CLINICAL STUDY PROTOCOL

Study Title:	A Phase 3, Double-Blind Extension Study Evaluating the Efficacy and Safety of Two Different Dose Levels of Single-Agent Idelalisib (GS-1101) for Previously Treated Chronic Lymphocytic Leukemia *A Companion Trial to Study GS-US-312-0116: A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Efficacy and Safety of Idelalisib (GS-1101) in Combination with Rituximab for Previously Treated Chronic Lymphocytic Leukemia*
Sponsor:	Gilead Sciences, Inc. 199 East Blaine Street Seattle, WA 98102 USA 333 Lakeside Drive Foster City, CA 94404 USA
IND Number:	101254
EudraCT Number:	2011-006293-72
Indication:	Chronic Lymphocytic Leukemia
Protocol ID:	GS-US-312-0117
Gilead Sciences Medical Monitor:	Name: PPD Telephone: PPD Office Fax: PPD Mobile Telephone: PPD E-mail: PPD
Protocol Version/Date:	Version 1.0 (Original) 23 January 2012 Version 2.0 (Amendment 1) 23 January 2013 Version 3.0 (Amendment 2) 10 September 2013 Version 4.0 (Amendment 3) 16 December 2013 Version 5.0 (Amendment 4) 27 May 2014 Version 6.0 (Amendment 5) 10 October 2014 Version 7.0 (Amendment 6) 28 March 2016 Version 8.0 (Amendment 7) 05 August 2016 Version 9.0 (Amendment 8) 24 October 2016 Version 10.0 (Amendment 9) 21 September 2017

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PROTOCOL SYNOPSIS

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Study Title:	A Phase 3, Double-Blind Extension Study Evaluating the Efficacy and Safety of Two Different Dose Levels of Single-Agent Idelalisib (GS-1101) as Therapy for Patients with Previously Treated Chronic Lymphocytic Leukemia *A Companion Study to Study GS-US-312-0116: A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Efficacy and Safety of Idelalisib (GS-1101) in Combination with Rituximab as Therapy for Patients with Previously Treated Chronic Lymphocytic Leukemia*
Study Centers Planned:	Approximately 90 centers in the United States and in Europe
IND Number:	101254
EudraCT Number:	2011-006293-72
Objectives:	• To evaluate the effect of idelalisib (formerly GS-1101) on the onset, magnitude, and duration of tumor control • To compare tumor control in subjects receiving rituximab alone in Study GS-US-312-0116 to that observed in the same subjects when receiving the standard dose of idelalisib alone in Study GS-US-312-0117 • To assess the effect of idelalisib on measures of subject well-being, including overall survival (OS), health-related quality of life (HRQL), and performance status • To assess the effects of idelalisib on disease-associated biomarkers and to evaluate potential mechanisms of resistance to idelalisib • To characterize exposure to idelalisib as determined by treatment administration and evaluation of idelalisib plasma concentrations over time • To describe the safety profile observed with idelalisib • To estimate health resource utilization associated with administration of idelalisib

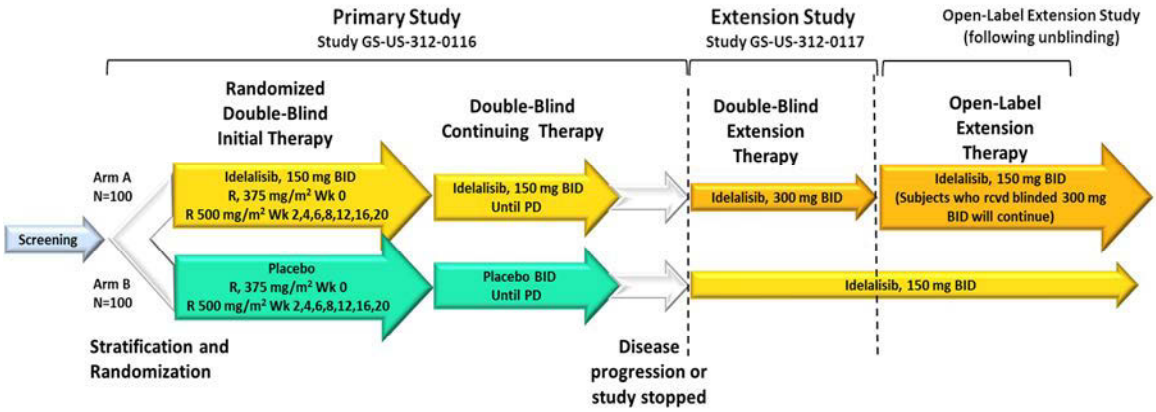
Study Design:

This study is being conducted as part of an overall clinical program evaluating the efficacy and safety of idelalisib in the therapy of patients with previously treated chronic lymphocytic leukemia (CLL).

