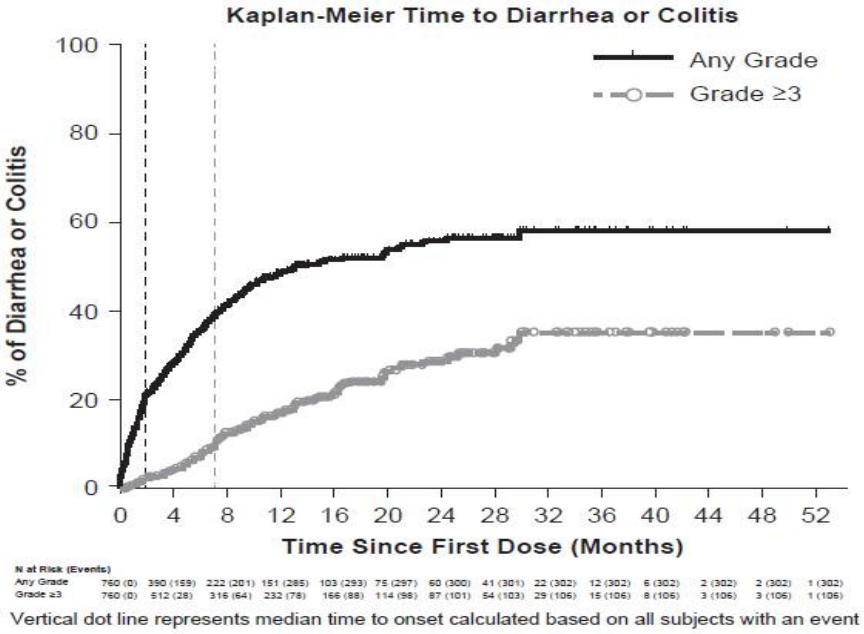
Among patients receiving rituximab in combination with chemotherapy, rare instances of life-threatening bowel obstruction or perforation has been observed {Ram 2009}, primarily in patients with NHL. In post-marketing reports, the mean time to documented gastrointestinal perforation was 6 (range 1–77) days from start of chemoimmunotherapy. It is hard to draw a definite conclusion regarding the role of rituximab in these cases, as the affected patients had multiple risk factors including lymphomatous involvement of the gastrointestinal tract, other gastrointestinal disorders, and/or the risk of concomitant treatments with chemoradiotherapy and corticosteroids. Very isolated instances of inflammatory bowel disease have been seen in patients receiving rituximab {Ardelean 2010}.

5.4.2.1. 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}.

5.4.2.2. Differentiation Between Small-bowel and Large-bowel Diarrhea

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 volumes with gross blood frequently found in the stool. Consider a colonoscopic evaluation and biopsy.

5.4.3. Hepatic Events

Transaminase Elevations: Consistent with observations in a dog toxicology study, reversible asymptomatic ALT/AST increases were also 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 have been 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 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.

HBV Reactivation: HBV reactivation can occur in patients treated with anti-CD20 antibodies. Subjects who are HBc antibody positive/HBV DNA PCR negative at screening will be monitored for potential HBV reactivation (manifest as detectable HBV DNA by quantitative PCR). 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 will be tested monthly for the duration of anti-CD20 therapy and every 3 months for 1 year following the last dose of rituximab 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 anti-CD20 therapy and start appropriate treatment for HBV. In the event of HBV reactivation, please contact the Medical Monitor regarding continuation of idelalisib.

Product labeling for bendamustine indicates that the drug should be used with caution in patients with hepatic impairment of Grade ≥2 {Cephalon 2012}. As indicated in Table 5-6, bendamustine administration should be delayed until any abnormalities of ALT, AST, or bilirubin are Grade ≤1. Dose modifications of bendamustine for Grade ≥3 bilirubin elevations appear warranted.

5.4.4. 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 febrile neutropenia, have occurred in subjects treated with idelalisib. For subjects who develop Grade 3 neutropenia, blood counts must be monitored at least weekly until ANC ≤ Grade 2. For subjects who develop Grade 4 neutropenia, idelalisib must be interrupted and blood counts monitored at least weekly until ANC is Grade ≤ 2. Idelalisib may be resumed at a lower dose when ANC ≤ Grade 3. Neutropenia should be managed according to established clinical guidelines.

Rituximab-induced B-cell depletion occurred in 70% to 80% of patients with NHL {Genentech Inc 2011}. Frequencies of Grade ≥3 cytopenias have included lymphopenia (40%), neutropenia (6%), leucopenia (4%), anemia (3%), and thrombocytopenia (2%). Suppression of CD4+ counts has not been evident. Decreased IgM and IgG serum levels occurred in 14% of patients with NHL. Rituximab has not commonly been associated with bone marrow suppression; thus, alterations in rituximab for such events during combination therapy are not planned unless neutropenia is prolonged and refractory to standard of care growth factor support. In subjects with persistent neutropenia despite G-CSF administration, rituximab doses may be delayed for as long as 4 weeks to allow recovery of neutrophil counts to Grade ≤ 3 (see Table 5-6).

Almost all patients treated with bendamustine/rituximab have experienced myelosuppression {Fischer 2011, Iannitto 2011}. Reductions in ANC, lymphocytes (including prolonged lymphocytopenia [< 600/µl] and low CD4-positive T-cell counts [< 200/µl]), platelets, and hemoglobin have been observed. Hematological nadirs are commonly observed several weeks after drug administration and may be observed for at least 7-9 months after the completion of treatment. Serious and fatal infections have occurred with bendamustine hydrochloride, including bacterial (sepsis, pneumonia) and opportunistic infections such as Pneumocystis jirovecii pneumonia (PJP), varicella zoster virus (VZV), and cytomegalovirus (CMV). Lymphocytopenia and CD4-positive T-cell depletion are more pronounced when bendamustine is combined with rituximab. Patients with lymphocytopenia and low CD4-positive T-cell count following treatment with bendamustine hydrochloride are more susceptible to (opportunistic) infections. Therefore, patients should be monitored for respiratory signs and symptoms throughout treatment. Patients should be advised to report new signs of infection, including fever or respiratory symptoms, promptly. Discontinuation of bendamustine hydrochloride should be considered if there are signs of (opportunistic) infections. Among patients with an eC_{Cr} of <70 mL/minute, substantially higher rates of myelosuppression and neutropenic infection were observed among patients with CLL receiving bendamustine/rituximab {Fischer 2011}.

Because bendamustine commonly causes severe myelosuppression, dose modification provisions during combination therapy will modify the bendamustine dose. At the conclusion of chemoimmunotherapy, subjects with protracted or symptomatic neutropenia or thrombocytopenia during continuing single-agent study drug therapy (idelalisib/placebo) may warrant a study drug dose modification if myelosuppression is unresponsive to G-CSF supportive care or is symptomatic.

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

5.4.5. 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 trimethoprim-sulfamethoxazole or other established prophylaxis for PJP throughout the course of idelalisib treatment. Prophylaxis must continue for a period of 2 to 6 months after the last dose of idelalisib 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. Subjects must permanently discontinue idelalisib upon diagnosis of PJP.

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, consideration should be given to administering pre-emptive CMV therapy.

Serious bacterial, fungal, and new or reactivated viral infections have occurred during and for ~1 year following rituximab-based therapy {Gea-Banacloche 2010}. New or reactivated viral infections in patients receiving rituximab have included CMV, herpes simplex virus, parvovirus B19, varicella zoster virus, West Nile virus, HBV (see Section 5.4.3) and HCV.

Infection, including pneumonia and sepsis, has been reported in patients taking bendamustine in clinical trials and in post-marketing reports. Infection has been associated with hospitalization, septic shock and death. Patients with myelosuppression following treatment with bendamustine are more susceptible to infections. There may be an increased risk of skin toxicity when bendamustine is given together with trimethoprim-sulfamethoxazole.

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.

5.4.6. Infusion Reactions

Rituximab can cause severe, including fatal, infusion reactions {Genentech Inc 2011}. Patients with pre-existing cardiac or pulmonary conditions, those who experienced prior cardiopulmonary adverse reactions to rituximab, and those with high numbers of circulating malignant cells ($\geq 25 \times 10^9$/L) may be at particular risk. Severe reactions typically occur during the first infusion and are generally less frequent and less severe with subsequent infusions. The time to onset of infusion toxicity ranges from 30 to 120 minutes. Rituximab-induced infusion reactions and sequelae include urticaria, hypotension, angioedema, hypoxia, bronchospasm, pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation, cardiogenic shock, and/or anaphylactoid events.

For a subject who is experiencing a Grade ≥3 rituximab-related infusion reaction, the rituximab infusion should be interrupted and the infusion rate decreased. Medical management (eg, oxygen, epinephrine, bronchodilators, and/or glucocorticoids) should be instituted, as needed. Upon improvement of symptoms, the infusion may be continued at 50% of the previous rate. At the discretion of the investigator, rituximab therapy may be permanently discontinued in subjects with Grade 4 infusion reactions or with reactions requiring substantial intervention.

For a subject with a greater risk of infusion reactions due to a pretreatment ALC of ≥25 x 10^9/L, the Day 1 rituximab infusion may be limited to 100 mg total drug (ie, 1 vial of rituximab) and the remainder of the planned total rituximab dose may be administered prior to bendamustine on Day 2.

Infusion reactions attributed to bendamustine have occurred in clinical trials. Symptoms have included fever, chills, pruritus, and rash. In rare instances severe anaphylactic and anaphylactoid reactions have occurred, particularly in the second and subsequent cycles of therapy. There are postmarketing reports of bendamustine extravasations resulting in hospitalizations from erythema, marked swelling, and pain. Precautions should be taken to avoid extravasation, including monitoring of the intravenous infusion site for redness, swelling, pain, infection, and necrosis during and after administration of bendamustine.

Measures to prevent severe bendamustine infusions reactions, including antihistamines, antipyretics, and corticosteroids can be considered in subsequent cycles in patients who have previously experienced Grade 1 or 2 bendamustine-induced infusion reactions. Discontinuation of bendamustine should be considered in patients with Grade ≥3 bendamustine-related infusion reactions.

5.4.7. Progressive Multifocal Leukoencephalopathy

Progressive multifocal leukoencephalopathy (PML) due to polyomavirus JC has been observed in patients who have received rituximab therapy {Carson 2009} for hematologic malignancies. The specific causal role of rituximab is unknown because many of these patients had other risk factors (eg, low CD4+ counts) and the majority had received rituximab in combination with chemotherapy or as part of a hematopoietic stem cell transplant. Most cases of PML were diagnosed within 12 months of the last infusion of rituximab.

The diagnosis of PML should be considered in any subject presenting with new-onset neurologic manifestations. Evaluation of PML may include consultation with a neurologist, brain MRI, and lumbar puncture with quantitative PCR assays targeting the DNAs of JC, VZV, CMV and HHV-6. Subjects diagnosed with PML should receive no further rituximab. Study drug (idelalisib/placebo) should also be permanently discontinued.

5.4.8. 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 and organizing pneumonia, respectively, without documented pulmonary infection.

Rituximab-related noninfectious pneumonitis has been described {Subramanian 2010} with an incidence of ~4.3% {Salmasi 2010}. In patients developing rituximab-associated pneumonitis, the mean time from the first rituximab infusion to the onset of respiratory symptoms was 3 months, with a peak incidence after administration of a mean cumulative dosage of 1600 mg/m^2 {Liote 2010}.

Pneumonias and pulmonary fibrosis have occurred in patients receiving bendamustine {Cephalon 2012}.

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.

For subjects with suspected Grade 1 pneumonitis, withhold idelalisib/placebo until resolution to baseline. Upon resolution to baseline, idelalisib/placebo may be resumed at a lower dose level or discontinued at investigator discretion. For subjects with suspected Grade $\geq$ 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/placebo must be discontinued permanently and therapy initiated as clinically appropriate.

Cases of organizing pneumonia, some with fatal outcome, have occurred with idelalisib. In subjects presenting with serious lung events, idelalisib should be interrupted and the subject assessed for an explanatory etiology. If organizing pneumonia is diagnosed, treatment with idelalisib should be permanently discontinued and the subject treated accordingly.

5.4.9. 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.

There are reports of pre-malignant and malignant diseases that have developed in subjects who have been treated with bendamustine, including myelodysplastic syndrome, myeloproliferative disorders, acute myeloid leukemia, and bronchial carcinoma. The specific association of the therapeutic agents with these types of events has not been determined.

5.4.10. Tumor Lysis Syndrome

Tumor lysis syndrome has not been observed with idelalisib monotherapy.

When idelalisib is combined with other agents known to induce tumor lysis syndrome, prophylaxis with agents such as allopurinol may be considered. The benefit versus risk of prophylactic agents must be carefully considered given a potential of increased risk of severe skin toxicity.

Subjects with tumor lysis syndrome should receive rapid reversal of hyperkalemia, intravenous hydration, antihyperuricemic agents, and appropriate cardiac and renal support, including dialysis as indicated. Upon recovery to baseline functioning, such subjects should continue study treatment including study drug (idelalisib/placebo).

5.4.11. Cardiac Disorders

Fatal cases of myocardial infarction and cardiac failure have been reported with bendamustine hydrochloride treatment. Subjects with concurrent or history of cardiac disease should be observed closely.

5.4.12. 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.

Reproduction studies of rituximab in cynomolgus monkeys at maternal exposures similar to human therapeutic exposures have shown no teratogenic effects {Genentech Inc 2011}. However, B-cell lymphoid tissue was reduced in the offspring of these animals; B-cell counts returned to normal levels and immunologic function was restored within 6 months of birth. In humans, B-cell lymphocytopenia generally lasting <6 months can occur postnatally in infants exposed to rituximab in utero. Rituximab is secreted in the milk of lactating cynomolgus monkeys, and IgG is excreted in human milk {Genentech Inc 2011}. However, antibodies in breast milk do not enter the neonatal infant circulations in substantial amounts. It is not known whether rituximab is secreted into human milk.

Bendamustine is a mutagen and clastogen. Single intraperitoneal doses of bendamustine in mice and rats administered during organogenesis caused an increase in resorptions, skeletal and visceral malformations, and decreased fetal body weights. It is not known whether bendamustine is excreted in human milk. Impaired spermatogenesis, azoospermia, and total germinal aplasia have been reported in male patients treated with alkylating agents, especially in combination

with other drugs. In some instances spermatogenesis may return in patients in remission, but this may occur only several years after intensive chemotherapy has been discontinued.

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 Section 5.6.4). If a female study participant becomes pregnant or decides to breastfeed during the course of the study, all study therapy (idelalisib/placebo, rituximab and bendamustine) must be discontinued.

5.4.13. PJP 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 two 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 the drug 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; 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.

5.4.14. 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.

5.4.15. Further Safety Information

Further safety information regarding the study drug may be found in the investigator brochure for idelalisib. Further information regarding bendamustine and rituximab can be found in the respective product information.

5.5. Emergency Unblinding

In the event of a medical emergency where breaking the blind is required to provide medical care to the subject, the investigator may obtain treatment assignment directly from the IWRS system for that subject. Gilead recommends but does not require that the investigator contact the Gilead medical monitor before breaking the blind. Treatment assignment should remain blinded unless that knowledge is necessary to determine subject emergency medical care. The rationale for unblinding must be clearly explained in source documentation and on the case report form/electronic case report form (CRF/eCRF), along with the date on which the treatment assignment was obtained. The investigator is requested to contact the Gilead medical monitor promptly in case of any treatment unblinding.

Blinding of study treatment is critical to the integrity of this clinical trial and therefore, if a subject's treatment assignment is disclosed to the investigator, the subject will have study treatment discontinued. All subjects will be followed until study completion unless consent to do so is specifically withdrawn by the subject.

Gilead Drug Safety and Public Health (DSPH) may independently unblind cases for expedited reporting of suspected unexpected serious adverse reactions (SUSARs).

5.6. Concomitant and Supportive Therapy

To the extent possible, administration of any prescription or over-the-counter drug products other than study medication should be minimized during the study period. Subjects should be discouraged from use of street drugs, herbal remedies, self-prescribed drugs, tobacco products, or excessive alcohol at any time during the clinical study.

If considered necessary for the subject's well-being, drugs for concomitant medical conditions or for symptom management may be given at the discretion of the investigator. The decision to authorize the use of any drug other than study drug should take into account subject safety, the medical need, the potential for drug interactions, the possibility for masking symptoms of a more significant underlying event, and whether use of the drug will compromise the outcome or integrity of the study

Subjects should be instructed about the importance of the need to inform the clinic staff of the use of any drugs or remedies (whether prescribed, over-the-counter, or illicit) before and during the course of the study. Any concomitant drugs taken by a subject during the course of the study and the reason for use should be recorded on the eCRFs.

Information regarding use or restrictions on specific concomitant medications, dietary measures, or other interventions is provided below.

5.6.1. Anticancer or Experimental Therapies Other than Investigational Treatments

Except for corticosterioids (see Section 5.6.5), no other systemic anticancer therapies (including chemotherapy, radiation, antibody therapy, immunotherapy, or other experimental therapies) of any kind are permitted while the subject is receiving study treatment with idelalisib. Discuss the use of topical anticancer agents (eg, topical 5-FU) with the medical monitor. Subjects are not allowed to participate concurrently in any other therapeutic clinical study.

5.6.2. Antibiotics

Investigators must initiate antibiotic prophylaxis against pneumocystis infection (eg, with trimethoprim-sulfamethoxazole, dapsone, aerosolized pentamidine, or atovaquone) beginning prior to study drug administration. Such support may also offer the benefit of reducing the risk for other bacterial infections {Green 2007}. Investigator discretion and local practices or guidelines may be followed. It should be realized that there may be an increased risk of skin toxicity in subjects receiving bendamustine together with trimethoprim-sulfamethoxazole.

For subjects who develop an infection, appropriate medical therapy (with antibiotics, antifungals, or antiviral) or other interventions should be instituted. When appropriate, subjects may continue with study drug (idelalisib/placebo) and bendamustine/rituximab during treatment for the infection; however, subjects who develop PJP must permanently discontinue study drug.

5.6.3. Antiemetics and Antidiarrheals

Drug-related nausea and/or vomiting have not been commonly observed with idelalisib or rituximab. Bendamustine is moderately emetogenic. Subjects who experience nausea or vomiting while on study therapy may receive antiemetics based on the judgment of the treating physician and local institutional practices. At the occurrence of persistent nausea or vomiting of severity Grade ≥1, it is suggested that the subject receive an oral or transdermal serotonin antagonist (eg, dolasetron, granisetron, ondansetron, tropisetron, palonosetron).Other classes of antiemetic medications that may be employed include dopamine antagonists or benzodiazepines.

As needed, subjects may be prescribed loperamide (Imodium® or others) or diphenoxylate and atropine (Lomotil®) to control diarrheal symptoms.

5.6.4. Contraception

In the context of this protocol, a female subject is considered to be of childbearing potential unless she has had a hysterectomy, a bilateral tubal ligation, or a bilateral oophorectomy; has medically documented ovarian failure (with serum estradiol and FSH levels within the institutional postmenopausal range and a negative serum or urine βHCG); or is menopausal (defined as age ≥54with amenorrhea for >12 months or amenorrhea for >6 months with serum estradiol and FSH levels within the institutional postmenopausal range).

Sexually active females of childbearing potential must agree to use a protocol-recommended method of contraception throughout the study and for 30 days from the last dose of study drug (idelalisib/placebo) or >12 months from the last dose of rituximab (whichever is later). The investigator should counsel subjects on the most effective methods for avoiding pregnancy during the trial. Protocol-recommended contraceptive methods are described in Table 5-7.