Within this program, the primary clinical trial (Study GS-US-312-0116) is a Phase 3, multicenter, 2-arm, randomized, double-blind, placebo-controlled, parallel-group study.

This clinical trial (Study GS-US-312-0117) is a separate, multicenter, 2-arm, double-blind, parallel-group extension study that is a companion trial to Study GS-US-312-0116; in this trial, compliant subjects from GS-US-312-0116 who are tolerating primary study therapy but experience definitive CLL progression are eligible to receive active blinded idelalisib therapy at the standard dose or a higher dose, with allocation based on the original primary study randomization. In the event GS-US-312-0116 is stopped early due to overwhelming efficacy following an interim analysis or at the final analysis, subjects who are on Study GS-US-312-0116 at that time may transition to GS-US-312-0117. Additionally, GS-US-312-0117 will become an open-label study offering idelalisib 150 mg BID to GS-US-312-0116 subjects who were randomized to placebo, and subjects randomized to idelalisib will continue idelalisib at 150 mg BID.

Study Schema:



Treatment Groups

Blinded Portion

- Arm A: Idelalisib + rituximab (Study GS-US-312-0116)
  ⇒high-dose idelalisib (300 mg BID) (Study GS-US-312-0117)
- Arm B: Placebo + rituximab (Study GS-US-312-0116)
  ⇒standard-dose idelalisib (150 mg BID) (Study GS-US-312-0117)

	Open-Label Extension Portion (following unblinding) • Arm A: subjects already on 300 mg BID will continue, and newly enrolled subjects will receive 150 mg BID • Arm B: subjects already on 150 mg BID will continue, and newly enrolled subjects will receive 150 mg BID Treatment Assignment • Assignment to Arm A or Arm B with allocation based on the original primary study randomization • Implementation through an interactive web response system (IWRS) Stratification Not applicable for Study GS-US-312-0117
Number of Subjects Planned:	Total of up to ~180 subjects (up to ~90 subjects per treatment arm)
Target Population:	Subjects in the primary Phase 3 study (GS-US-312-0116) who are compliant, are tolerating primary study therapy, and 1) have definitive progression of CLL while receiving primary study drug therapy (idelalisib/placebo) or 2) are actively participating in Study GS-US-312-0116 at the time the study is stopped, including if stopped early due to overwhelming efficacy following an interim analysis.
Duration of Treatment:	Study drug 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. Idelalisib administration will be continued only in subjects whose benefit-risk profile is deemed positive by the investigator.
Diagnosis and Main Eligibility Criteria:	Inclusion Criteria Subjects must meet all of the following conditions to be eligible for enrollment into the study: 1) Participation in Study GS-US-312-0116. 2) Occurrence of confirmed, definitive CLL progression while receiving study drug therapy (idelalisib /placebo) in Study GS-US-312-0116. ***Note: Definitive disease progression is CLL progression based on standard criteria and occurring for any reason (ie, increasing lymphadenopathy, organomegaly, or bone marrow involvement; decreasing platelet count, hemoglobin, or neutrophil count; or worsening of disease-related symptoms) other than lymphocytosis***. ***Subjects must have confirmation by the sponsor working in collaboration with an independent review committee (IRC) that the disease has progressed on the primary clinical trial (Study GS-US-312-0116) before receiving secondary idelalisib therapy on this extension trial (Study GS-US-312-0117).***

3) 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]).
4) Permanent cessation of Study GS-US-312-0116 treatment (rituximab and/or idelalisib/placebo) and no intervening or continuing therapy (including radiotherapy, chemotherapy, immunotherapy, or investigational therapy) for the treatment of CLL. ***Note: Subjects may receive corticosteroids to manage CLL manifestations.***
5) The time from permanent cessation of Study GS-US-312-0116 treatment (rituximab and/or idelalisib/placebo) and the initiation of Study GS-US-312-0117 therapy is ≤12 weeks. ***Note: Study procedures performed as part of Study GS-US-312-0116 need not be repeated and can be used as screening procedures for Study GS-US-312-0117 if performed within 4 weeks prior to initiation of study drug therapy on Study GS-US-312-0117.***
6) Karnofsky performance score of ≥40.
7) Required baseline laboratory data (within 4 weeks prior to initiation of study treatment) as shown in the table below. ***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. Subjects with any degree of neutropenia, thrombocytopenia, or anemia due to CLL or prior therapy may enroll.***

Required Screening Laboratory Values

Organ System	Parameter	Required Value
Hepatic	Serum total bilirubin	≤1.5 x ULN (unless elevated due to Gilbert's syndrome)
	Serum ALT	≤2.5 x ULN
	Serum AST	
Renal	eC_{Cr} [a]	>30 ml/min
Pregnancy	β-HCG [b]	Negative

a As calculated by the Cockcroft-Gault formula {Cockcroft 1976}
b 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, AST=aspartate aminotransferase, eC_{Cr}=estimated creatinine clearance, ULN=upper limit of normal