Table 5-7. Protocol-Recommended Contraceptive Methods

	Combination Methods	
Individual Methods	**Hormonal Methods** (One method to be used with a barrier method)	**Barrier Methods** (Both of these methods to be used OR one of these methods to be used with a hormonal method)
IUD • Copper T 380A IUD • LNg 20 IUD **Tubal sterilization** **Hysterectomy**	**Estrogen and progesterone** • Oral contraceptives • Transdermal patch • Vaginal ring **Progesterone** • Injection • Implant	• Diaphragm with spermicide • Male condom (with spermicide)

Abbreviation: IUD=intrauterine device

In the context of this protocol, a male subject is considered able to father a child unless he has had a bilateral vasectomy with documented aspermia or a bilateral orchiectomy, or is receiving ongoing testicular suppression with a depot luteinizing hormone-releasing hormone (LH-RH) agonist (eg, goserelin acetate [Zoladex®]), leuprolide acetate [Lupron®]), or triptorelin pamoate [Trelstar®]).

Sexually active male subjects who can father a child must limit intercourse to female partners who are surgically sterile, post-menopausal, or using effective contraception (as noted in Table 5-7); or agree to use a protocol-recommended method of contraception during heterosexual intercourse throughout the study and until >6 months following the last dose of bendamustine or ≥90 days following the last dose of study drug (whichever is later) (as noted in Table 5-7).

The Gilead Sciences medical monitor should be consulted regarding any questions relating to childbearing status or contraception.

5.6.5. Corticosteroids

Subjects may receive topical, inhaled, enteric, or systemic corticosteroids while on study. It should be realized that the use of systemic corticosteroids in patients with CLL may confound interpretation of antitumor effects mediated by study drug treatment (idelalisib/placebo or rituximab). However, systemic corticosteroids should be used to prevent rituximab infusion reactions. Low-dose corticosteroids for treatment of rheumatological conditions are permitted. In addition, subjects who develop conditions that may be alleviated by systemic corticosteroid therapy are permitted to receive such drugs and are not required to discontinue study participation.

5.6.6. Granulocyte Colony-Stimulating Factors and Erythropoietin

Granulocyte-macrophage colony-stimulating factor (GM-CSF) should not be administered given the potential for GM-CSF-related inflammatory symptoms.

G-CSF (filgrastim, PEG-filgrastim, lenograstim) may be administered in response to Grade 4 neutropenia or neutropenic complications; use should be particularly considered if providing hematopoietic support might help to maintain study drug treatment (see Table 5-6).

While erythropoietic agents (eg, erythropoietin or darbepoetin) may be administered for Grade ≥3 anemia, their use in this study is discouraged given the potential to confound assessments of improvements in bone marrow function related to study drug.

Reference may be made to the American Society of Clinical Oncology guidelines {Rizzo 2008, Smith 2006}.

5.6.7. Drugs that Inhibit/Induce CYP3A-Dependent Metabolism

Idelalisib is metabolized primarily via aldehyde oxidase and in part by CYP3A. A clinical drug-drug interaction study indicated that administration of a potent CYP3A inhibitor together with idelalisib resulted in an ~80% increase in idelalisib plasma exposures (AUC) (see Section 1.3.5.1.), which is not considered to be clinically relevant and suggesting that idelalisib is a weak CYP3A substrate. Preliminary data indicate when coadministered with rifampin, a highly potent inducer of CYP3A, idelalisib exposures are ~75% lower. Coadministration of potent inducers of CYP3A with idelalisib should be avoided; a list of strong inducers is provided in Table 5-8:

Table 5-8. Known strong inducers of CYP3A

Effect on CYP3A	Drug Class	Medications
Strong CYP3A Inducers	Antimycobacterial	Rifampin
	Anticonvulsants	carbamazepine, phenytoin
	Foods/herbs	St. John's wort

Abbreviation: CYP=cytochrome P450 enzyme

5.6.8. Drugs that undergo CYP3-A-Dependent Metabolism

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

5.6.9. Immunization

Because of its actions to inhibit PI3Kδ-dependent B-cell function, high doses of idelalisib can impair primary or secondary responses to immunization in animals.

In randomized clinical trials, rituximab has been shown to reduce the antibody response to pneumococcal vaccination (a T-cell-independent antigen) or to anti-keyhole limpet hemocyanin antibodies (a novel protein antigen) {Genentech Inc 2011}. Response to tetanus toxoid vaccine (a T−cell-dependent antigen with existing immunity) or maintenance of a positive Candida skin test (as a measure of T-cell-mediated delayed-type hypersensitivity) was not altered.

The specific clinical relevance of these findings with idelalisib or rituximab is unknown. However, for subjects who are at substantial risk of an infection (eg, influenza) that might be prevented by immunization, consideration should be given to providing the vaccine prior to initiation of study therapy.

Of note, the safety of immunization with live viral vaccines following idelalisib or rituximab therapy has not been studied and vaccination with live virus vaccines during study treatment is not recommended.

5.6.10. Surgery

There are no known effects of idelalisib on coagulation or wound healing. Pending receipt of additional information, study drug (idelalisib/placebo) may be continued in the peri-procedural period in subjects who require surgery or invasive procedures.

5.6.11. Diet

There are no specific dietary restrictions in the study. Study drug (idelalisib/placebo) may be taken with or without food.

5.7. Duration of Study Drug

Subjects may continue receiving study drug (idelalisib/placebo) until the occurrence of any events requiring study drug discontinuation as defined in Section 5.8.

Subjects may continue to receive rituximab until the earliest of a maximum of 6 infusions or the occurrence of any events requiring rituximab discontinuation as defined in Section 5.8.

Subjects may continue to receive bendamustine until the earliest of a maximum of 12 infusions or the occurrence of any events requiring bendamustine discontinuation as defined in Section 5.8.

Bendamustine may be continued even if rituximab is discontinued due to rituximab-specific toxicity. Similarly, rituximab may be continued even if bendamustine is discontinued due to bendamustine-specific toxicity. Subjects who are tolerating study drug (idelalisib/placebo) should continue study drug even if bendamustine or rituximab are discontinued due to bendamustine- or rituximab-related toxicities or due to an inability to continue bendamustine- or rituximab therapy.

5.8. Discontinuation of Study Drug

All study participants may receive idelalisib/placebo indefinitely and may receive rituximab through 6 infusions and bendamustine through 12 infusions as noted in Section 5.7. However:

- Any subject has the right to discontinue study drug, rituximab, or bendamustine at any time.
- Any subject who has objective evidence based on IRC review of definitive CLL progression will discontinue study drug.

- Any subject that is unable to tolerate a rechallenge with protocol-described, dose-modified study drug (idelalisib/placebo) at Dose Level –1 (100 mg/dose BID) (see Section 5.3.5) should be withdrawn from the study drug.
- Any subject who becomes pregnant or begins breastfeeding must discontinue study drug.
- Any subject who becomes significantly noncompliant with study drug administration, study procedures, or study requirements should discontinue study drug.
- Any subject for whom the blind is intentionally broken by the subject or the study site should discontinue study drug.
- The investigator, in consultation with the Gilead Sciences medical expert, may discontinue study drug, rituximab, or bendamustine, if it is not in the subject's best interest to continue.
- Following study-wide unblinding**,** any subject randomized to Arm B should discontinue study drug.
- Any subject whose benefit-risk profile is not deemed positive by the investigator should discontinue study drug.
- Any subject who is diagnosed with any grade of SJS, TEN, PJP, or organizing pneumonia, or any subject diagnosed with Grade ≥2 pneumonitis should discontinue study drug.

If allowed by local regulations, Gilead Sciences may transition subjects from study drug to commercial drug supply when idelalisib becomes commercially available in the country where the subject is living.

Subjects who permanently discontinue study drug for a reason other than disease progression (as determined by the IRC) shall continue with regular assessments per the schedule of procedures until disease progression or another anticancer or experimental therapy is initiated.

5.9. Discontinuation from Study

Subject study participation may be ended due to any of the following reasons:

- Adverse event;
- Disease progression;
- Withdrawal of consent;
- Significant subject noncompliance with study drug administration, study procedures, or study requirements;
- Initiation of any additional systemic anticancer therapies (other than corticosteroids, see Section 5.6.5) including chemotherapy, radiation, antibody therapy, immunotherapy, or other experimental therapies;

- Physician's decision to remove the subject from the study;
- Pregnancy;
- The subject is lost to follow-up;
- Death;
- Discontinuation of study by the Sponsor, a Regulatory Agency, or an IRB or EC.

5.10. Study Treatment Rationale

Selection of the idelalisib treatment regimen (including starting dose level, dose-modifications and supportive care, schedule, duration, and conditions of administration) for this study has been based primarily on safety, exposure, and activity profiles from previous Phase 1 clinical studies involving healthy volunteers, patients with allergic rhinitis, and patients with refractory/relapsed lymphoid malignancies {Coutre 2011, de Vos 2011, Kahl 2011, Sharman 2011, Webb 2010}. The following information was considered in selecting the study drug dosing regimen for this study:

- Idelalisib was symptomatically well tolerated in patients with lymphoid malignancies receiving dose levels of 50 mg/dose BID through 350 mg/dose BID (the highest dose level tested). No specific MTD was apparent over the dose range tested. However, monitorable, reversible transaminase elevations were observed in some patients and may have been more frequent at higher dose levels (~10% rate among patients with CLL receiving starting doses of ≥150 mg/dose). Thus, while doses through 350 mg/dose BID appear tolerable, the starting dose of 150 mg/dose BID appears to appropriately balance safety with efficacy in idelalisib-naïve subjects.
- In an allergic rhinitis study, idelalisib induced statistically significant improvements in clinical and pharmacodynamic endpoints when administered at 100 mg/dose BID over 7 days. These data support the pharmacological relevance of idelalisib-mediated PI3Kδ inhibition when administered at a dose-level approximating that to be used in this Phase 3 study.
- A positive correlation was noted between idelalisib dose and measures of tumor control and chemokine normalization in patients with B-cell malignancies. The majority of patients appear to have tumor responses and protracted PFS when receiving starting doses of ≥100 mg/dose BID. Thus, treatment with a idelalisib at a starting dose of 150 mg/dose BID appears to offer most patients the potential to benefit from therapy.
- Increases in idelalisib plasma C_{max}, AUC, and C_{trough} values were less than dose-proportional in subjects with lymphoid malignancies; the dose-exposure evaluation indicated modest increases in plasma exposure at dose levels >150 mg BID. Thus, administration of a starting dose of idelalisib of 150 mg/dose BID appears appropriate to ensure adequate exposure in the majority of patients.

- In Phase 1 studies, the mean plasma $t_{1/2}$ of idelalisib was ~6.5 to 9.8 hours across all dose levels and there was no substantive plasma accumulation over 7 or 28 days.

- The changes in exposure observed when administering idelalisib after a high-fat, high-calorie meal are modest (~40% increase in mean AUC with no change in mean C_{max}). Thus, idelalisib can be administered with or without food.

- The idelalisib dose modification provisions described in the protocol are designed to balance a primary concern for subject safety with the potential for observing pharmacological and antitumor activity in circumstances under which a subject experiencing an adverse event may still be able to continue on therapy at a lower idelalisib dose level. The enhanced monitoring to be performed and the actions to be taken in response to toxicity are based on experience with interruption, dose-modification, rechallenge, and re-escalation already piloted in idelalisib Phase 1 trials. In addition, idelalisib antitumor activity has been observed in the Phase 1 studies across all dose levels tested, including doses in the range of the modified dose levels planned for this protocol. Thus, use of the lower dose level to accommodate individual subject tolerability in this protocol is justified because subjects receiving such an idelalisib dose level still have the potential for benefit.

- Study drug will be continued for each subject until the occurrence of disease progression. Such a strategy is considered appropriate under the assumption that persistent interference with PI3Kδ signaling in Arm A is likely to extend treatment effect. In addition, this design permits collection of further single-agent safety information without concomitant bendamustine/rituximab administration and thus is likely to enhance understanding of the overall safety profile of idelalisib.

Use of the reference therapies, rituximab and bendamustine, in this study is based on product labeling {Cephalon 2012, Genentech Inc 2011}, precedence established with rituximab and bendamustine in patients with CLL {Fischer 2011, Iannitto 2011}, and clinical observations relating to coadministration of bendamustine/rituximab with idelalisib {de Vos 2011, Sharman 2011}:

- Product labeling for use of rituximab in CLL describes intravenous administration of the drug in combination with fludarabine/cyclophosphamide chemotherapy every 4 weeks for a total of 6 infusions; the first rituximab dose is administered at dose of 375 mg/m^2 (Week 0) and the subsequent 5 doses are administered at a dose of 500 mg/m^2 (Weeks 4, 8, 12, 16, and 20). A similar schedule was adopted by the German CLL Study Group in establishing a regimen of bendamustine/rituximab {Fischer 2011}. The doses and schedule of the rituximab regimen used in both the control and treatment arms of this study are based on these past experiences.

- Product labeling for use of bendamustine in CLL describes intravenous administration of the drug on Days 1 and 2 every 4 weeks for a total of 12 infusions; a similar schedule was adopted by the German CLL Study Group in establishing a regimen of bendamustine/rituximab {Fischer 2011}. The data from Phase 1 evaluation documented a an

MTD of 70 mg/m^2 {Lissitchkov 2006}; this dose level was confirmed to have substantial activity based on the Phase 2 experience of the German CLL Study Group {Fischer 2011} and has been generally adopted as appropriate when bendamustine is coadministered with rituximab in patients who had received prior therapy {Cheson 2010}.

- Truncation of bendamustine/rituximab therapy at 6 months is consistent with recommendations in product labeling and the existing Phase 2 data {Fischer 2011, Iannitto 2011} in patients with previously treated CLL.

- In a Phase 1, single-arm, dose-ranging study, concomitant administration of idelalisib at dose of 150 mg/dose BID together with bendamustine or bendamustine/rituximab has been shown to be safe and active {de Vos 2011, Sharman 2011}.

- Recommendations for managing rituximab- and bendamustine-related adverse events, and delay, dose-modifying, or discontinuing rituximab therapy for specific adverse events are consistent with experience described in product labeling {Cephalon 2012, Genentech Inc 2011}.

- Consistent with the current product package insert, subjects who are HBc antibody positive at screening shall be monitored for HBV reactivation (manifest as detectable HBV DNA by quantitative PCR). Subjects will be tested monthly for the duration of rituximab therapy and every 3 months thereafter for 1 year from the end of therapy.

6. STUDY PROCEDURES

6.1. Enrollment and Study Management Procedures

6.1.1. Subject Recruitment

Study candidates comprise subjects with CLL who are being followed at the specified study sites or are referred to the study sites. Subjects will be enrolled from investigational sites in the US and Europe. The site principal investigator, designated sub-investigators, or other designees will discuss the possibility of participation directly with subjects who may be appropriate candidates for the study. The study sponsor will post a description of the study on the ClinicalTrials.gov website.

Promotional information generated by the sponsor or investigational sites will be submitted for IRB/IEC review.

6.1.2. Subject Compensation for Participation

For subjects requesting such assistance, reasonable reimbursements for the costs of travel required to participate in this study will be provided by the study sponsor. To receive payment for travel, subjects will need to submit the original travel receipts to the research study staff at the investigational site.

However, other than medical care that may be provided, subjects will not be paid for participation in the study. Payments for such items as lost wages, disability, discomfort due to injury, or meals obtained while waiting at the clinical research center will not be provided. Through the informed consent process, study candidates will be notified that their insurance company could be charged for standard care that is a component of this research study and that subjects may be responsible for co-payments and deductible payments that are typical for their insurance coverage.

6.1.3. Screening

The investigator must inform each prospective subject of the nature of the study, explain the potential risks, and obtain written informed consent from the subject and/or a legal guardian prior to performing any study-related screening procedures. At the time the study candidate signs the informed consent, a site representative should access the IWRS to indicate that a study candidate is being screened. The user will need to supply the IWRS with required information identifying the site and subject. The IWRS will use this information to assign a subject number and maintain a central screening log that tracks screening, screen failures, and randomization.

Any consented subject who is excluded from the study before randomization will be considered a screen failure. All screen failures must be documented along with an adequate description of the reason the subject was considered a screen failure. If available, information should be provided as to why the subject did not meet eligibility criteria, withdrew consent, experienced an intercurrent illness, or had other events that precluded randomization.

Study GS-US-312-0115 shares many screening requirements with Study GS-US-312-0116 and GS-US-312-0119. In some instances, a patient may initiate screening for one trial but may prove ineligible for that study and may subsequently be judged to be eligible for another of these idelalisib studies. To reduce the burden to such a study candidate and to avoid redundancy of assessments that do not affect the safety of trial subjects, the following screening assessments performed for any of Study GS-US-312-0115, GS-US-312-0116, or GS-US-312-0119 can be used in screening for another of these trials or for rescreening for the same study. These tests do not need to be repeated if they fall into the screening windows defined below and there has been no intervening therapy for CLL between the time of the test and randomization to the study:

- CLL peripheral blood or bone marrow evaluations (ie, FISH, DNA mutational analysis, flow cytometry, and cytology) used for determining stratification and CLL prognosis – if obtained within 12 weeks prior to randomization

- Baseline CT/MRI scan – if obtained within 6 weeks prior to randomization

6.2. Explanation of Study Visits

The specific study procedures to be conducted for each subject enrolled in the study are presented in tabular form in Appendix 7 are described in the sections that follow. Additional information on the study procedures is provided in the study manual.

For visits at which HRQL and healthy utility data are obtained, it is important that the subject be administered the FACT-Leu and the EQ-5D before any other procedures are performed and before any study-related information is communicated to the subject; this is necessary to avoid biasing the PRO responses provided by the subject. Once the subject has completed the FACT-Leu and the EQ-5D assessments, the remaining procedures may be performed.

At visits involving idelalisib administration and pharmacokinetic sampling in the clinic, care should be taken to perform procedures with the appropriate timing relative to idelalisib administration. The actual sample collection times of pharmacokinetic blood specimens should be recorded. If a heparinized venous catheter is placed for sample collection in order to avoid repeated needle sticks, at least 2 mL of blood should be removed and discarded prior to each sample collection in order to avoid heparin contamination of the sample.

At the visits designated as a laboratory-only visits (Visits 4, 7, 10, 13, 16, and 19), subjects will have laboratory assessments that may be performed at the investigational site or at an accredited local laboratory or clinic that is convenient for the subject/caregiver. If blood is collected at a local laboratory, samples are not to be analyzed at the local laboratory. For these visits, subjects and/or caregivers will be provided with central laboratory kits that will contain materials necessary for the collection and shipment of the laboratory samples by the local laboratory clinic to the central laboratory.

At Visit 2 (Randomization and Treatment Start), local hematology results lab values (full CBC) should be obtained in addition to the required central lab values in order to prevent missing baseline results, should the central lab results become compromised (eg, due to hemolysis, etc.).

Throughout the study, local lab results may be requested in the event central laboratory results are not available for assessment of disease response, progression, safety monitoring, or the evaluation of a significant event.

In addition to clinical assessments of tumor status, CT or MRI imaging of the neck, chest, abdomen, and pelvis will be performed as a component of tumor assessments during the study based on the rationale provided in Section 3.5.1.

6.2.1. Visit 1 and Screening Period (Clinic Visit)

The initial screening visit is designated as Visit 1. At Visit 1, the investigator must inform each prospective study participant of the nature of the study, explain the potential risks, and obtain written informed consent from the study candidate and/or legal guardian prior to performing any study-related screening procedures. Once the informed consent document has been signed, the subject may undergo the screening procedures. The presence of radiographically measurable lymphadenopathy will be confirmed by the IRC during the screening period.

In order to optimize scheduling convenience for the subject and for the investigational staff, screening procedures may be performed over as many days as necessary provided that screening is completed within 4 weeks prior to randomization. Of note, the screening period may be extended to 6 weeks in subjects for whom there is a delay in the analysis of stratification variables (p53 mutation/17p deletion status or IgHV mutation status) or a delay in the acquisition of adequate baseline radiographic imaging data.

The tests and evaluations outline in Table 6-1 will be performed at Visit 1 or during the screening period prior to randomization.

Table 6-1. Procedures and Assessments at Visit 1 (Screening Period)

Assessment or Procedure	Explanation
Informed consent	To be obtained before any screening procedures are initiated
IWRS access	Access IWRS to document that subject is in screening and obtain subject number
Medical history	Including relevant information regarding CLL history, stage of disease (Rai and Binet staging system) reasons for treatment, prior therapies for CLL, documentation of relapsed or refractory CLL, and past history of other medically significant medical conditions
CIRS assessment	Recording of comorbid conditions using the CIRS scoring instrument (see Appendix 6)
Concomitant medications	Recording of ongoing concomitant medication use
Performance status	Using Karnofsky performance status criteria (see Appendix 3)
Oxygen saturation	To be assessed by pulse oximetry while subject is breathing room air
Physical examination	Including assessment of height, weight, lymph nodes, spleen, and liver
Serum virology	Including HBsAg, HBc antibody, HCV antibody, HIV antibody, CMV serology; if HCV antibody is positive, subjects must be evaluated for the presence of circulating HCV viral RNA
Serum β-HCG	Women of childbearing potential only
CLL peripheral blood evaluation	Including FISH for chromosome 11q deletion, 13q deletion, 17p deletion and 12 trisomy; DNA mutational analysis for p53, IgHV (including IgHV3-21), and other genes of interest in CLL (eg, Notch); flow cytometry for CD5, CD10, CD11c, CD19, CD20, CD23, CD38, CD45, kappa and lambda light chains, and ZAP-70; cytology for karyotyping
CLL serology	Serum β_2 microglobulin
Coagulation	aPTT, PT, INR
Urinalysis	Including pH, protein, glucose, ketones, bilirubin, urobilinogen, blood, nitrite, leukocyte esterase
Hematology	Including hematocrit, hemoglobin, erythrocyte count; absolute counts of leukocytes, neutrophils, lymphocytes, monocytes, eosinophils, basophils, platelet count
Serum chemistry	Including sodium, potassium, chloride, glucose, urea, creatinine, calcium, phosphorus, total protein, albumin, ALT, AST, ALP, GGT, total bilirubin, LDH, uric acid, cholesterol, triglycerides
12-lead ECG	To be obtained while subject is resting in the supine position
Radiology assessment	CT or MRI imaging of neck, chest, abdomen, and pelvis, to be scheduled within 6 weeks prior to randomization
Bone marrow biopsy and aspirate	To be performed at investigator discretion in subjects for whom assessment of extent of CLL involvement and bone marrow cellularity is important in determining eligibility

Abbreviations: β-HCG=beta human chorionic gonadotropin, ALP=alkaline phosphatase, ALT=alanine aminotransferase, aPTT=activated partial thromboplastin time, AST=aspartate aminotransferase, CIRS=cumulative illness rating scale, CLL=chronic lymphocytic leukemia, CMV=cytomegalovirus, CT=computed tomography, DNA=deoxyribonucleic acid, ECG=electrocardiogram, FISH= fluorescence in-situ hybridization, GGT=gamma--glutamyltransferase, HBc antibody=anti-hepatitis B core antibody, HBsAg=hepatitis B surface antigen, HBV=hepatitis B virus, HCV=hepatitis C virus, HIV=human immunodeficiency virus, INR=international normalized ratio, IgHV=immunoglobulin heavy chain variable region, IWRS=interactive web response system, LDH=lactate dehydrogenase, MRI=magnetic resonance imaging, PT=partial thromboplastin time, RNA=ribonucleic acid, ZAP-70=zeta-associated protein 70

6.2.2. Visit 2 (Clinic Visit – Randomization and Treatment Start)

The procedures outlined in Table 6-2 will be performed at Visit 2.

Table 6-2. Procedures and Assessments at Visit 2 (Day 1)

Assessment or Procedure	Explanation
Pre-Treatment Procedures and Assessments	
FACT-Leu	HRQL instrument (Appendix 2) to be administered before any other procedures are performed and before any study-related information is communicated to the subject
EQ-5D	Health utility instrument (Appendix 4) to be administered after FACT-Leu but before other procedures are performed and before study-related information is communicated to the subject
Adverse events	Recording of adverse events occurring since the initiation of the screening period
Concomitant medications	Recording of concomitant medication use since the initiation of the screening period
Performance status	Using Karnofsky performance status criteria (see Appendix 3)
Oxygen saturation	To be assessed by pulse oximetry while subject is breathing room air
Physical examination	Including assessment of weight, lymph nodes, spleen, and liver
Urine β-HCG dipstick	For women of child-bearing potential only; serum β-HCG or urine dipstick pregnancy test must be negative prior to randomization and initial study treatment
Hematology	Including hematocrit, hemoglobin, erythrocyte count; absolute counts of leukocytes, neutrophils, lymphocytes, monocytes, eosinophils, basophils, platelet count. An additional sample should also be collected and analyzed locally.
Serum chemistry	Including sodium, potassium, chloride, glucose, urea, creatinine, calcium, phosphorus, total protein, albumin, ALT, AST, ALP, GGT, total bilirubin, LDH, uric acid, cholesterol, triglycerides
Circulating cells	Including cells for analysis of PI3K/AKT/mTOR pathway activation and quantitation of CD4+, CD5+, CD8+, CD16/CD56+, CD19+, and CD+20 cells by flow cytometry
Biomarkers	Collection of plasma and serum for evaluation of circulating chemokines and cytokines
Serum Igs	Including quantitative levels of IgA, IgE, IgG, and IgM
Genotyping and expression analysis	Including blood for DNA, RNA and protein isolation for potential future assessment of biomarkers (subjects may choose to not provide DNA sample)
Idelalisib pharmacokinetics	Pre-dose collection of plasma sample for idelalisib pharmacokinetics (with recording of the date and actual clock time of blood collection)
HBV DNA by PCR	Only subjects who are HBc antibody positive and HBV DNA negative at screening, per Section 5.4.3.
IWRS access	Access of IWRS to stratify and randomize subject, and to obtain study drug bottle number

Assessment or Procedure	Explanation
Study Treatment Administration	
Study drug administration	First dose of study drug (idelalisib/placebo) to be administered to the subject in clinic (with recording of the date and actual clock time of the study drug administration)
Pretreatment	Antipyretic and antihistamine to be administered to the subject at the same time as study drug (idelalisib/placebo) and ~30 minutes prior to rituximab infusion; an intravenous corticosteroid and antiemetics may also be given as premedications per local practices
Rituximab infusion	Rituximab, 375 mg/m^2, to be administered by intravenous infusion ~30 minutes after pretreatment
Bendamustine infusion	Bendamustine intravenous infusion to be started at completion of rituximab; bendamustine to be administered over ~60 minutes.
Rituximab infusion severity and duration assessment	Worst severity of rituximab infusion reaction to be graded and total duration of rituximab infusion to be recorded
Post-Treatment Procedures and Assessments	
Idelalisib pharmacokinetics	Post-dose collection of plasma sample for idelalisib pharmacokinetics at 1.5 hours +/- 30 mins after study drug administration (with recording of the date and actual clock time of blood collection)
Study drug dispensing	Dispensing of 12-week supply of study drug (idelalisib/placebo) to the subject with instructions for self-administration at home
Instruction regarding in-clinic study drug dosing	Instruction to the subject that the morning dose of study drug (idelalisib/placebo) should not be taken on the day of the next treatment clinic visit.

Abbreviations: β-HCG=beta human chorionic gonadotropin, AKT=AKT (a serine/threonine protein kinase), ALP=alkaline phosphatase, ALT=alanine aminotransferase, AST=aspartate aminotransferase, DNA=deoxyribonucleic acid, EQ-5D=EuroQoL Five-Dimension, FACT-Leu=Functional Assessment of Cancer Therapy-Leukemia, GGT=gamma-glutamyltransferase, HRQL=health-related quality of life, Ig=immunoglobulin, IWRS=interactive web response system, LDH=lactate dehydrogenase, mTOR=mammalian target of rapamycin, PI3K=phosphatidylinositol 3-kinase, RNA=ribonucleic acid

6.2.3. Visits 3, 6, 9, 12, 15, and 18 (Clinic Visit –Bendamustine Administration)

The procedures outlined in Table 6-3 will be performed at Visits 3, 6, 9, 12, 15, and 18 (Day 2 of treatment cycle).

Table 6-3. Procedures and Assessments at Visits 3, 6, 9, 12, 15, and 18 (+1 Day)

Assessment or Procedure	Explanation
Study Treatment Administration	
Study drug	Morning dose of study drug (idelalisib/placebo) to be taken orally by the subject at home.
Pretreatment	Antiemetics may be given to minimize bendamustine-related nausea.
Bendamustine infusion	Bendamustine intravenous infusion to be administered over ~60 minutes.

6.2.4. Visits 4, 7, 10, 13, 16, and 19 (Laboratory Visits)

The procedures outlined in Table 6-4 will be performed at Visits 4, 7, 10, 13, 16, and 19.

Table 6-4. Procedures and Assessments at Visits 4, 7, 10, 13, 16, and 19 (±2 Days)

Assessment or Procedure	Explanation
Hematology[a]	Including hematocrit, hemoglobin, erythrocyte count; absolute counts of leukocytes, neutrophils, lymphocytes, monocytes, eosinophils, basophils, platelet count
Serum chemistry[a]	Including ALT, AST, ALP, GGT, total bilirubin, LDH

a More frequent (eg, weekly) hematology/serum chemistry assessments may be appropriate in subjects experiencing Grade ≥3 myelosuppression or ALT/AST elevations.
Abbreviations: ALP=alkaline phosphatase, ALT=alanine aminotransferase, AST=aspartate aminotransferase, GGT=gamma-glutamyltransferase, LDH=lactate dehydrogenase

6.2.5. Visit 5 (Clinic Visit)

The procedures outlined in Table 6-5 will be performed at Visit 5.

Table 6-5. Procedures and Assessments at Visit 5 (±2 Days)

Assessment or Procedure	Explanation
Pre-Treatment Procedures and Assessments	
FACT-Leu	HRQL instrument (Appendix 2) to be administered before any other procedures are performed and before any study-related information is communicated to the subject
EQ-5D	Health utility instrument (Appendix 4) to be administered after FACT-Leu but before other procedures are performed and before study-related information is communicated to the subject
Adverse events	Recording of adverse events occurring since the last clinic visit
Concomitant medications	Recording of concomitant medication use since the last clinic visit
Performance status	Using Karnofsky performance status criteria (see Appendix 3)
Oxygen saturation	To be assessed by pulse oximetry while subject is breathing room air
Physical examination	Including assessment of weight, lymph nodes, spleen, and liver
Urine β-HCG dipstick	For women of child-bearing potential only
Hematology	Including hematocrit, hemoglobin, erythrocyte count; absolute counts of leukocytes, neutrophils, lymphocytes, monocytes, eosinophils, basophils, platelet count
Serum chemistry	Including sodium, potassium, chloride, glucose, urea, creatinine, calcium, phosphorus, total protein, albumin, ALT, AST, ALP, GGT, total bilirubin, LDH, uric acid, cholesterol, triglycerides
Circulating cells	Including cells for analysis of PI3K/AKT/mTOR pathway activation and quantitation of CD4+, CD5+, CD8+, CD16/CD56+, CD19+, and CD+20 cells by flow cytometry
Biomarkers	Collection of plasma and serum for evaluation of circulating chemokines and cytokines

Assessment or Procedure	Explanation
Serum Igs	Including quantitative levels of IgA, IgE, IgG, and IgM
Idelalisib pharmacokinetics	Recording of the date and actual clock time of the last prior subject self-administration of study drug (should be the prior evening dose); pre-dose collection of plasma sample for idelalisib pharmacokinetics (with recording of the date and actual clock time of the date and actual clock time of blood collection)
HBV DNA by PCR	Only subjects who are HBc antibody positive and HBV DNA negative at screening, per Section 5.4.3.
IWRS access	Access of IWRS to document subject visit
Study Treatment Administration	
Study drug administration	Morning dose of study drug (idelalisib/placebo) to be administered to the subject in clinic (with recording of the date and actual clock time of the study drug administration)
Pretreatment	Antipyretic and antihistamine to be administered to the subject at the same time as study drug (idelalisib/placebo) and ~30 minutes prior to rituximab infusion; an intravenous corticosteroid and antiemetics may also be given as premedications per local practices
Rituximab infusion	Rituximab, 500 mg/m^2, to be administered by intravenous infusion ~30 minutes after pretreatment
Bendamustine infusion	Bendamustine intravenous infusion to be started at completion of rituximab; bendamustine to be administered over ~60 minutes.
Rituximab infusion severity and duration assessment	Worst severity of rituximab infusion reaction to be graded and total duration of rituximab infusion to be recorded
Post-Treatment Procedures and Assessments	
Idelalisib pharmacokinetics	Post-dose collection of plasma sample for idelalisib pharmacokinetics at 1.5 hours +/- 30 mins after study drug administration (with recording of the date and actual clock time of blood collection)
Instruction regarding in-clinic study drug dosing	Instruction to the subject that the morning dose of study drug (idelalisib/placebo) should not be taken on the day of the next treatment clinic visit

Abbreviations: AKT=AKT (a serine/threonine protein kinase), ALP=alkaline phosphatase, ALT=alanine aminotransferase, AST=aspartate aminotransferase, EQ-5D=EuroQoL Five-Dimension, FACT-Leu=Functional Assessment of Cancer Therapy-Leukemia, HRQL=health-related quality of life, GGT=gamma-glutamyltransferase, Ig=immunoglobulin, IWRS=interactive web response system, LDH=lactate dehydrogenase, mTOR=mammalian target of rapamycin, PI3K=phosphatidylinositol 3-kinase

6.2.6. Visits 8, 14, and 17 (Clinic Visits – Rituximab and Bendamustine Administration)

The procedures outlined in Table 6-6 will be performed at Visits 8, 14, and 17.

Table 6-6. Procedures and Assessments at Visits 8, 14, and 17 (±2 Days)

Assessment or Procedure	Explanation
Pre-Treatment Procedures and Assessments	
FACT-Leu	HRQL instrument (Appendix 2) to be administered before any other procedures are performed and before any study-related information is communicated to the subject
EQ-5D	Health utility instrument (Appendix 4) to be administered after FACT-Leu but before other procedures are performed and before study-related information is communicated to the subject
Adverse events	Recording of adverse events occurring since the last clinic visit
Concomitant medications	Recording of concomitant medication use since the last clinic visit
Performance status	Using Karnofsky performance status criteria (see Appendix 3)
Oxygen saturation	To be assessed by pulse oximetry while subject is breathing room air
Physical examination	Including assessment of weight, lymph nodes, spleen, and liver
Urine β-HCG dipstick	For women of child-bearing potential only
Hematology	Including hematocrit, hemoglobin, erythrocyte count; absolute counts of leukocytes, neutrophils, lymphocytes, monocytes, eosinophils, basophils, platelet count
Serum chemistry	Including sodium, potassium, chloride, glucose, urea, creatinine, calcium, phosphorus, total protein, albumin, ALT, AST, ALP, GGT, total bilirubin, LDH, uric acid, cholesterol, triglycerides
Circulating cells	Including cells for analysis of PI3K/AKT/mTOR pathway activation and quantitation of CD4+, CD5+, CD8+, CD16/CD56+, CD19+, and CD+20 cells by flow cytometry
Biomarkers	Collection of plasma and serum for evaluation of circulating chemokines and cytokines
Serum Igs	Including quantitative levels of IgA, IgE, IgG, and IgM
Idelalisib pharmacokinetics	Recording of the date and actual clock time of the last prior subject self-administration of study drug (should be the prior evening dose); pre-dose collection of plasma sample for idelalisib pharmacokinetics (with recording of the date and actual clock time of the date and actual clock time of blood collection)
HBV DNA by PCR	Only subjects who are HBc antibody positive and HBV DNA negative at screening, per Section 5.4.3.
IWRS access	Access of IWRS to document subject visit

Assessment or Procedure	Explanation
Study Treatment Administration	
Study drug administration	Morning dose of study drug (idelalisib/placebo) to be administered to the subject in clinic (with recording of the date and actual clock time of the study drug administration)
Pretreatment	Antipyretic and antihistamine to be administered to the subject at the same time as study drug (idelalisib/placebo) and ~30 minutes prior to rituximab infusion; an intravenous corticosteroid and antiemetics may also be given as premedications per local practices
Rituximab infusion	Rituximab, 500 mg/m^2, to be administered by intravenous infusion ~30 minutes after pretreatment
Bendamustine infusion	Bendamustine intravenous infusion to be started at completion of rituximab; bendamustine to be administered over ~60 minutes.
Post-Treatment Procedures and Assessments	
Idelalisib pharmacokinetics	Post-dose collection of plasma sample for idelalisib pharmacokinetics at 1.5 hours +/- 30 mins after study drug administration (with recording of the date and actual clock time of blood collection)
Instruction regarding in-clinic study drug dosing	Instruction to the subject that the morning dose of study drug (idelalisib/placebo) should not be taken on the day of the next treatment clinic visit

Abbreviations: AKT=AKT (a serine/threonine protein kinase), ALP=alkaline phosphatase, ALT=alanine aminotransferase, AST=aspartate aminotransferase, EQ-5D=EuroQoL Five-Dimension, FACT-Leu=Functional Assessment of Cancer Therapy-Leukemia, HRQL=health-related quality of life, GGT=gamma-glutamyltransferase, Ig=immunoglobulin, IWRS=interactive web response system, LDH=lactate dehydrogenase, mTOR=mammalian target of rapamycin, PI3K=phosphatidylinositol 3-kinase

6.2.7. Visit 11 (Radiology and Clinic Visit – Rituximab and Bendamustine Administration)

The procedures outlined in Table 6-7 will be performed at Visit 11.

Table 6-7. Procedures and Assessments at Visit 11 (±3 Days)

Assessment or Procedure	Explanation
Pre-Visit Tumor Assessment	
Radiology assessment	CT or MRI imaging of neck, chest, abdomen, and pelvis within 1 week prior to the visit; the assessment should be done even if study drug has been interrupted.
Pre-Treatment Procedures and Assessments	
FACT-Leu	HRQL instrument (Appendix 2) to be administered before any other procedures are performed and before any study-related information is communicated to the subject
EQ-5D	Health utility instrument (Appendix 4) to be administered after FACT-Leu but before other procedures are performed and before study-related information is communicated to the subject
Adverse events	Recording of adverse events occurring since the last clinic visit
Concomitant medications	Recording of concomitant medication use since the last clinic visit
Study drug return/ accounting	Counting of returned study drug (idelalisib/placebo)
Performance status	Using Karnofsky performance status criteria (see Appendix 3)
Oxygen saturation	To be assessed by pulse oximetry while subject is breathing room air
Physical examination	Including assessment of weight, lymph nodes, spleen, and liver
Urine β-HCG dipstick	For women of child-bearing potential only
Hematology	Including hematocrit, hemoglobin, erythrocyte count; absolute counts of leukocytes, neutrophils, lymphocytes, monocytes, eosinophils, basophils, platelet count
Serum chemistry	Including sodium, potassium, chloride, glucose, urea, creatinine, calcium, phosphorus, total protein, albumin, ALT, AST, ALP, GGT, total bilirubin, LDH, uric acid, cholesterol, triglycerides
Circulating cells	Including cells for analysis of PI3K/AKT/mTOR pathway activation and quantitation of CD4+, CD5+, CD8+, CD16/CD56+, CD19+, and CD+20 cells by flow cytometry
Biomarkers	Collection of plasma and serum for evaluation of circulating chemokines and cytokines
Serum Igs	Including quantitative levels of IgA, IgE, IgG, and IgM
Bone marrow biopsy and aspirate	To be performed post-baseline to confirm response category in subjects with potential CR by radiological assessments. If the subject does not otherwise meet criteria for CR, it is not necessary to obtain a follow-up bone marrow biopsy/aspirate to establish CR.
Idelalisib pharmacokinetics	Recording of the date and actual clock time of the last prior subject self-administration of study drug (should be the prior evening dose); pre-dose collection of plasma sample for idelalisib pharmacokinetics (with recording of the date and actual clock time of the date and actual clock time of blood collection)

Assessment or Procedure	Explanation
HBV DNA by PCR	Only subjects who are HBc antibody positive and HBV DNA negative at screening, per Section 5.4.3.
IWRS access	Access of IWRS to obtain study drug bottle number
Study Treatment Administration	
Study drug administration	Morning dose of study drug (idelalisib/placebo) to be administered to the subject in clinic (with recording of the date and actual clock time of the study drug administration)
Pretreatment	Antipyretic and antihistamine to be administered to the subject at the same time as study drug (idelalisib/placebo) and ~30 minutes prior to rituximab infusion; an intravenous corticosteroid and antiemetics may also be given as premedications per local practices
Rituximab infusion	Rituximab, 500 mg/m^2, to be administered by intravenous infusion ~30 minutes after pretreatment
Bendamustine infusion	Bendamustine intravenous infusion to be started at completion of rituximab; bendamustine to be administered over ~60 minutes.
Post-Treatment Procedures and Assessments	
Idelalisib pharmacokinetics	Post-dose collection of plasma sample for idelalisib pharmacokinetics at 1.5 hours +/- 30 mins after study drug administration (with recording of the date and actual clock time of blood collection)
Study drug dispensing	Dispensing of 12-week supply of study drug (idelalisib/placebo) to the subject with instructions for self-administration at home
Instruction regarding in-clinic study drug dosing	Instruction to the subject that the morning dose of study drug (idelalisib/placebo) should not be taken on the day of the next treatment clinic visit

Abbreviations: AKT=AKT (a serine/threonine protein kinase), ALP=alkaline phosphatase, ALT=alanine aminotransferase, AST=aspartate aminotransferase, CT=computed tomography, EQ-5D=EuroQoL Five-Dimension, FACT-Leu=Functional Assessment of Cancer Therapy-Leukemia, HRQL=health-related quality of life, GGT=gamma-glutamyltransferase, Ig=immunoglobulin, IWRS=interactive web response system, LDH=lactate dehydrogenase, MRI=magnetic resonance imaging, mTOR=mammalian target of rapamycin, PI3K=phosphatidylinositol 3-kinase

6.2.8. Visit 20 (Radiology and Clinic Visit)

The procedures outlined in Table 6-8 will be performed at Visit 20.

Table 6-8. Procedures and Assessments at Visit 20 (±3 Days)

Assessment or Procedure	Explanation
Pre-Visit Tumor Assessment	
Radiology assessment	CT or MRI imaging of neck, chest, abdomen, and pelvis within 1 week prior to the visit; assessment should be done even if study drug has been interrupted.
Pre-Treatment Procedures and Assessments	
FACT-Leu	HRQL instrument (Appendix 2) to be administered before any other procedures are performed and before any study-related information is communicated to the subject
EQ-5D	Health utility instrument (Appendix 4) to be administered after FACT-Leu but before other procedures are performed and before study-related information is communicated to the subject
Adverse events	Recording of adverse events occurring since the last clinic visit
Concomitant medications	Recording of concomitant medication use since the last clinic visit
Study drug return/ accounting	Counting returned study drug (idelalisib/placebo)
Performance status	Using Karnofsky performance status criteria (see Appendix 3)
Oxygen saturation	To be assessed by pulse oximetry while subject is breathing room air
Physical examination	Including assessment of weight, lymph nodes, spleen, and liver
Urine β-HCG dipstick	For women of child-bearing potential only
Hematology	Including hematocrit, hemoglobin, erythrocyte count; absolute counts of leukocytes, neutrophils, lymphocytes, monocytes, eosinophils, basophils, platelet count
Serum chemistry	Including sodium, potassium, chloride, glucose, urea, creatinine, calcium, phosphorus, total protein, albumin, ALT, AST, ALP, GGT, total bilirubin, LDH, uric acid, cholesterol, triglycerides
Circulating cells	Including cells for analysis of PI3K/AKT/mTOR pathway activation and quantitation of CD4+, CD5+, CD8+, CD16/CD56+, CD19+, and CD+20 cells by flow cytometry
Biomarkers	Collection of plasma and serum for evaluation of circulating chemokines and cytokines
Serum Igs	Including quantitative levels of IgA, IgE, IgG, and IgM
Bone marrow biopsy and aspirate	To be performed post-baseline to confirm response category in subjects with potential CR by radiological assessments. If the subject does not otherwise meet criteria for CR, it is not necessary to obtain a follow-up bone marrow biopsy/aspirate to establish CR.
Idelalisib pharmacokinetics	Recording of the date and actual clock time of the last prior subject self-administration of study drug (should be the prior evening dose); pre-dose collection of plasma sample for idelalisib pharmacokinetics (with recording of the date and actual clock time of the date and actual clock time of blood collection)
HBV DNA by PCR	Only subjects who are HBc antibody positive and HBV DNA negative at screening, per Section 5.4.3
IWRS access	Access of IWRS to obtain study drug bottle number

Assessment or Procedure	Explanation
Study Treatment Administration	
Study drug administration	Morning dose of study drug (idelalisib/placebo) to be administered to the subject in clinic (with recording of the date and actual clock time of the study drug administration)
Post-Treatment Procedures and Assessments	
Idelalisib pharmacokinetics	Post-dose collection of plasma sample for idelalisib pharmacokinetics at 1.5 hours +/- 30 mins after study drug administration (with recording of the date and actual clock time of blood collection)
Study drug dispensing	Dispensing of 12-week supply of study drug (idelalisib/placebo) to the subject with instructions for self-administration at home

Abbreviations: AKT=AKT (a serine/threonine protein kinase), ALP=alkaline phosphatase, ALT=alanine aminotransferase, AST=aspartate aminotransferase, CT=computed tomography, EQ-5D=EuroQoL Five-Dimension, FACT-Leu=Functional Assessment of Cancer Therapy-Leukemia, HRQL=health-related quality of life, GGT=gamma-glutamyltransferase, Ig=immunoglobulin, IWRS=interactive web response system, LDH=lactate dehydrogenase, MRI=magnetic resonance imaging, mTOR=mammalian target of rapamycin, PI3K=phosphatidylinositol 3-kinase

6.2.9. Visits 21 and 23 (Clinic Visits)

The procedures outlined in Table 6-9 will be performed at Visits 21 and 23.

Table 6-9. Procedures and Assessments at Visits 21 and 23 (±3 Days)

Assessment or Procedure	Explanation
FACT-Leu	HRQL instrument (Appendix 2) to be administered before any other procedures are performed and before any study-related information is communicated to the subject
EQ-5D	Health utility instrument (Appendix 4) to be administered after FACT-Leu but before other procedures are performed and before study-related information is communicated to the subject
Adverse events	Recording of adverse events occurring since the last clinic visit
Concomitant medications	Recording of concomitant medication use since the last clinic visit
Performance status	Using Karnofsky performance status criteria (see Appendix 3)
Oxygen saturation	To be assessed by pulse oximetry while subject is breathing room air
Physical examination	Including assessment of weight, lymph nodes, spleen, and liver
Urine β-HCG dipstick	For women of child-bearing potential only
Hematology	Including hematocrit, hemoglobin, erythrocyte count; absolute counts of leukocytes, neutrophils, lymphocytes, monocytes, eosinophils, basophils, platelet count
Serum chemistry	Including sodium, potassium, chloride, glucose, urea, creatinine, calcium, phosphorus, total protein, albumin, ALT, AST, ALP, GGT, total bilirubin, LDH, uric acid, cholesterol, triglycerides
Circulating cells	Including cells for analysis of PI3K/AKT/mTOR pathway activation and quantitation of CD4+, CD5+, CD8+, CD16/CD56+, CD19+, and CD+20 cells by flow cytometry
Biomarkers	Collection of plasma and serum for evaluation of circulating chemokines and cytokines
Serum Igs	Including quantitative levels of IgA, IgE, IgG, and IgM
HBV DNA by PCR	Only subjects who are HBc antibody positive and HBV DNA negative at screening, per Section 5.4.3.
IWRS access	Access of IWRS to document subject visit

Abbreviations: AKT=AKT (a serine/threonine protein kinase), ALP=alkaline phosphatase, ALT=alanine aminotransferase, AST=aspartate aminotransferase, EQ-5D=EuroQoL Five-Dimension, FACT-Leu=Functional Assessment of Cancer Therapy-Leukemia, HRQL=health-related quality of life, GGT=gamma-glutamyltransferase, Ig=immunoglobulin, IWRS=interactive web response system, LDH=lactate dehydrogenase, mTOR=mammalian target of rapamycin, PI3K=phosphatidylinositol 3-kinase

6.2.10. Visits 22 and 24 (Radiology and Clinic Visits)

The procedures outlined in Table 6-10 will be performed at Visits 22 and 24.

Table 6-10. Procedures and Assessments at Visits 22 and 24 (±3 Days)

Assessment or Procedure	Explanation
Pre-Visit Tumor Assessment	
Radiology assessment	CT or MRI imaging of neck, chest, abdomen, and pelvis within 1 week prior to the visit; the assessment should be done even if study drug has been interrupted.
Visit Procedures and Assessments	
FACT-Leu	HRQL instrument (Appendix 2) to be administered before any other procedures are performed and before any study-related information is communicated to the subject
EQ-5D	Health utility instrument (Appendix 4) to be administered after FACT-Leu but before other procedures are performed and before study-related information is communicated to the subject
Adverse events	Recording of adverse events occurring since the last clinic visit
Concomitant medications	Recording of concomitant medication use since the last clinic visit
Study drug return/ accounting	Counting returned study drug (idelalisib/placebo)
Performance status	Using Karnofsky performance status criteria (see Appendix 3)
Oxygen saturation	To be assessed by pulse oximetry while subject is breathing room air
Physical examination	Including assessment of weight, lymph nodes, spleen, and liver
Urine β-HCG dipstick	For women of child-bearing potential only
Hematology	Including hematocrit, hemoglobin, erythrocyte count; absolute counts of leukocytes, neutrophils, lymphocytes, monocytes, eosinophils, basophils, platelet count
Serum chemistry	Including sodium, potassium, chloride, glucose, urea, creatinine, calcium, phosphorus, total protein, albumin, ALT, AST, ALP, GGT, total bilirubin, LDH, uric acid, cholesterol, triglycerides
Circulating cells	Including cells for analysis of PI3K/AKT/mTOR pathway activation and quantitation of CD4+, CD5+, CD8+, CD16/CD56+, CD19+, and CD+20 cells by flow cytometry
Biomarkers	Collection of plasma and serum for evaluation of circulating chemokines and cytokines
Serum Igs	Including quantitative levels of IgA, IgE, IgG, and IgM
HBV DNA by PCR	Only subjects who are HBc antibody positive and HBV DNA negative at screening, per Section 5.4.3.
Bone marrow biopsy and aspirate	To be performed post-baseline to confirm response category in subjects with potential CR by radiological assessments. If the subject does not otherwise meet criteria for CR, it is not necessary to obtain a follow-up bone marrow biopsy/aspirate to establish CR.
IWRS access	Access of IWRS to obtain study drug bottle number
Study drug dispensing	Dispensing of 12-week supply of study drug (idelalisib/placebo) to the subject with instructions for self-administration at home

Abbreviations: AKT=AKT (a serine/threonine protein kinase), ALP=alkaline phosphatase, ALT=alanine aminotransferase, AST=aspartate aminotransferase, CT=computed tomography, EQ-5D=EuroQoL Five-Dimension, FACT-Leu=Functional Assessment of Cancer Therapy-Leukemia, HRQL=health-related quality of life, GGT=gamma-glutamyltransferase, Ig=immunoglobulin, IWRS=interactive web response system, LDH=lactate dehydrogenase, MRI=magnetic resonance imaging, mTOR=mammalian target of rapamycin, PI3K=phosphatidylinositol 3-kinase

6.2.11. Visit 25 and Subsequent Visits (Every 12 Weeks) (Radiology and Clinic Visits)

The procedures outlined in Table 6-11 will be performed at Visit 25 and subsequent visits.

Table 6-11. Procedures and Assessments at Visit 25 and Subsequent Visits (Every 12 Weeks [±7 Days])

Assessment or Procedure	Explanation
Pre-Visit Tumor Assessment	
Radiology assessment[b]	CT or MRI imaging of neck, chest, abdomen, and pelvis within 1 week prior to the visit; the assessment should be done even if study drug has been interrupted.
Visit Procedures and Assessments	
FACT-Leu	HRQL instrument (Appendix 2) to be administered before any other procedures are performed and before any study-related information is communicated to the subject
EQ-5D	Health utility instrument (Appendix 4) to be administered after FACT-Leu but before other procedures are performed and before study-related information is communicated to the subject
Adverse events	Recording of adverse events occurring since the last clinic visit
Concomitant medications	Recording of concomitant medication use since the last clinic visit
Study drug return/ accounting	Counting returned study drug (idelalisib/placebo)
Performance status	Using Karnofsky performance status criteria (see Appendix 3)
Oxygen saturation	To be assessed by pulse oximetry while subject is breathing room air
Physical examination	Including assessment of weight, lymph nodes, spleen, and liver
Urine β-HCG dipstick	For women of child-bearing potential only
Hematology	Including hematocrit, hemoglobin, erythrocyte count; absolute counts of leukocytes, neutrophils, lymphocytes, monocytes, eosinophils, basophils, platelet count
Serum chemistry	Including sodium, potassium, chloride, glucose, urea, creatinine, calcium, phosphorus, total protein, albumin, ALT, AST, ALP, GGT, total bilirubin, LDH, uric acid, cholesterol, triglycerides
CMV viral load	CMV viral load testing **approximately every 4 weeks** throughout the course of idelalisib treatment
Circulating cells	Including cells for analysis of PI3K/AKT/mTOR pathway activation and quantitation of CD4+[a], CD5+, CD8+, CD16/CD56+, CD19+and CD+20 cells by flow cytometry
Immune monitoring	Lymphocyte subset panel using flow cytometry (immunophenotyping), serum CH50 level
Biomarkers	Collection of plasma and serum for evaluation of circulating chemokines and cytokines
Serum Igs	Including quantitative levels of IgA, IgE, IgG, and IgM

Assessment or Procedure	Explanation
HBV DNA by PCR	Only subjects who are HBc antibody positive and HBV DNA negative at screening, per Section 5.4.3.
Bone marrow biopsy and aspirate	To be performed post-baseline to confirm response category in subjects with potential CR by radiological assessments. If the subject does not otherwise meet criteria for CR, it is not necessary to obtain a follow-up bone marrow biopsy/aspirate to establish CR.
IWRS access	Access of IWRS to obtain study drug bottle number
Study drug dispensing	Dispensing of 12-week supply of study drug (idelalisib/placebo) to the subject with instructions for self-administration at home

a CD4+ T-cell count must be performed upon idelalisib discontinuation and continued until count is > 200 cells/mcL, at which point PJP prophylaxis may be discontinued
b As of Amendment 10, Version 11, CT/MRI assessments will no longer be performed at the every 12 week scheduled visits, and will only be performed at the time of clinically-suspected disease progression or at study discontinuation.
Abbreviations: AKT=AKT (a serine/threonine protein kinase), ALP=alkaline phosphatase, ALT=alanine aminotransferase, AST=aspartate aminotransferase, CMV=cytomegalovirus, CT=computed tomography, EQ-5D=EuroQoL Five-Dimension, FACT-Leu=Functional Assessment of Cancer Therapy-Leukemia, HRQL=health-related quality of life, GGT=gamma-glutamyltransferase, Ig=immunoglobulin, IWRS=interactive web response system, LDH=lactate dehydrogenase, MRI=magnetic resonance imaging, mTOR=mammalian target of rapamycin, PI3K=phosphatidylinositol 3-kinase

6.2.12. End-of-Study Visit (Clinic Visit)

At the time of discontinuation from the study, the subject should have the procedures and assessments performed as documented in Table 6-12. An end-of-study CT/MRI tumor assessment should be performed unless the subject already has radiographic confirmation of definitive disease progression or a CT/MRI has been performed within 4 weeks prior to the end-of-study visit.

Table 6-12. Procedures and Assessments at End-of-Study Visit

Assessment or Procedure	Explanation[a]
Radiology assessment[a]	CT or MRI imaging of neck, chest, abdomen, and pelvis
FACT-Leu	HRQL instrument (Appendix 2) to be administered before any other procedures are performed
EQ-5D	Health utility instrument (Appendix 4) to be administered after FACT-Leu but before any other procedures are performed
Adverse events	Recording of adverse events occurring since prior visit; if a clinically significant adverse event or abnormal result is observed that is not resolved by the end-of-treatment visit, repeat evaluations should be performed to document resolution or stabilization of the abnormality
Concomitant medications	Recording of concomitant medication used since prior visit
Study drug return/ accounting	Counting returned study drug (idelalisib/placebo)
Performance status	Using Karnofsky performance status criteria (see Appendix 3)
Oxygen saturation	To be assessed by pulse oximetry while subject is breathing room air

Assessment or Procedure	Explanation[a]
Physical examination	Including assessment of weight, lymph nodes, spleen, and liver
Serum β-HCG	Women of childbearing potential only
CLL peripheral blood evaluation	Including FISH for chromosome 11q deletion, 13q deletion, 17p deletion and 12 trisomy; DNA mutational analysis for p53, IgHV (including IgHV3-21), and other genes of interest in CLL (eg, Notch); flow cytometry for CD5, CD10, CD11c, CD19, CD20, CD23, CD38, CD45, kappa and lambda light chains, and ZAP-70; cytology for karyotyping
CLL serology	Serum β_2 microglobulin
Genotyping and expression analysis	Including blood for DNA, RNA and protein isolation for potential future assessment of biomarkers (subjects may choose to not provide DNA sample)
Hematology	Including hematocrit, hemoglobin, erythrocyte count; absolute counts of leukocytes, neutrophils, lymphocytes, monocytes, eosinophils, basophils, platelet count
Serum chemistry	Including sodium, potassium, chloride, glucose, urea, creatinine, calcium, phosphorus, total protein, albumin, ALT, AST, ALP, GGT, total bilirubin, LDH, uric acid, cholesterol, triglycerides
Circulating cells	Including cells for analysis of PI3K/AKT/mTOR pathway activation and quantitation of CD4+[b], CD5+, CD8+, CD16/CD56+, CD19+, and CD+20 cells by flow cytometry
Biomarkers	Collection of plasma and serum for evaluation of circulating chemokines and cytokines
Serum Igs	Including quantitative levels of IgA, IgE, IgG, and IgM
HBV DNA by PCR	Only subjects who are HBc antibody positive and HBV DNA negative at screening, per Section 5.4.3.
Immune monitoring	Lymphocyte subset panel using flow cytometry (immunophenotyping), serum CH50 level
IWRS	Access IWRS to document that subject has permanently discontinued study therapy

a An end-of-study CT/MRI tumor assessment should be performed unless the subject already has radiographic confirmation of definitive disease progression or a CT/MRI has been performed within 4 weeks prior to the end-of-study visit.
b CD4+ T-cell count must be performed upon idelalisib discontinuation and continued until count is > 200 cells/mcL, at which point PJP prophylaxis may be discontinued.

Abbreviations: β-HCG=beta human chorionic gonadotropin, AKT=AKT (a serine/threonine protein kinase), ALP=alkaline phosphatase, ALT=alanine aminotransferase, AST=aspartate aminotransferase, CLL=chronic lymphocytic leukemia, CMV=cytomegalovirus, CT=computed tomography, EQ-5D=EuroQoL Five-Dimension, FACT-Leu=Functional Assessment of Cancer Therapy-Leukemia, FISH= fluorescence in-situ hybridization, GGT=gamma-glutamyltransferase, Ig=immunoglobulin, IgH_V=immunoglobulin heavy-chain variable-region, IWRS=interactive web response system, LDH=lactate dehydrogenase, MRI=magnetic resonance imaging, mTOR=mammalian target of rapamycin, PI3K=phosphatidylinositol 3-kinase, RNA=ribonucleic acid, ZAP-70=zeta-associated protein 70

6.2.13. 30-Day and Long-Term Follow-up

A 30-day follow-up visit will be performed 30 (+ 5) days following the end-of-study visit; 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 of study drug.

Long-term, follow-up for survival will be conducted at ~6-month intervals for 5 years, starting at the end-of-study visit. Information may be gathered during a routine clinic visit or other contact with the subject, or via telephone. Information gathered will include medical status, anti-tumor treatments, secondary malignancies, and survival.

6.3. Sample Storage

Subjects will be asked to consent to allow a portion of the blood and tissue samples collected at study visits or as part of standard of care during study participation to be stored. The stored samples may be used by the Sponsor or its research partners to further investigate the safety and mechanism of action of the study drug and to investigate the effects of treatment on the disease. At the conclusion of this study, these samples will be retained in storage by the Investigator or Gilead Sciences, Inc. for a period up to 10 years.

6.4. Blood Collection

The maximum amount of blood to be drawn at a visit is ~125 mL and the total amount of blood to be drawn over the initial 52-week study period (including the 4-week screening period and through Week 48 of the study including a possible end-of-therapy visit) is ~490 mL. For a 40-kg person (the smallest participant expected to enroll in the study), this equates to maximum blood volume per body weight per visit of ~2.8 mL/kg and a total blood volume per body weight per average 6-week period of ~1.4 mL/kg. These quantities of blood are within accepted limits of 3.0 mL/kg of body weight for a single blood draw and 7.0 mL/kg of body weight for a 6-week period.

Specific details regarding blood sample collection and processing requirements will be provided separately in the study manual.

Serum and plasma may be retained for subjects who have provided specific informed consent for sample banking. As noted in Section 10.1.4 of the protocol, subject confidentiality will be maintained, but sufficient information will be retained to permit sample data to be connected with the unique subject number assigned to each study participant. These samples will be retained consistent with the information provided in Section 10.1.5 of the protocol.

6.5. Study Procedure Rationale

The planned study assessments and timing have been selected as appropriate for screening of subjects, for determination of drug- or disease-related toxicities, for dose modification during the study, for characterization of drug exposure and desired pharmacological effects, and for evaluation of drug activity. The scheduling of testing is designed to collect a complete safety and pharmacology data set while maintaining subject tolerance of study procedures. The planned schedule of tumor assessments is consistent with expected rate of changes and appropriately balances precise measurement of tumor control with the expense and subject inconvenience associated with clinical and radiological procedures. For discussion of the rationale for endpoint selection, see Section 3.5.

7. EFFICACY ASSESSMENTS

7.1. Tumor Status Assessments

The determination of CLL response and progression will be based on standardized IWCLL criteria {Hallek 2008}, as specifically modified for this study to reflect current recommendations which consider the mechanism of action of idelalisib and similar drugs {Cheson 2012}. During the course of the study, investigators will periodically assess the status of each subject's CLL. 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 10.4.3). The findings of the IRC will be considered primary for analyses of PFS and other tumor control endpoints.

7.2. Method of Assessment

In addition to clinical examination, imaging-based evaluation will be used in this study in all subjects enrolled. CT scan is the preferred method for radiographic tumor assessment. MRI scanning may be used at the investigator's discretion in subjects for whom this may be a preferred alternative to CT scanning; however, if MRI is performed, a non-contrast CT of the chest should be performed. Contrast-enhanced scanning is preferred, but iodine-containing or gadolinium contrast material may be omitted in subjects for whom use of a contrast agent would be medically contraindicated. Chest x-ray, ultrasound, endoscopy, laparoscopy, 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 study treatment and follow-up. However, if a subject is imaged without contrast at baseline, subsequent assessments should be performed with contrast, unless the subject cannot tolerate the contrast.

All relevant clinical and radiographic information required to make each tumor status assessment must be made available for source verification and for submission to the IRC (see Section 10.4.3).

CT/MRI performed as standard of care, prior to signing the ICF and within 6 weeks of randomization, may be used to fulfill the screening requirement. If this option is used the scans must follow the same conditions set above.

7.3. Timing of Assessments

During screening, clinical and imaging-based tumor assessments should be performed within 6 weeks prior to randomization. Clinical tumor assessments should be performed at each clinical visit. On-study CT/MRI tumor assessments should be performed as indicated in Appendix 7. As of Amendment 10, Version 11, CT/MRI assessments will no longer be performed at the every 12 week scheduled visits, and will only be performed at the time of clinically-suspected disease progression or at study discontinuation. An end-of-study CT/MRI tumor assessment should be performed unless the subject already has radiographic confirmation of disease progression within

4 weeks prior. If a subject permanently discontinues study drug prior to objective documentation of CLL progression, investigators should continue further follow-up ~12-week intervals until CLL progression is documented by the central IRC.

7.4. Identification and Follow-up of Tumor Lesions and Organomegaly

7.4.1. Index Lesions

At baseline, 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 during treatment. The cross-sectional dimensions (the largest cross-sectional diameter, ie, the LD × the LPD will be recorded (in cm) for each index lesion. The PPDs will be calculated. The PPDs and the SPDs for all index lesions will be calculated and recorded. The baseline SPDs will be used as references by which objective tumor 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 centimeters and all PPDs and SPDs will be reported in centimeters squared.

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 one 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. Based on this convention, a CR may be achieved even if an SPD value is >0 cm^2, (ie, if all lymph nodes measure <1.0 cm^2).

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

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 will 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.

7.4.2. Spleen and Liver

CCI [redacted]

7.4.3. 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 treatment. 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 tumor response during treatment. Measurements are not required and these lesions should be followed as “present” or “absent”.

7.5. Definitions of Tumor Response and Progression

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

The best overall response will be determined. The best overall response 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 tumor response. Where imaging data are available, these data will supersede physical examination data in determining tumor status.

7.5.1. 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 $>1.5 \times 10^9$/L without need for exogenous growth factors (eg, G-CSF)
  - Platelet count $\geq 100 \times 10^9$/L without need for exogenous growth factors
  - Hemoglobin ≥110 g/L (11.0 g/dL) without red blood cell transfusions or need for exogenous growth factors (eg, erythropoietin)

Note: 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 as a CR with incomplete marrow recovery (CRi).

7.5.2. Partial Response

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

- No evidence of new disease
- 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≥4 x 10^9/L), a decrease in peripheral blood ALC by ≥50% from baseline or a decrease to <4 x 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 Section 7.4.2
  - In a subject with enlargement of the liver at baseline, a hepamegaly response as defined in Section 7.4.2
  - A decrease by ≥50% from baseline in the CLL marrow infiltrate or in B-lymphoid nodules
- 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:
  - ANC >1.5 x 10^9/L or ≥50% increase over baseline without need for exogenous growth factors (eg, G-CSF)
  - Platelet count ≥100 x 10^9/L or ≥50% increase over baseline without need for exogenous growth factors
  - 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)

7.5.3. 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

7.5.4. Definitive Progressive Disease

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

- Evidence of any new disease:
  - A new node that measures >1.5 cm in the LD and >1.0 cm in the LPD
  - New or recurrent splenomegaly, with a minimum LVD of 14 cm
  - New or recurrent hepatomegaly, with a minimum LVD of 20 cm
  - Unequivocal reappearance of an extra-nodal lesion that had resolved (ie, had previously been assigned a PPD of 0 cm^2)
  - A new unequivocal extra-nodal lesion of any size
  - New non-index disease (eg, effusions, ascites, or other organ abnormalities related to CLL)

Note: 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:
  - Increase from the nadir by ≥50% in the SPD of index lesions
  - Increase from the nadir by ≥50% in the LD if an individual node or extra-nodal mass that now has an LD of >1.5 cm and an LPD of > 1.0 cm
  - 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)
  - 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)
  - Unequivocal increase in the size of non-index disease (eg, effusions, ascites, or other organ abnormalities related to CLL)
  - Transformation to a more aggressive histology (eg, Richter syndrome) as established by biopsy (with the date of the biopsy 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

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

  — 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

Note: Due to the possibility of bendamustine-induced toxicity, the above criteria for platelet or hemoglobin decrease in subjects receiving bendamustine may not be indicative of definitive disease progression in the absence of other objective evidence of worsening CLL. If there is uncertainty regarding whether there is true progression, the subject should continue study treatment and remain under close observation pending confirmation of progression status by the IRC. In particular, worsening of constitutional symptoms in the absence of objective evidence of worsening CLL will not be considered definitive disease progression; in such subjects, both CLL-related and non-CLL-related causes for the constitutional symptoms should be considered. Worsening of disease during temporary interruption of study treatment (eg, for intercurrent illness) is not necessarily indicative of resistance to study treatment. In these instances, CT/MRI or other relevant evaluations should be considered in order to document whether definitive disease progression has occurred. If subsequent evaluations suggest that the subject is experiencing persistent definitive CLL progression, then the date of progression should be the timepoint at which progression was first objectively documented.

7.5.5. Non-Evaluable

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 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).

Note: 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.

7.5.6. No Disease

Subjects have a status of ND if all of the following conditions occur:

- No index disease noted at baseline or on-treatment.
- No non-index disease noted at baseline or on-treatment.

- No enlargement of the liver or spleen at baseline or on-treatment
- 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 treatment

7.6. 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 therapy as described in Section 5.8.

7.7. Documentation of Definitive CLL Progression

Of importance, CLL response and progression data will be subjected to IRC review (see Section 5.8). ***If there is uncertainty regarding whether there is definitive progression, the subject should continue study drug pending confirmation of progression status by the IRC.***

8. SAFETY ASSESSMENTS

8.1. Adverse Event Definitions

8.1.1. Adverse Event

An adverse event (AE) is any untoward medical occurrence in a clinical study subject administered a pharmaceutical product which; the event does not necessarily have a causal relationship with study drug administration or usage. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. 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:

- Lymphocytosis
- 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 (eg, hospitalization for elective surgery, social and/or convenience admissions)
- Overdose without clinical sequelae (see Section 5.2.1.8)
- 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 CRF.

In this study, any of the following events will be considered an adverse event:

- Any complication that occurs as a result of a protocol-mandated procedure (eg, venipuncture, biopsy) in the screening, on-treatment, or post-treatment periods.
- Any pre-existing condition that increases in severity or changes in nature during or as a consequence of study drug administration. Worsening manifestations of the underlying cancer (eg, increase in pain, tumor flare reaction, tumor lysis syndrome) may be considered adverse events in this study.

- Any injury or accident occurring during the screening, on-treatment, or post-treatment periods. If a medical condition is known to have caused the injury or accident (eg, a fall secondary to dizziness), the medical condition (dizziness) and the accident (fall) should be reported as 2 separate adverse events.

- Any abnormality in physiological testing or a physical examination finding that requires clinical intervention or further investigation (beyond ordering a repeat [confirmatory] test).

- Any laboratory (eg, clinical chemistry, hematology, urinalysis) or investigational abnormality (eg, ECG, X-ray) independent of the underlying medical condition that requires clinical intervention, results in further investigation (beyond ordering a repeat [confirmatory] test), or leads to investigational medicinal product interruption or discontinuation unless it is associated with an already reported clinical event. If the laboratory abnormality is part of a syndrome, the syndrome or diagnosis (eg, anemia) not the laboratory result (eg, decreased hemoglobin) should be recorded.

- A complication related to pregnancy or termination of a pregnancy (see Section 5.4.11 for additional information).

8.1.2. Serious Adverse Event

A serious adverse event (SAE) is defined as an event that results in any of the following:

- Death

- Life-threatening situation (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.

- 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 medical or surgical intervention to prevent one of the outcomes listed above. Examples of such events might include:

  — Allergic bronchospasm requiring intensive treatment in an emergency room or at home

  — New cancers or blood dyscrasias

  — Convulsions that do not result in hospitalization

  — Development of drug dependency or drug abuse

Medical and scientific judgment must be exercised to determine whether such an event is reportable under expedited reporting rules.

Infections resulting from contaminated medicinal product will be considered a medically important event and subject to expedited reporting requirements.

Given the endpoints of the study, in order to maintain the integrity of the study the following events that are assessed as unrelated to IMP 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 IMPs caused or contributed to the disease progression (i.e., by a means other than lack of effect). Unrelated disease progression and death due to 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. The safety information from this study will also be reviewed by an independent DMC on an ongoing basis. The DMC can have access to partially blinded or unblinded data in order to determine if it is safe to continue the study according to the protocol.

8.1.3. 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 Section 8.7. 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 5.4.

8.2. 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.

8.2.1. Assessment of Causality for Study Drugs and Procedures

The investigator or qualified subinvestigator is responsible for assessing the relationship to IMP therapy 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)

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

All SAEs, regardless of cause or relationship, that 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 CRF/eCRF database and Gilead DSPH as instructed. This also includes any SAEs resulting from protocol-associated procedures performed from screening onwards.

All AEs, regardless of cause or relationship, that occur from initiation of study medication until 30 days after last administration of study IMP must be reported to the CRF database as instructed.

Any SAEs and deaths that occur after the post treatment follow-up visit but within 30 days of the last dose of study IMP, regardless of causality, should also be reported.

All AEs should be followed up until resolution if possible. If by the last day on study (including the off-study medication follow-up period) the AE has not resolved, then the AE will be followed up until the investigator and/or Gilead Sciences determine that the subject's condition is stable. However, Gilead Sciences may request that certain AEs be followed until resolution.

Investigators are not obligated to actively seek SAEs after the above 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 IMP, he/she should promptly document and report the event to Gilead DSPH.

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

- At the time of study start, SAEs will be reported using a paper serious adverse event reporting form. During the study conduct, sites may transition to an electronic SAE (eSAE) system. Gilead will notify sites in writing and provide training and account information prior to implementing an eSAE system.

Serious Adverse Event Paper Reporting Process

All SAEs will be recorded on the serious adverse event report form and submitted by faxing the report form within 24 hours of the investigator's knowledge of the event to the attention of Gilead DSPH or to the designated CRO.

8.4. Gilead Reporting Requirements

Depending on relevant local legislation or regulations, including the applicable US FDA Code of Federal Regulations, 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 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 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 investigator's brochure 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 or 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.

8.5. Grading of the Severity of an Adverse Event

The severity of adverse events will be graded using the CTCAE, Version 4.03 (provided 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 adverse event. For purposes of consistency with the CTCAE, these intensity grades are defined in Table 8-1.

Table 8-1. 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 adverse event should be noted. Severe is a measure of intensity; thus, a severe reaction is not necessarily a serious reaction. For example, a headache may be severe in intensity, but would not be classified as serious unless it met one of the criteria for serious events listed in Section 8.1.2 above.

8.6. Adverse Event Reporting Period

The start of the adverse event reporting for a study subject will coincide with signing of the informed consent. The end of the adverse-event-reporting period occurs 30 days after the discontinuation of study or when any ongoing drug-related adverse events and/or serious adverse events have resolved or become stable. A subject withdrawn from the study because of an adverse event must be followed until the clinical outcome from the adverse event is determined. The investigator should use appropriate judgment in ordering additional tests as necessary to monitor the resolution of events ongoing at the completion of study treatment. Gilead Sciences may request that certain adverse events be followed longer. Investigators are not obligated to actively seek information regarding the occurrence of new serious adverse events beginning after the 30-day post-study period. However, if the investigator learns of such a serious adverse event and that event is deemed relevant to the use of the study drug, he/she should promptly document and report the event. A longer reporting period applies in the case of pregnancy (see Section 8.9.1).

8.7. Adverse Event Reporting Requirements

8.7.1. Site Reporting Requirements

Classification of an event as serious or nonserious (see Section 8.1.2) determines the reporting procedures to be followed by the site.

Site reporting requirements for adverse events are summarized in Table 8-2, below.

Table 8-2. Site Reporting Requirements for Adverse Events

Classification	Reporting Time	Reporting Action
Serious	Within 24 hours	Fax report on designated serious adverse event report form to PPD Pharmacovigilance[a], and to the site IRB/IEC, as per local IRB/IEC requirements; include copies of relevant source documents[b] (eg, progress notes, autopsy reports, laboratory and diagnostic test results, discharge summaries) in communication to PPD Pharmacovigilance[a]
	Per eCRF submission procedure[c]	Record and submit information on appropriate eCRFs
Nonserious	Per eCRF submission procedure	Record and submit information on appropriate eCRFs

a See contact information in Table 8-3 below.
b Subject name, address, and other personal identifiers should be obscured but without losing the traceability of a document to the study subject identifiers.
c CLL progression or death due to CLL progression should be reported by the investigator as a serious adverse event only if it is assessed that the study drugs caused or contributed to the CLL progression (ie, by a means other than lack of effect). Unrelated events of CLL progression should be captured on the appropriate eCRF.
Abbreviations: CLL=chronic lymphocytic leukemia, eCRF=case report form, IRB/IEC= Institutional Review Board/ Independent Ethics Committee

For serious adverse events, in addition to completing the adverse event portion of the eCRF, the serious adverse event report form must also be completed. The information in the adverse event portion of the eCRF page and the serious adverse event report form(s) must match or be reconciled. Where the same data are collected, the forms must be completed in a consistent manner. For example, the same adverse event term should be used on both forms. Particularly for fatal or life-threatening events, copies of progress notes, autopsy reports, laboratory and diagnostic test results, discharge summaries, and other relevant documents should be e-mailed or faxed when requested and applicable. Follow-up information to the serious adverse event should be clearly documented as “follow up” in the serious adverse event report form and must be faxed to these same parties. Gilead Sciences may request additional information from the investigator to ensure the timely completion of accurate safety reports.

The subject’s name, address, and other personal identity information should be obscured on any source documents (eg, progress notes, nurses’ notes, laboratory and diagnostic test results, discharge summaries). Only the subject’s study number, initials, or date of birth are to be provided.

The serious adverse event report form must be communicated to PPD Pharmacovigilance, and to the site IRB/IEC (if required by local regulations) within 24 hours. In the rare event that the investigator does not become aware of the occurrence of a serious adverse event immediately (for example, if a subject initially seeks treatment elsewhere), the investigator is to report the event within 24 hours after learning of it and to document his/her first awareness of the adverse event.

Contact details for PPD Pharmacovigilance and for the Gilead study medical monitor are provided in Table 8-3:

Table 8-3. Contact Information for Reporting Serious Adverse Events

Function	Contact Information
PPD Pharmacovigilance (US)	Facsimile: PPD
PPD Pharmacovigilance (International)	Facsimile: +44 PPD
Gilead Sciences Medical Monitor	Name: PPD Title: Director, Clinical Research Office Telephone: PPD Mobile Telephone: PPD E-mail: PPD

8.7.2. Reporting of Adverse Events Relating to the Primary Endpoint and Other Anticipated Medical Events in the Study Population

To maintain the integrity of the study, progression of CLL and death related to progression of CLL will not be reported to Gilead Sciences as serious adverse events unless it is assessed that the study drug caused or contributed to CLL progression or death related to CLL progression (ie, by a means other than lack of effect). These events will be exempt from global expedited reporting requirements for the duration of the study because they define the primary efficacy endpoint for this study. All events of progression of CLL and death related to progression of CLL, regardless of relationship to study drug, will be reported in the eCRFs and, as appropriate, in the final clinical study report and in any relevant aggregate safety reports.

Disease progression information from this study will be reviewed by an independent DMC on an ongoing basis.

8.8. Special Situations Reporting Requirements

8.8.1. Definitions of Special Situations

Special situation reports include all reports of medication error, abuse, misuse, overdose, lack of effect reports and pregnancy reports regardless of an associated AE. Also includes 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.

A pregnancy report is used to report any pregnancy in female subjects on study or 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 or 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).

Lack of effect is defined as a situation where there is apparent failure of the medicinal product or medical technology to bring about the intended beneficial effect on the individual in a defined population with a given medical problem, under ideal conditions of use.

Product complaint is defined as complaints arising from potential deviations in the manufacture, packaging, or distribution of the medicinal product.

8.9. Instructions for Reporting Special Situations

8.9.1. Instructions for Reporting Pregnancies

The investigator should report all pregnancies that are identified after the subject first consents to participate in the study (ie, signs the informed consent) and throughout the study, including the post study drug follow-up period, to PPD Pharmacovigilance or Gilead DSPH using the pregnancy report form within 24 hours of becoming aware of the pregnancy. Refer to the CRF/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 therefore should be reported as such. 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 PPD Pharmacovigilance or 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 and Fax: PPD

Pregnancies of female partners of male study subjects exposed to Gilead or other study drugs must also be reported and relevant information should be submitted to PPD Pharmacovigilance or 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, fax number PPD or email PPD

8.9.2. Reporting Other Special Situations

All other special situation reports must be reported on the special situations report form and forwarded to PPD Pharmacovigilance or Gilead DSPH within 24 hours of the investigator becoming aware of the situation. These reports must consist of situations that involve study IMP, but do not apply to concomitant medications. Except for situations that result in AEs, special situations involving concomitant medications will not be reported. Any inappropriate use of medications prohibited by this protocol should not be reported as "misuse," but may be more appropriately documented as a protocol deviation.

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.

9. STATISTICAL CONSIDERATIONS

9.1. Analyis Objectives

As noted in Section 3.1, the primary objective of this clinical trial will be to evaluate the effect of the addition of idelalisib to bendamustine/rituximab on PFS.

As described in Section 3.2, the secondary objectives of this clinical trial will focus on determining the effect of the addition of idelalisib to bendamustine/rituximab on the onset, magnitude, and duration of tumor control; measures of patient well-being (including OS, HRQL; and changes in subject performance status); disease-associated biomarkers and potential mechanisms of resistance; treatment administration; safety; and health resource utilization

9.2. Analysis Endpoints

9.2.1. Primary Endpoint

The primary endpoint of the study is PFS, as defined in Section 3.3.

9.2.2. Secondary and Tertiary Endpoints

The secondary and tertiary endpoints of the study are defined in Section 3.4, grouped in categories relating to tumor control, patient well-being, pharmacodynamic markers of drug activity and resistance, exposure, safety, and pharmacoeconomics.

Of these endpoints, 4 endpoints are designated as secondary endpoints for which sequential testing will be performed to control Type 1 error rate (see Section 9.3.4.6). These secondary endpoints will be ORR, lymph node response rate, OS, and CR rate. Other endpoints will be considered tertiary.

9.3. Analysis Conventions

9.3.1. Analysis Sets

9.3.1.1. Intent-to-Treat Analysis Set

The ITT analysis set includes all subjects who are randomized regardless of whether subjects receive any study drug(s), or receive a different regimen from the regimen they were randomized to. Treatment assignment will be designated according to randomization.

This analysis set will be used in the analyses of subject characteristics, PFS, ORR, OS, and CR rate. The analysis of PFS based on the ITT analysis set will be considered the primary analysis of the study. Subjects in the ITT analysis set who do not have sufficient baseline or on-study tumor status information to be adequately assessed for response status (ie, the best overall responses of NE and ND) will be included in the denominator in the calculation of response rates.

9.3.1.2. Per-Protocol Analysis Set

The PP analysis set includes data from subjects in the ITT analysis set who meet the general criteria defining the target population for this study, are adherent to the protocol, are compliant with study drug treatment, and are evaluable for relevant efficacy endpoints. Treatment assignment will be desingnated according to the actual treatment received. The specific classification of subjects to be included in the PP analysis set will be included in the statisticial analysis plan which will be finalized prior to the database lock.

The PP analysis set will be used in sensitivity analyses of the primary and secondary efficacy endpoints: PFS, ORR, lymph node response rate, and CR rate.

9.3.1.3. Safety Analysis Set

A safety analysis set will include data from subjects who receive ≥1 dose of study treatment, with treatment assignments designated according to the actual treatment received.

This analysis set will be used in the analyses of safety variables as well as study treatment administration (for idelalisib, placebo, rituximab, and bendamustine), and post-study therapy.

9.3.1.4. Pharmacodynamic and/or Pharmacokinetic Analysis Sets

The pharmacodynamic and/or pharmacokinetic analysis sets include data from subjects in the safety analysis set who have the necessary baseline and on-study measurements to provide interpretable results for the specific parameters of interest.

These analysis sets will be used in the analyses of AKT phosphorylation, chemokines/cytokines, and idelalisib plasma concentrations.

9.3.2. Data Handling Conventions

9.3.2.1. General Methods

By-subject listings will be created for important variables from each eCRF module. Summary tables for continuous variables will contain the following statistics: N (number in population), 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. Unless otherwise indicated, 95% CIs for binary variables will be calculated using the binomial distribution (exact method) and will be 2-sided. Data will be described and summarized by relevant treatment arm, analysis set, and timepoint. As appropriate, changes from baseline to each subsequent timepoint will be described and summarized by treatment arm. Similarly, as appropriate, the best change from baseline during the study will also be described and summarized by treatment arm. Graphical techniques (eg, waterfall plots, Kaplan-Meier curves, line plots) may be used when such methods are appropriate and informative.

The baseline value used in each analysis will be the last (most recent) pre-treatment value (or pre-randomization value for non-treated subjects). Subjects with discrepancies between the stratification factor values at randomization and the actual values as documented on data review will be categorized in the analyses according to the actual values. In the situation that there is insufficient information in a stratum (ie, if there are <6 subjects or there is no informative event in a stratum), that stratum will be pooled with the smallest adjacent stratum for stratified analyses; the smallest stratum is defined as that stratum having the fewest number of subjects or the fewest number of events in case the former is a tie and the adjacent stratum is defined as a stratum having 2 factors of the 3 at the same level. Data from all sites will be pooled for all analyses. Analyses will be based upon the observed data unless methods for handling missing data are specified. If there is a significant degree of non-normality, analyses may be performed on log-transformed data or nonparametric tests may be applied, as appropriate.

Unless otherwise specified, all analyses will be 2-sided at the 0.05 level of significance.

9.3.2.2. Calculation of Tumor Control and Patient Well-Being Variables

Tumor control assessments will be based on standardized IWCLL criteria {Hallek 2008}, as specifically modified for this study considering the pharmacology of idelalisib, rituximab, and bendamustine. The individual and composite endpoints of response and progression CCI [redacted] will be determined. Tumor control will be documented at each assessment by response category (eg, CR, PR, SD, definitive PD) as defined for each response parameter, SPD value, percentage change in SPD values from baseline or nadir, date that response is first documented and date of definitive CLL progression.

The date of definitive CLL progression will be the timepoint at which progression is first identified by relevent objective radiographic or laboratory data. Because of the characteristic redistribution lymphocytosis that expected with PI3Kδ inhibition, lymphocyte count will be ignored in the evaluations of progression. Changes in tumor status as provided by the investigator and changes in tumor status as adjudicated by the IRC (see Section 10.4.3) will be described. The findings of the IRC will be considered primary for analyses of PFS and other tumor control endpoints.

The following censoring conventions will be applied:

- **PFS:** Data from surviving, non-progressing subjects will be censored at the earliest of the time of initiation of antitumor treatment other than the study treatment or the last time that lack of definitive CLL progression was objectively documented. Data from 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.
- CCI [redacted]

- CCI [redacted].
- CCI [redacted]
- CCI [redacted]
- CCI [redacted].
- CCI [redacted]

9.3.3. Subject Disposition and Baseline Characteristics

A listing of all ITT analysis set subjects will be generated to describe site, subject number, first screening date, first treatment date, subject stratification, randomized study drug assignment (idelalisib/placebo), actual study drug assignment, the longest duration of study drug and rituximab treatment, and the reason for discontinuing study treatment. Available information on subjects who were screened or registered but not randomized or not treated will be listed separately. A table will be created summarizing these categories in terms of number and percent for the ITT analysis set.

Subject baseline characteristics will be listed and summarized by treatment arm and stratification factor for the ITT analysis set. Imbalances in subject characteristics may be compared using the Wilcoxon rank-sum test for continuous variables and the Fisher's exact test for categorical variables.

9.3.4. Efficacy Analyses

9.3.4.1. Primary and Supportive Analyses of the Primary Endpoint

For the primary efficacy analysis, the difference in PFS between the treatment arms will be assessed in the ITT analysis set using Kaplan-Meier methods and the stratified log-rank test, adjusted for the stratification factors. Medians, ranges, the proportion of subjects who are progression-free at 24 and 48 weeks from randomization (based on Kaplan-Meier estimates), hazard ratios and corresponding 95% CIs (as calculated using a Cox proportional hazards regression model) will be presented. The significance level of the primary analysis will be adjusted as appropriate to account for alpha spending at the planned interim analyses (see Section 9.5.1).

The following exploratory sensitivity analyses will be performed:

The Cox regression approach will be used to explore the influence of the stratification factors, other baseline characteristics, and treatment on PFS. Beyond the stratification variables, additional baseline subject characteristics may be included as covariates, focusing on those with expected prognostic significance, particularly if these show imbalance between treatment groups. For the Cox regression modeling, a stepwise selection process will be applied to these variables to identify the final subset of relevant factors. Each prognostic factor will be preliminarily evaluated in the Cox regression model. Only the variables significant at the 0.20 level will be considered to build the multivariate model. A forward selection process will be applied to these variables to identify the final subset of relevant factors. Once a model has been established, treatment will be added to the final subset of factors to study its effect on the model. Treatment-by-factor interactions will be explored for the subset of factors included in the final model.

9.3.4.2. Other Time-to-Event Tumor Control and Survival Endpoints

CCI

9.3.4.3. Categorical Endpoints

Differences between Arms A and B for ORR, CR and PR rates, 1 CCI In the analyses of ORR, subjects who do not have sufficient baseline or on-study tumor assessment to characterize response will be counted as failures. For all analyses, odds ratios and the corresponding 95% CIs will be presented.

The potential influence of subject baseline characteristics and of treatment on response rates will be explored with logistic regression modeling.

9.3.4.4. Continuous Endpoints

CCI [redacted]

9.3.4.5. Health-Related Quality of Life and Performance Status

The FACT-Leu questionnaire data will be scored, processed, and standardized (ranging from 0-100) according to the user manual. Missing items in a subscale will be imputed consistently with the user manual instructions. Data collected from the FACT-Leu instrument will not be reconciled with adverse event or laboratory data or with EQ-D5 findings.

The mean change from baseline in mean scores to each subsequent assessment will be summarized. The best change from baseline during the study, defined as the highest value among all post-baseline visits minus the baseline value, will also be summarized. Subjects who are lost-to-follow-up will be excluded, ie, missing data will not be imputed. In the analyses of FACT-Leu data, particular focus will be placed on changes in subject reports relating to CLL (focusing specifically on fever, chills, night sweats, lymphadenopathy, and fatigue).

9.3.4.6. Control of Type I Error Rate in Efficacy Analyses

In the efficacy analyses, the following procedures will be implemented to preserve the overall type I error rate across the primary and secondary endpoints of the study at a 2-sided significance level of 0.032.

The primary endpoint analysis will serve as the gatekeeper for the secondary endpoint analyses, ie, the primary efficacy hypothesis must be rejected at the 2-sided 0.05 significance level before the efficacy hypotheses for the secondary efficacy endpoints can be tested. The secondary endpoints will be the following:

- ORR
- Lymph node response rate
- OS
- CR rate

If the primary hypothesis is rejected, the 4 secondary endpoints will be sequentially tested at the 2-sided 0.032 significance level in the order listed above. If a null hypothesis is not rejected, formal sequential testing will be stopped and only nominal significance will be cited for the remaining secondary endpoints. Analyses and p-values will be reported for all the efficacy endpoints, including the primary endpoint, the secondary endpoints, and all of the tertiary endpoints.

9.3.5. Exposure and Safety Analyses

9.3.5.1. Study Drug Administration and Study Drug Compliance

Descriptive information will be provided by treatment arm regarding the number of doses of idelalisib, placebo, rituximab, and bendamustine prescribed, the total number of doses taken, the percent of expected doses taken, the number of days (or infusions) of treatment, and the number and timing of prescribed dose reductions and interruptions.

Study drug (idelalisib/placebo) compliance will be described by treatment arm in terms of the proportion of study drug actually taken based on returned pill count relative to the amount that was dispensed (taking into account physician-prescribed reductions and interruptions).

9.3.5.2. Idelalisib Plasma Concentrations

Bioanalytical analyses will performed independently so that the study team and investigators will not have knowledge of data from individual subjects. For Arm A, the idelalisib plasma concentrations immediately pre-dose and at 1.5 hours after administration of the dose of study drug at each relevant clinic visit will be summarized by treatment and visit using descriptive statistics.

9.3.5.3. Prior, Concomitant, and Post-Treatment Medication Use

Prior, concomitant, and post-treatment medications will be coded by means of the World Health Organization Drug Dictionary (WHODRUG) dictionary into Anatomical-Therapeutic-Chemical classification (ATC) codes.

Descriptions of prior medication use will be focused on drugs and regimens used as treatments for CLL. To the extent available, information on the sequencing, type, dose, schedule, timing, duration of use, and efficacy of prior regimens will be provided. In addition, details regarding response and duration of the last prior antineoplastic therapy before randomization will be described.

The type and timing of use of concomitant medications will be listed and summarized by type and treatment arm. Information regarding the type and use of specific supportive medications (eg, pneumocystis prophylaxis, hematopoietic growth factors, corticosteroids) during study treatment will be described.

9.3.5.4. Adverse Events

All adverse events will be listed. The focus of adverse event summarization will be on treatment-emergent adverse events. A treatment-emergent adverse event is defined as an adverse event that occurs or worsens in the period from the first dose of study treatment (idelalisib, placebo, rituximab, or bendamustine) to 30 days after the last dose of study drug. Adverse events will be classified using MedDRA (http://www.meddramsso.com) with descriptions by System Organ Class, High-Level Group Term, High-Level Term, Preferred Term, and Lower-Level Term. The severity of adverse events will be graded by the investigator according to the CTCAE, Version 4.03 (*http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf*), whenever possible. If a CTCAE criterion does not exist for a specific type of adverse event, the grade corresponding to the appropriate adjective will be used by the investigator to describe the maximum intensity of the adverse event: Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), Grade 4 (life threatening), or Grade 5 (fatal). The relationship of the adverse event to the study drug will be categorized as related or unrelated.

Treatment-emergent adverse events will be summarized by treatment arm. Summary tables will be presented to show the number of subjects reporting treatment-emergent adverse events by severity grade and corresponding percentages. A subject who reports multiple treatment-emergent adverse events within the same Preferred Term (or System Organ Class) is counted only once for that Preferred Term (or System Organ Class) using the worst severity grade. Adverse event descriptions will be presented by decreasing frequency for a given System Organ Class and Preferred Term.

Separate listings and summaries will be prepared for the following types of treatment-emergent adverse events:

- Study-drug-related adverse events
- Adverse events that are Grade ≥3 in severity
- Adverse events leading to study drug (idelalisib/placebo) interruption and/or dose modification
- Adverse events leading to study drug discontinuation
- Serious adverse events (with categorization of the primary reason that the adverse event is considered serious, eg, death, hospitalization, etc)

The severity of rituximab-related infusion reactions and of the total durations of rituximab infusions will be compared to determine whether idelalisib pretreatment modifies the magnitude of such events or alters the length of the rituximab infusion due to such events; the focus of this analysis will be on the first 2 rituximab infusions (ie, those on Day 1 and on Day 29 of therapy). Comparisons will be done using the Chi-square test for severity grade and the Wilcoxon rank-sum test for infusion duration.

Separate listings and summaries will be prepared for long-term follow-up safety data (see Section 6.2.13).

9.3.5.5. 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, worsens by ≥1 grade in the period from the first dose of study drug (idelalisib, placebo, rituximab, or bendamustine) to 30 days after the last dose of study drug. 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 programmatically graded according to CTCAE severity grade, when applicable. For parameters for which a CTCAE scale does not exist, reference ranges from the central 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 treatment arm, and by visit. Summary tables will be presented for each relevant assay to show the number of subjects by CTCAE severity grade with corresponding percentages. For parameters for which a CTCAE scale does not exist, the frequency of subjects with values below, within, and above the normal ranges will be summarized. Subjects will be characterized only once for a given assay, based on their worst severity grade observed during a period of interest (eg, during the study or from baseline to a particular visit).

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. Separate listings and summaries will be prepared for laboratory abnormalities that are Grade ≥3 in severity.

9.3.5.6. Oxygen Saturation Values

All oxygen saturation data will be listed. Summaries of oxygen saturation data will be based on observed data and will be reported as % saturation. Data and changes from baseline will be summarized by treatment arm and by visit. Summary tables will be presented for values below 92% and for declines from baseline of ≥5% to show the number of subjects with corresponding percentages. Subjects will be characterized only once for each of these categorizations, based on their lowest value observed during a period of interest (eg, during the study or from baseline to a particular visit).

9.3.6. Other Analyses

9.3.6.1. Health Care Resource Utilization

The EQ-D5 questionnaire data will be scored, processed, and standardized according to the user manual. As for the FACT-Leu, data will be analyzed using appropriate methods to account for incomplete completion of questionnaires. Data collected from the EQ-D5 will not be reconciled with adverse event or laboratory data or with FACT-Leu findings.

Health care resource utilization data collection will be based on information provided in the eCRFs and will be focused on the most relevant direct medical resource utilization such as physician visits, laboratory tests, medications (including dose and route), medical procedures, interventions (eg, transfusions), and hospitalizations.

The basic approach to the health economic analysis will be to combine the resource utilization data from the trial with data on unit prices (collected separately) to estimate total costs in preparation for a full-cost analysis.

The perspective of this analysis will be that of the third-party payer and the hospital over a lifetime horizon in the base case. One possibility is that the addition of idelalisib to bendamustine/rituximab will reduce costs directly and, if so, perhaps no further analysis will be required. A second possibility is that the addition of idelalisib to bendamustine/rituximab will increase costs overall. In this latter case the increase in costs due to adding idelalisib to treatment will be compared relative to the health care gains as measured by duration of tumor control, the symptom-free survival period, life-years saved (gained), utility gains or other measure of appropriate clinical benefits. In order to facilitate the calculation of utilities for use in the cost effectiveness analyses, the health status of subjects will be evaluated using PFS, Karnofsky performance status, FACT-Leu, and EQ-5D. One-way, 2-way, and probabilistic sensitivity analyses will be conducted to assess the robustness of the results.

9.3.6.2. Data Explorations

Changes in biomarkers during acquisition of resistance will be evaluated descriptively. Data explorations may be performed to evaluate potential associations between subject characteristics and outcome measures. Similarly, explorations may be performed to assess the potential associations between different outcomes measures (eg, relationships between HRQL changes and clinical/radiographic endpoints of tumor control).

9.4. Sample Size

9.4.1. Sample Size Calculation

Based on data from prior studies with bendamustine/rituximab {Fischer 2011, Iannitto 2011}, it is reasonable to assume that administration of the combination to subjects with previously treated CLL in Arm B of this trial will result in a median PFS of ~15 months. An improvement in median PFS from 15 months to 22.5 months due to the addition of idelalisib to bendamustine/rituximab in Arm A of the study would correspond to a benefit ratio of 1.5 (hazard ratio 0.67). This treatment effect seems achievable in view of the fact that the Phase 1-2 multicenter experience with single-agent idelalisib in heavily pretreated patients has indicated a median PFS of >14 months {Coutre 2011}.

It is assumed that PFS times are exponentially distributed in each of the 2 arms. With a hazard ratio equal to 1 under the null hypothesis of no difference between the 2 treatment arms and a hazard ratio of 0.67 under the alternative hypothesis of superiority of the idelalisib-containing combination, 260 events (definitive CLL progressions) is required to achieve a power of 0.90 based on a stratified log-rank test with a 2-sided significance level of 0.05. Further

assuming a planned accrual period of 18 months (with approximately half of the subjects enrolled during the initial 60% of the accrual period, and the remaining half of the subjects enrolled during the last 40% of the accrual period), a minimum follow-up period of 24 months, and an expectation that 15% of subjects will be lost to follow-up (7% during the accrual period and 8% during the follow-up period), ~195 subjects per treatment arm (~390 total) are to be enrolled in order to achieve the expected number of events by the end of the planned minimum 24-month follow-up period. This sample size will also provide a substantial safety database for the idelalisib/bendamustine/rituximab combination therapy; the safety data set provided by the idelalisib-treated subjects (N~195) in this study compares favorably with the safety data set derived from the randomized pivotal registration trial for bendamustine (N=153) {Knauf 2009}. If the planned subject enrollment does not appear adequate to accrue the expected number of events within the proposed follow-up period, the sample size may be adjusted upward.

9.4.2. Blinded Sample Size Re-estimation

Prior to completion of enrollment, Gilead Sciences may perform a review of blinded data to evaluate the overall event rate. If the planned subject accrual does not appear adequate to generate the expected number of events within the proposed follow-up period, the sample size may be adjusted upward.

9.5. Timing of Analyses

9.5.1. Interim Analysis

The DMC will have access to serious adverse events requiring expedited reporting and will be provided with accumulating safety data on a regular basis. An interim safety review will be conducted by the DMC at ~6 months after the first subject is enrolled. Thereafter, interim safety reviews will be performed by the DMC at intervals of ~6 months; the specific frequency of these reviews will depend upon the rate at which the trial is enrolled, the nature of any emerging safety signals, and monitoring recommendations from the DMC. At each review, all available safety data will be summarized and evaluated.

An unblinded review of all available efficacy and safety data will be conducted by the DMC after ~66% of the expected number of 260 events (definitive CLL progressions per IRC or deaths) have occurred. These analyses offer the opportunity to assess for evidence of substantial clinical benefit or for evidence that establishing clinical benefit is unlikely. For these analyses, all available PFS data will be evaluated. The interim analyses will employ the primary analysis method that is planned for the final analysis of the PFS endpoint (see Section 9.3.4.1).

Stopping the study for substantial evidence of idelalisib benefit will be considered if the PFS is significantly better in Arm A compared to Arm B. The significance level for this interim analysis will be 0.001. Based on the assumptions of the study and the timing of the planned analysis, boundary-crossing probabilities for the trial are depicted in Table 9-1.

Table 9-1. Boundary-Crossing Probabilities at Interim and Final Analyses Based on the Assumptions of the Study

Analysis	Expected Events [a] n (%)		Boundary-Crossing Probabilities at Each Analysis	
			Under the Null Hypothesis	Under the Alternative Hypothesis
Interim	172	(66%)	0.001	0.266
Final	260	(100%)	0.049	0.633

a Definitive CLL progressions or deaths

Alternatively, stopping the study will be considered if the planned interim analyses indicate that obtaining a significant improvement in PFS in Arm A relative to Arm B appears futile. For this futility analysis, the DMC will be provided with the conditional power at the time of the planned interim analysis (ie, when ~66% of the expected number of 260 events have occurred, per IRC). The DMC will be requested to consider recommending termination of the study if the conditional power is <0.10.

9.5.2. Final Efficacy Analysis

The final efficacy analysis will be conducted after approximately the 260th event (definitive CLL progression or death). It is expected that this number of events will occur after a minimum of 24 month follow-up. The timing of the final analysis may be altered appropriately if the study is stopped early or if an upward adjustment of the sample size is performed as described in Section 9.4.2. Once any outstanding data queries have been resolved, the database will be locked the blind will be broken, and the efficacy analysis of the study will be performed.

9.5.3. Follow-up Analyses

After the final analysis, additional supplemental analyses of efficacy and safety may be performed to satisfy regulatory requirements and to perform long-term efficacy, safety, and OS follow-up.

10. RESPONSIBILITIES

10.1. Investigator Responsibilities

10.1.1. Compliance with Ethical and Regulatory Guidelines

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), with 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.

This study is also subject to and will be conducted in accordance with 21 CFR, part 320, 1993, "Retention of Bioavailability and Bioequivalence Testing Samples."

Because this is a "covered" clinical trial, the investigator will ensure adherence to 21 CFR, Part 54, 1998; a covered clinical trial is any "study of a drug or device in humans submitted in a marketing application or reclassification petition subject to this part that the applicant or FDA relies on to establish that the product is effective (including studies that show equivalence to an effective product) or that make a significant contribution to the demonstration of safety." This requires that investigators and all sub-investigators must provide documentation of their financial interest or arrangements with Gilead Sciences, or proprietary interests in the drug being studied. This documentation must be provided before participation of the investigator and any subinvestigator in the trial. The investigator or subinvestigator agrees to notify Gilead Sciences of any change in reportable financial interests during the study and for 1 year following completion of the study. Study completion is defined as the date that the last subject has completed the protocol-defined activities.

10.1.2. Institutional Review Board/Independent Ethics Committee

This protocol 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) will be submitted by the investigator to an IRB (for sites enrolling in the US) and to an IEC for sites enrolling outside of the US). Approval from the IRB/IEC must be obtained before starting the study and should be documented in a letter to the investigator specifying the protocol number, protocol version, protocol date, documents reviewed, and date on which the committee met and granted the approval.

Any modifications or amendments made to the protocol after receipt of the initial IRB/IEC approval must also be submitted to the IRB/IEC for approval before implementation. Only changes necessary to eliminate apparent immediate hazards to the subjects may be initiated prior to IRB/IEC approval. In that event, the investigator must notify the IRB/IEC and Gilead Sciences in writing within 5 working days after implementation.

The investigator shall submit a progress report, at least once yearly, to the IRB/IEC, and must provide a copy to Gilead Sciences. As soon as possible after completion or termination of the study, the investigator will submit a final report to the IRB/IEC and to Gilead Sciences. This report should include the dates of initiation and completion of the trial, a description of any changes in study procedures or amendments to the protocol, any deviations from the protocol, the number and type of subjects evaluated, the number of subjects who discontinued (and the reasons for discontinuation), the number of subjects who completed the trial, and the results of the trial, including a description of any adverse events. Gilead Sciences will assist the investigator in the preparation of this report, as needed.

10.1.3. Informed Consent

After adequately, explaining the aims, methods, objectives, and potential hazards of the study and before undertaking any study-related procedures, the investigator is responsible for obtaining written informed consent from each individual participating in this study. The investigator must utilize an IRB/IEC-approved consent form for documenting written informed consent. Each informed consent will be appropriately signed and dated by the subject or the subject's legally authorized representative and the person obtaining consent.

The approved informed consent must not be changed without prior approval by Gilead Sciences and the IRB/IEC.

10.1.4. Confidentiality

The investigator must assure that each subject's anonymity will be strictly maintained and that each subject's identity is protected from unauthorized parties. Only subject initials, date of birth, and an identification code (but no subject names) should be recorded on any form or biological sample submitted to the Gilead Sciences or designees (eg, laboratories), or to the IRB/IEC. However, sufficient information must be retained at the site to permit sample data and data in the database to be connected with the unique subject number assigned to each study participant.

The investigator agrees that all information received from Gilead Sciences, including but not limited to the idelalisib investigator brochure, this protocol, eCRFs, the investigational new drug, and any other study information, remain the sole and exclusive property of Gilead Sciences 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 Sciences. 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.

10.1.5. Study Files and Retention of Records and Biological Samples

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 2 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, the 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 referenced in the monitoring plan for the study, and 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, eg, history, physical examination, and confirmation of diagnosis (to support inclusion and exclusion criteria)
- Participation in trial (including trial number)
- Trial 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 trial medication (including relevant drug dispensing and return information)
- Record of all adverse events and other safety parameters (including start and end date, causality and intensity)
- Concomitant medication (including start and end date and dose if relevant dose changes occur)
- Date of trial completion and reason for discontinuation, if applicable

All clinical study documents must be retained by the investigator until at least 2 years after the last approval of a marketing application in an ICH region (ie, the US, Europe, or Japan) and until there are no pending or contemplated 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 required by applicable regulatory requirements, by local regulations, or by an agreement with Gilead Sciences. The investigator must notify Gilead Sciences before destroying any clinical study records. The investigator will promptly notify Gilead Sciences in the event of accidental loss or destruction of any study records.

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

If the investigator cannot guarantee this archiving requirement at the study site for any or all of the documents, special arrangements must be made between the investigator and Gilead Sciences to store these in sealed containers outside of the site so that they can be returned sealed to the investigator in case of a regulatory audit. When source documents are required for the continued care of the subject, appropriate copies should be made for storage outside of the site.

Biological samples including tissue and blood samples collected as a study procedure or as standard of care during study participation will be stored and maintained by the investigator until notification is received from Gilead Sciences that the retained samples and records are no longer required. The investigator must obtain written permission from Gilead Sciences before disposing of any retained samples. The investigator should promptly notify Gilead Sciences in the event of accidental loss or destruction of any study samples. With the permission of Gilead Sciences, the retained samples may be transferred to an acceptable designee, such as another investigator, another institution, a contract storage site, or to Gilead Sciences.

10.1.6. Case Report Forms

An eCRF is required and must be completed for each enrolled subject, with all required study data accurately recorded such that the information matches the data contained in medical records (eg, physicians' notes, nurses' notes, clinic charts, or other study-specific source documents). As required by the protocol, eCRFs should also be completed for those subjects who fail to complete the study (even during a prerandomization screening period). If a subject withdraws from the study, the reason must be noted on the eCRF. If a subject is withdrawn from the study because of a treatment-limiting adverse event, thorough efforts should be made to clearly document the outcome.

The eCRFs for this study will exist within a Web-based electronic data capture (EDC) system. After the investigator or the investigator's designees (eg, research coordinators) have been appropriately trained, they will be given access to the EDC system and will enter the data required by the protocol into the EDC system. Any change of data will be made via the EDC system, with all changes tracked by the system to provide an audit trail.

The eCRF must be completed and signed by the principal investigator or subinvestigator (as appropriate) within a reasonable time period after data collection. This signature serves to attest that the information contained in the eCRF is true.

10.1.7. Drug Accountability

As described in the relevant sections for (see Section 5.2.1.7 for idelalisib, Section 5.2.2.7 for rituximab, and Section 5.2.3.7 for bendamustine), the investigator is responsible for ensuring adequate accountability of all used and unused investigational medicinal product, placebos, and comparators. This responsibility includes acknowledgment of receipt of each shipment of study product (quantity and condition), subject dispensing records, and returned or destroyed study product. Dispensing records will document quantities received from Gilead Sciences and quantities dispensed to subjects, including lot number, date dispensed, subject identifier number, subject initials, and the initials of the person dispensing the medication.

At study initiation, the monitor will evaluate the site's standard operating procedure for investigational medicinal product disposal/destruction in order to ensure that it complies with Gilead Sciences requirements. Drug may be returned or destroyed on an ongoing basis during the study if appropriate. At the end of the study, following final drug inventory reconciliation by the monitor, the study site will dispose of and/or destroy all unused investigational medicinal product supplies, including empty containers, according to these procedures. If the site cannot meet Gilead Sciences' requirements for disposal, arrangements will be made between the site and Gilead Sciences or its representative for destruction or return of unused investigational medicinal product supplies.

All drug supplies and associated documentation will be periodically reviewed and verified by the study monitor over the course of the study.

10.1.8. Inspections

The investigator should understand that source documents for this trial should be made available to appropriately qualified personnel from Gilead Sciences or its representatives, to IRBs/IECs, and to regulatory authority or health authority inspectors. It is important that the investigator and relevant institutional personnel are available during monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

10.1.9. Protocol Compliance

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

10.2. Sponsor Responsibilities

10.2.1. Protocol Modifications

Protocol modifications, except those intended to reduce immediate risk to study subjects, will be made only by Gilead Sciences. All protocol modifications must be submitted to the IRB/IEC in accordance with local requirements. Except as noted in Section 10.1.2, IRB/IEC approval must be obtained before changes can be implemented.

10.2.2. Communications with Regulatory Authorities

Gilead Sciences, working either directly or through designees, will assume responsibility for regulatory interactions with relevant regulatory authorities. Gilead Sciences will maintain an IND for idelalisib in support of the study in the US and will maintain similar regulatory applications with other regulatory authorities, as required for conduct of the study. In fulfilling this responsibility, Gilead Sciences (or a designee) will collect, assemble, and communicate all required regulatory documents (eg, Form FDA 1572, investigator financial disclosure forms, protocol and protocol amendments, investigator brochures, informed consent documents, annual reports) as required by regulation. Gilead Sciences (or a designee) will also assume responsibility for adverse event reporting to regulatory authorities as described in Section 8.7.2.

10.2.3. Data Management

EDC will be used to enter study data eCRFs and to transfer the data into a study-specific electronic database. During the data collection process, automated quality assurance programs will be used to identify missing data, selected protocol violations, out-of-range data, and other data inconsistencies. Requests for data clarification or correction will be forwarded to the investigative site for resolution. As appropriate, eCRFs, listings, tables, and SAS datasets will be provided to the investigational sites for review.

Quality assurance and quality control systems will be implemented and maintained according to written standard operating procedures to ensure that the data are generated, recorded, and reported in compliance with the protocol, GCP, and applicable regulatory requirements. Data collection and storage systems will provide audit trail, security mechanisms, and electronic signature capabilities that meet the requirements of FDA Title 21 of CFR Part 11 regarding electronic records and electronic signatures.

Data security will be controlled through appropriate and specific restriction of access only to data and systems required by individual users to accomplish their roles in the data management process. Individual login and password protections will be employed at study sites and at Gilead Sciences or its designee. The database will exist on physically secured servers. Data backups will be done regularly and will be stored in separate facilities. Printed documents relating to the study will be secured when not under review.

10.2.4. Study Reporting and Publication

Gilead Sciences may make information obtained during this study available in order to further the scientific or business needs of the company or as required by law or regulation. In this regard, Gilead Sciences may provide study information to private or public organizations (eg, business partners, collaborators, consultants, CROs, investors, other physicians who are conducting similar studies, funding organizations, regulatory authorities, or other government authorities).

Gilead Sciences will prepare a clinical study report for submission to relevant regulatory agencies. Gilead Sciences will ensure that the report meets the standards set out in the ICH Guideline for Structure and Content of Clinical Study Reports (ICH E3). An abbreviated report may be prepared in certain cases, as appropriate

Gilead Sciences intends that the data from this study will be presented and published. Gilead Sciences will work in collaboration with the principal investigators in preparing presentations and writing manuscripts for publication.

- Investigators may publish or present the results of the study generated by their individual site either with the advanced written consent of Gilead or > 2 years after the completion of the study at all participating institutions.

No such communication, presentation, or publication will include Gilead Sciences' confidential information (see Section 10.1.4).

The investigator will submit to Gilead Sciences any proposed publication or presentation along with the respective scientific journal or presentation forum prior to submission of the publication (at least 30 days prior to manuscripts and 15 days prior for abstracts and oral presentations). The investigator will comply with Gilead Sciences' request to delete references to its confidential information (other than the study results) in any paper or presentation. If deemed necessary by Gilead Sciences, the investigator also agrees to withhold publication or presentation for an additional 60 days in order to obtain patent protection.

10.3. Joint Investigator/Sponsor Responsibilities

10.3.1. Access to Information for Monitoring

In accordance with ICH Good Clinical Practice (ICH GCP) guidelines, the study monitor must have direct access to the investigator's source documentation in order to verify the data recorded in the eCRFs for consistency.

The monitor is responsible for routine review of the eCRFs 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 eCRFs. The investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

10.3.2. Access to Information for Auditing or Inspections

Representatives of regulatory authorities or of Gilead Sciences 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 Sciences medical monitor immediately. The investigator agrees to provide to representatives of a regulatory agency or Gilead Sciences access to records, facilities, and personnel for the effective conduct of any inspection or audit.

10.3.3. Public Notification of Study Conduct

Consistent with Section 113 of the Food and Drug Modernization Act of 1997 (FDAMA) and with requirements of the International Committee of Medical Journal Editors (ICMJE) as a condition of consideration for publication of study results, Gilead Sciences will be responsible for ensuring that this protocol is listed at the ClinicalTrials.gov website (or equivalent) and that information at the website relating to study design and conduct is appropriately updated during the course of the study. In order to facilitate this process, investigators will need to supply Gilead Sciences with appropriate contact information for study site personnel.

10.3.4. 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 authorities and IRB/IECs. In terminating the study, Gilead Sciences and the investigator will assure that adequate consideration is given to the protection of the subjects' interests.

10.4. Study Committees

10.4.1. Study Steering Committees

A study steering committee (SSC) may be responsible for assisting Gilead Sciences with protocol development, review of any study amendments, and coordination of study conduct, interpretation of data, and presentation and publication of study results may be instituted during the conduct of the study. The SSC will comprise the Gilead Sciences medical monitor for the study, the responsible Gilead Sciences biostatistician, the Gilead Sciences study director, and several clinicians with expertise in the care of subjects with CLL. Other specialists may be invited to participate as members of the SSC at any time if additional expertise is desired. The Gilead Sciences study director will serve as the chair of the SSC.

10.4.2. Data Monitoring Committee

A DMC, operating autonomously from Gilead Sciences, the clinical investigators, and the SSC, will be responsible for providing independent recommendations to Gilead Sciences about evolving risk-benefit observed in the course of the study and any modifications required during the course of the study. The DMC will consist of a biostatistician and ≥2 physicians experienced in treating patients with lymphoid malignancies. The DMC will be chaired by one of these individuals. DMC members must not be actively involved in study design, conduct, or subject accrual and must not have financial, proprietary, professional, or other interests that may affect impartial, independent decision-making. Specialists may be invited to participate as non-voting members at any time if additional expertise is desired. The DMC will formally interact with the external SSC members through the sharing of meeting minutes. Informal interactions between the DMC and external SSC members will be limited. The DMC will operate under a charter developed as a collaborative document between Gilead Sciences and the DMC.

The primary responsibility of the DMC is to protect the safety and welfare of subjects participating in this clinical trial and to ensure the integrity of the clinical trial. In general, the DMC will be responsible for:

- Examining accumulated safety, efficacy, and other relevant data during the course of the study in order to make recommendations concerning continuation, termination, or modification of the study
- Reviewing the general progress of the study as regards subject accrual, study conduct, and protocol violations
- Reviewing major study design modifications proposed by Gilead Sciences or by the SSC prior to implementation of those modifications
- Providing expert advice to the Gilead Science medical monitor on an ad hoc basis regarding matters such as safety concerns or diagnostic evaluations in individual subjects

Based on the results of its deliberations during the course of the study, the DMC can recommend continuation of the study unchanged, study interruption, study termination, modification of the trial, or alteration in the DMC monitoring plan.

10.4.3. Independent Review Committee

An IRC will be established to provide a blinded review of radiographic data and pertinent clinical data in order to provide expert interpretation of changes in tumor status. The IRC will include ≥1 independent board-certified radiologist and ≥1 independent board-certified hematologist or oncologist, and will be managed by a CRO selected by Gilead Sciences. The review of radiographic and clinical data by the IRC will be performed on an ongoing basis. The specifics of the IRC's processes and reading methods will be described in an independent review charter developed by the contracted imaging facility in conjunction with Gilead Sciences. The findings of the IRC will be considered primary for analyses of PFS and other tumor control endpoints.

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12. APPENDICES

Appendix 1. Investigator Signature Page

GILEAD SCIENCES, INC.
333 Lakeside Drive
Foster City, CA 94404 USA

STUDY ACKNOWLEDGEMENT

A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Efficacy and Safety of Idelalisib (GS-1101) in Combination with Bendamustine and Rituximab for Previously Treated Chronic Lymphocytic Leukemia

GS-US-312-0115, Version 11.0, 21 September 2017

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

PPD

Gilead Sciences Medical Monitor

PPD

Signature

September 21, 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
Printed Name

Signature

Date

Site Number

Appendix 2. Functional Assessment of Cancer Therapy: Leukemia

FACT-Leu (Version 4)

Below is a list of statements that other people with your illness have said are important**. Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

	PHYSICAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

19 November 2007
Page 1 of 3

FACT-Leu (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	EMOTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

FACT-Leu (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
BRM3	I am bothered by fevers (episodes of high body temperature)	0	1	2	3	4
P2	I have certain parts of my body where I experience pain	0	1	2	3	4
BRM2	I am bothered by the chills	0	1	2	3	4
ES3	I have night sweats	0	1	2	3	4
LEU1	I am bothered by lumps or swelling in certain parts of my body (e.g., neck, armpits, or groin)	0	1	2	3	4
TH1	I bleed easily	0	1	2	3	4
TH2	I bruise easily	0	1	2	3	4
HI12	I feel weak all over	0	1	2	3	4
BMT6	I get tired easily	0	1	2	3	4
C2	I am losing weight	0	1	2	3	4
C6	I have a good appetite	0	1	2	3	4
An7	I am able to do my usual activities	0	1	2	3	4
N3	I worry about getting infections	0	1	2	3	4
LEU5	I feel uncertain about my future health	0	1	2	3	4
LEU6	I worry that I might get new symptoms of my illness	0	1	2	3	4
BRM9	I have emotional ups and downs	0	1	2	3	4
LEU7	I feel isolated from others because of my illness or treatment	0	1	2	3	4

Appendix 3. Performance Status Scoring System

Karnofsky Performance Status		
General Description	**Score**	**Specific Description**
Able to carry on normal activity and to work; no special care needed.	100	Normal; no complaints; no evidence of disease.
	90	Able to carry on normal activity; minor signs or symptoms of disease.
	80	Normal activity with effort; some signs or symptoms of disease.
Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed.	70	Cares for self; unable to carry on normal activity or to do active work.
	60	Requires occasional assistance, but is able to care for most of personal needs.
	50	Requires considerable assistance and frequent medical care.
Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly.	40	Disabled; requires special care and assistance.
	30	Severely disabled; hospital admission is indicated although death not imminent.
	20	Very sick; hospital admission necessary; active supportive treatment necessary.
	10	Moribund; fatal processes progressing rapidly.
	0	Dead

Appendix 4. EuroQoL-5 Dimensions (EQ-5D)

By placing a checkmark in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

- I have no problems in walking about ☐
- I have some problems in walking about ☐
- I am confined to bed ☐

Self-Care

- I have no problems with self-care ☐
- I have some problems washing or dressing myself ☐
- I am unable to wash or dress myself ☐

Usual Activities (e.g., work, study, housework, family, or leisure activities)

- I have no problems with performing my usual activities ☐
- I have some problems with performing my usual activities ☐
- I am unable to perform my usual activities ☐

Pain/Discomfort

- I have no pain or discomfort ☐
- I have moderate pain or discomfort ☐
- I have extreme pain or discomfort ☐

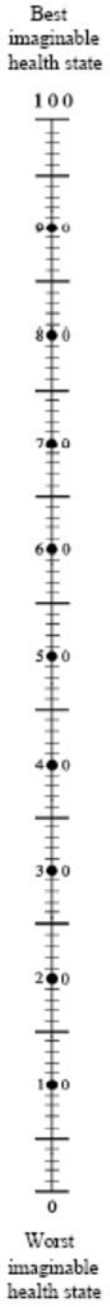
Anxiety/Depression

- I am not anxious or depressed ☐
- I am moderately anxious or depressed ☐
- I am extremely anxious or depressed ☐

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state today



Appendix 5. Cockcroft-Gault Method for Estimating Creatinine Clearance

Formulas for calculating the estimated creatinine clearance (eC_{cr}) are provided in the table below. The formula appropriate to the units in which serum creatinine was measured and the subject's gender should be used.

Serum Creatinine Units	Gender	Formula
mg/dL	Males	eC_{cr} [mL/min] $= \frac{(140\text{-subject age [years]}) \times \text{subject weight [kilograms]} \times 1}{72 \times \text{subject serum creatinine [mg/dl]}}$
	Females	eC_{cr} [mL/min] $= \frac{(140\text{-subject age [years]}) \times \text{subject weight [kilograms]} \times 0.85}{72 \times \text{subject serum creatinine [mg/dl]}}$
µM/dL	Males	eC_{cr} [mL/min] $= \frac{(140\text{-subject age [years]}) \times \text{subject weight [kilograms]} \times 1.23}{\text{Subject serum creatinine [mg/dl]}}$
	Females	eC_{cr} [mL/min] $= \frac{(140\text{-subject age [years]}) \times \text{subject weight [kilograms]} \times 1.04}{\text{Subject serum creatinine [mg/dl]}}$

Abbreviation: eCcr=estimated creatinine clearance

Appendix 6. CIRS List of Comorbid Conditions

The CIRS used in this protocol is designed to provide an assessment of recurrent or ongoing chronic comorbid conditions, classified by 14 organ systems. Using the drop-down lists of organ-specific diagnoses, please select any conditions present in the study subject. If the subject has a recurrent or ongoing chronic conditions that are not described in the list for a given organ system, please indicate the name of the conditions under "other chronic condition" for that organ system. Please take into account that CLL-induced discomfort, symptoms, or disability should not be considered. If additional explanation would be helpful, text comments may be inserted.

Organ System	Diagnosis	Comment
Cardiac	Chronic heart failure	
	Angina pectoris	
	Medically relevant arrhythmia	
	Valve dysfunction	
	Congenital heart disease	
	Cardiomyopathy	
	Myocarditis	
	Chronic pericarditis	
	Endocarditis	
	Other chronic cardiac condition:	
	Other chronic cardiac condition:	
Vascular	Hypertension	
	Thrombosis	
	Peripheral diabetic microvascular disease	
	Peripheral artery disease	
	Aortic aneurysm	
	Aortitis	
	Raynaud disease	
	Vasculitis	
	Other chronic vascular condition:	
	Other chronic vascular condition	

Organ System	Diagnosis	Comment
Hematological/ Immunological	Sickle cell anemia	
	Hemoglobinopathy	
	Polycythemia	
	Thrombocythemia	
	Hemophilia	
	Paroxysmal nocturnal hemoglobinuria	
	Thrombotic thrombocytopenic purpura	
	Dysfibrinogenemia	
	HIV	
	Other chronic hematological or immunological condition:	
	Other chronic hematological or immunological condition	
Respiratory	Asthma	
	Chronic obstructive pulmonary disease	
	Cystic fibrosis	
	Emphysema	
	Chronic bronchitis	
	Chronic pleural effusions	
	Pulmonary fibrosis	
	Sarcoidosis	
	Pulmonary embolism	
	Pulmonary arterial hypertension	
	Lung cancer	
	Other chronic respiratory condition:	
	Other chronic respiratory condition	

Organ System	Diagnosis	Comment
Ophthalmological/ otolaryngological	Loss of vision	
	Glaucoma	
	Cataract	
	Macular degeneration	
	Diabetic retinopathy	
	Loss of hearing	
	Otitis/chronic otitis	
	Vestibular impairment	
	Vertigo	
	Temporomandibular disorder	
	Sialolithiasis	
	Chronic sinusitis	
	Laryngeal/pharyngeal disorders	
	Other chronic ophthalmological or otolaryngological condition:	
Upper Gastrointestinal	Chronic esophagitis	
	Dysphagia	
	Achalasia	
	Gastroduodenal ulceration	
	Celiac disease	
	Irritable bowel syndrome	
	Short bowel syndrome	
	Malnutrition	
	Malabsorption	
	Small bowel obstruction	
	Hernia	
	Pseudomyxoma peritonei	
	Upper gastrointestinal cancer	
	Other chronic upper gastrointestinal condition:	
	Other chronic upper gastrointestinal condition:	

Organ System	Diagnosis	Comment
Lower Gastrointestinal	Diverticulitis	
	Inflammatory bowel disease	
	Volvulus	
	Colon cancer	
	Other chronic lower gastrointestinal condition:	
	Other chronic lower gastrointestinal condition:	
Hepatic/ Pancreatic	Chronic hepatitis or hepatic cirrhosis	
	Biliary obstructive disorders	
	Pancreatitis	
	Hepatic, biliary, or pancreatic cancer	
	Other chronic hepatic or pancreatic condition:	
	Other chronic hepatic or pancreatic condition:	
Renal	Chronic kidney disease	
	Diabetic nephropathy	
	Pyelonephritis	
	Renal cancer	
	Other chronic renal condition:	
	Other chronic renal condition	
Gynecological/ Urological	Recurrent/chronic urinary tract infection	
	Nephrolithiasis	
	Bladder dysfunction	
	Vaginal/vulvar disease	
	Uterine/ovarian disease	
	Prostatitis	
	Bladder, uterine, ovarian, prostate, or other cancer	
	Prostate hypertrophy	
	Other chronic gynecological or urological condition:	
	Other chronic gynecological or urological condition:	

Organ System	Diagnosis	Comment
Dermatologic/ musculoskeletal	Dermatitis	
	Dermatomyositis	
	Myopathy	
	Gout	
	Psoriasis	
	Keratosis	
	Urticaria	
	Scleroderma	
	Basal cell carcinoma	
	Squamous cell carcinoma	
	Melanoma	
	Osteomyelitis	
	Osteoarthritis	
	Rheumatoid arthritis	
	Spondyloarthritis	
	Temporal arteritis/polymyalgia rheumatica	
	Polychondritis	
	Fibromyalgia	
	Osteoporosis	
	Systemic lupus erythematosus	
	Dermatomyositis	
	Sjögren syndrome	
	Other chronic dermatological or musculoskeletal condition:	
	Other chronic dermatological or musculoskeletal condition:	

Organ System	Diagnosis	Comment
Neurological	Cerebrovascular disease (transient ischemic attack/stroke/hemorrhage)	
	Dementia	
	Parkinson disease	
	Non-Parkinsonian movement disorder (eg, ataxia/chorea)	
	Leukodystrophic disorders	
	Amyotrophic lateral sclerosis	
	Multiple sclerosis	
	Demyelinating disease	
	Guillain-Barré syndrome	
	Paralysis (eg, paraplegia/quadriplegia/hemiplegia)	
	Myelopathy	
	Cranial nerve disorder	
	Degenerative disk disease with nerve root compression	
	Migraine headaches	
	Seizure disorder	
	Secondary neuropathy (eg, diabetic/alcoholic/autoimmune)	
	Neurofibromatosis/tuberous sclerosis	
	Benign or malignant central nervous system tumor	
	Other chronic neurological condition:	
	Other chronic neurological condition:	
Endocrine/ Metabolic	Diabetes	
	Adrenal disorder	
	Thyroid disorder	
	Parathyroid disorder	
	Pheochromocytoma	
	Pituitary disorder	
	Hemochromatosis	
	Porphyria	
	Paget's disease	
	Endocrine or neuroendocrine tumor	
	Other chronic endocrine or metabolic condition:	
	Other chronic endocrine or metabolic condition:	

Organ System	Diagnosis	Comment
Psychiatric	Depression	
	Anxiety	
	Bipolar disorder	
	Paranoia	
	Schizophrenia	
	Neurosis	
	Personality disorder	
	Substance addiction/abuse	
	Posttraumatic stress disorder	
	Chronic fatigue syndrome	
	Other chronic psychiatric condition:	
	Other chronic psychiatric condition:	

Abbreviation: CIRS=Cumulative Illness Rating Scale

For each condition selected from the CIRS List of Comorbid Conditions, please rate the severity of that condition. For the severity rating, please use the scoring guidelines shown in the table below, considering the magnitude of symptoms, how manageable the condition is, and the extent of intervention required:

Score	Severity	Findings
1	Mild	Mild discomfort, symptoms or disability Easy to control Requiring either no therapy/medication or only as needed
2	Moderate	Moderate discomfort, symptoms or disability Manageable Requiring daily treatment or first-line therapy
3	Severe	Severe discomfort, symptoms or disability Hard to control Requiring second-line therapy or multiple medications
4	Extremely severe	Life threatening, permanently disabling disability, causing organ failure Poorly manageable Requiring urgent intervention or resistant to therapy

Abbreviation: CIRS=Cumulative Illness Rating Scale

Appendix 7. Schedule of Study Procedures

Period	Screen	Treatment																									Follow-up	
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25+		30 day	Long-term
Week	-4	0		2	4		6	8		10	12		14	16		18	20		22	24	30	36	42	48				
Study Day	Within -28 days	1	2	15	29	30	43	57	58	71	85	86	99	113	114	127	141	142	155	169	211	253	295	337	Q12 wks	End of Study	With-in +30 days	To +5 yrs
Visit Window			+1	±2	±2[a]	+1	±1	±2[a]	+1	±2	±3[a]	+1	±2	±2[a]	+1	±2	±2[a]	+1	±2	±3	±3	±3	±3	±3	±7			
Informed consent	X																											
Medical history	X																											
CIRS assessment	X																											
Serum virology	X																											
β-HCG (women of childbearing potential)	X	X			X			X			X			X			X			X	X	X	X	X	X	X		
CLL peripheral blood evaluation	X[d]																									X		
CLL serology	X																									X		
Coagulation	X																											
Urinalysis	X																											
12-lead ECG	X																											
Genotyping and expression analysis		X																								X		
IWRS	X	X			X			X			X			X			X			X	X	X	X	X	X	X		
HRQL/healthy utility – FACT-Leu/ EQ-5D		X			X			X			X			X			X			X	X	X	X	X	X	X		
Adverse events		X			X			X			X			X			X			X	X	X	X	X	X	X	X	
Concomitant medications		X			X			X			X			X			X			X	X	X	X	X	X	X	X	
Performance status	X	X			X			X			X			X			X			X	X	X	X	X	X	X		

Period	Screen	Treatment																								Follow-up	
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25+		30 day	Long-term
Week	-4	0		2	4		6	8		10	12		14	16		18	20		22	24	30	36	42	48				
Study Day	Within -28 days	1	2	15	29	30	43	57	58	71	85	86	99	113	114	127	141	142	155	169	211	253	295	337	Q12 wks	End of Study	With-in +30 days	To +5 yrs
Visit Window			+1	±2	±2[a]	+1	±1	±2[a]	+1	±2	±3[a]	+1	±2	±2[a]	+1	±2	±2[a]	+1	±2	±3	±3	±3	±3	±3	±7			
Oxygen saturation (by pulse oximetry)	X	X			X			X			X			X			X			X	X	X	X	X	X	X		
Physical exam (includes nodes, liver, spleen)	X	X			X			X			X			X			X			X	X	X	X	X	X	X		
Hematology/serum chemistry	X	X[b]		X[c]	X		X[c]	X		X[c]	X		X[c]	X		X[c]	X		X[c]	X	X	X	X	X	X	X		
Circulating cells/ biomarkers/ serum Igs/Immune monitoring		X			X			X			X			X			X			X	X	X	X	X	X	X[i]		
CMV viral load[j]																									X[j]			
HBV DNA by PCR[f]		X[f]			X[f]			X[f]			X[f]			X[f]			X[f]			X[f]		X[f]		X[f]	X[f]	X[f]	X[f]	X[f]
Idelalisib/ placebo administration in clinic		X			X			X			X			X			X			X								
Premedication		X	X		X	X		X	X		X	X		X	X		X	X											
Rituximab administration		X			X			X			X			X			X												
Bendamustine administration		X	X		X	X		X	X		X	X		X	X		X	X											
PJP prophylaxis[k]																									X[k]	X[k]		
CD4+ T-cell count[k] (related to PJP prophylaxis)																										X[k]		

Period	Screen	Treatment																								Follow-up	
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25+		30 day	Long-term
Week	-4	0		2	4		6	8		10	12		14	16		18	20		22	24	30	36	42	48				
Study Day	Within -28 days	1	2	15	29	30	43	57	58	71	85	86	99	113	114	127	141	142	155	169	211	253	295	337	Q12 wks	End of Study	Within +30 days	To +5 yrs
Visit Window			+1	±2	±2[a]	+1	±1	±2[a]	+1	±2	±3[a]	+1	±2	±2[a]	+1	±2	±2[a]	+1	±2	±3	±3	±3	±3	±3	±7			
Assess rituximab infusion severity and duration		X			X																							
Idelalisib pharmacokinetics		X			X			X			X			X			X			X								
Idelalisib/ placebo dispensing/ accounting		X									X									X		X		X	X	X		
Radiology assessment (CT/MRI)	X[d]										X[g]									X[g]		X[g]		X[g]	X[g,l]	X[a, h]		
Bone marrow biopsy/ aspirate	X[e]										X[e]									X[e]		X[e]		X[e]	X[e]			
Post-treatment CLL therapy																												X
Long-term follow-up																												X

a Windows for the specified clinic visits may be extended to account for delayed recovery from drug-related adverse events (eg, myelotoxicity)

b Hematology will be assessed locally at Visit 2, in addition to the central lab assessment, so that results will be available if the central lab results are compromised

c More frequent (eg, weekly) hematology/serum chemistry assessments may be appropriate in subjects experiencing Grade ≥3 myelosuppression or ALT/AST elevations Throughout the study, local lab results may be requested in the event central laboratory results are not available for assessment of disease response, progression, safety monitoring, or the evaluation of a significant event

d Radiology assessment (CT/MRI) if performed within <6 weeks of randomization and assessed to be adequate by the IRC and CLL peripheral blood evaluation if performed within <12 weeks of randomization and assessed to be adequate by the central lab do not need to be repeated

e A bone marrow biopsy/aspirate demonstrating CLL involvement following the last therapy must be available if Grade >2 neutropenia, thrombocytopenia, or anemia is present at screening, or at investigator discretion to determine extent of CLL involvement and bone marrow cellularity. Post-screening, to be performed to confirm response category in subjects with potential CR or to confirm a hematologically-based disease progression

f Only subjects who are HBc antibody positive and HBV DNA negative at screening. Subjects will be tested monthly for the duration of rituximab therapy and every 3 months thereafter for 1 year from the last dose of rituximab per Section 5.4.3.

g CT or MRI imaging of neck, chest, abdomen, and pelvis within 1 week prior to the study visit; assessment should be done even if study drug has been interrupted
h An end-of-study CT/MRI tumor assessment should be performed unless the subject already has radiographic confirmation of definitive disease progression or a CT/MRI has been performed within 4 weeks prior to the end of study visit.
i Circulating cells/serum Igs/Immune monitoring should be performed at the the End of Study visit.
j CMV viral load should be performed approximately every 4 weeks throughout idelalisib treatment. If unequivocal clinical or laboratory evidence of CMV infection is present, refer to Section 5.4.5 ("Infectious Events") for required actions.
k PJP prophylaxis: subjects must receive trimethoprim-sulfamethoxazole or other established prophylaxis for PJP throughout the course of idelalisib treatment and for 2 to 6 months following the last dose of idelalisib as specified in Section 5.4.5 ("Infectious Events").
l As of Amendment 10, Version 11, CT/MRI assessments will no longer be performed at the every 12 week scheduled visits, and will only be performed at the time of clinically-suspected disease progression or at study discontinuation.

Abbreviations: β-HCG=beta human chorionic gonadotropin, CIRS=chronic illness rating scale, CLL=chronic lymphocytic leukemia, CR=complete response, CT=computed tomography, CMV=cytomegalovirus, ECG=electrocardiogram, EQ-5D=EuroQoL Five-Dimension, FACT-Leu=Functional Assessment of Cancer Therapy-Leukemia, HRQL= health-related quality of life, Ig=immunoglobulin, IWRS=interactive web response system, MRI= magnetic resonance imaging, PJP= *Pneumocystis jirovecii* pneumonia.