8) 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. ***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 β-HCG), or is menopausal (defined as age ≥54 years with amenorrhea for >12 months or amenorrhea for >6 months with serum estradiol and FSH levels within the institutional postmenopausal range).***

9) For male subjects of childbearing potential having intercourse with females of childbearing potential, willingness to use a protocol-recommended method of contraception from the start of study drug (Visit 2) throughout the study and for 90 days following the last dose of study drug and to refrain from sperm donation from the start of study drug (Visit 2) throughout the study and for 90 days following the last dose of study drug. ***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®]).***

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

11) 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***.

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

Exclusion Criteria

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

1) Known histological transformation from CLL to an aggressive lymphoma (ie, Richter transformation).
2) Evidence of ongoing systemic bacterial, fungal, or viral infection at the time of the start of study treatment (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; anti-pneumocystis prophylaxis is encouraged.***
3) Pregnancy or breastfeeding.
4) Intentional breaking of the blind in Study GS-US-312-0116 by the investigator or the study subject.
5) Concurrent participation in another therapeutic clinical trial.
6) 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.

In the event Study GS-US-312-0116 is stopped early, subjects who are actively participating in Study GS-US-312-0116 will become eligible for this study, provided the following inclusion are met:

1) Participation in Study GS-US-312-0116 within 12 weeks of enrollment onto GS-US-312-0117.
2) 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.
3) For male subjects of childbearing potential having intercourse with females of childbearing potential, willingness to use a protocol-recommended method of contraception from the start of study drug (Visit 2) throughout the study and for 90 days following the last dose of study drug and to refrain from sperm donation from the start of study drug (Visit 2) throughout the study and for 90 days following the last dose of study drug.
4) In the judgment of the investigator, participation in the protocol offers an acceptable benefit-to-risk ratio when considering current CLL disease status, medical condition, and the potential benefits and risks of alternative treatments for CLL.

	5) 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.*** 6) 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.
Study Procedures/ Frequency:	Clinic/laboratory visits will occur every 2 weeks for the first 12 weeks, every 4 weeks between Weeks 12 and 24, and every 6 weeks between Weeks 24 and 48. Subjects continuing on study drug past Week 48 will have clinic visits every 12 weeks. Subjects will be assessed for safety at each visit. Subjects will be assessed for CLL disease status by physical and laboratory examinations at each visit and by CT or MRI at Weeks 8, 16, 24, 36, and 48 and every 12 weeks thereafter. As of Amendment 9, Version 10, 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. Following unblinding of the study: • Subjects who were randomized to idelalisib on Study GS-US-312-0116 and who received ≥ 24 weeks idelalisib will complete Visit 16+ twelve weeks from the date of their last radiology assessment (CT/MRI) and study visits will continue every 12 weeks thereafter. Visits 3 through 15 will not be required. • Subjects who have received < 24 weeks idelalisib will have all Study GS-US-312-0117 assessments completed per the Schedule of Procedures until they have received idelalisib for 24 weeks cumulative across both studies. After completion of 24 weeks of cumulative idelalisib treatment, Visit 16+ will be conducted 12 weeks from the date of their last radiology assessment (CT/MRI), after which time study visits will occur every 12 weeks.
Test Therapy, Dose, and Mode of Administration:	Blinded Portion • Arm A: Idelalisib, 300 mg/dose BID starting on Day 1 and administered continuously thereafter; the study drug will be provided as 2 tablets of active idelalisib for oral administration • Arm B: Idelalisib, 150 mg/dose BID starting on Day 1 and administered continuously thereafter; the study drug will be provided as 1 tablet of active idelalisib and 1 tablet of placebo for oral administration

	Open-Label Extension Portion (following unblinding) • Arm A: subjects already on 300 mg BID will continue, and newly enrolled subjects will receive 150 mg BID • Arm B: subjects already on 150 mg BID will continue, and newly enrolled subjects will receive 150 mg BID ***Note: At the Investigator's discretion, subjects who were randomized to placebo on study GS-US-312-0116 may delay initiation of idelalisib following enrollment on Study GS-US-312-0117 until the time of disease progression or until the investigator determines that the subject would benefit from initiation of idelalisib treatment***
Reference Therapy, Dose, and Mode of Administration:	Not applicable
Criteria for Evaluation:	*Tumor Control* • Progression-free survival (PFS) – defined as the interval from the start of study therapy 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 • 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 • Time to response (TTR) – defined as the interval from start of study therapy to the first documentation of CR or PR • Duration of response (DOR) – defined as the interval from the first documentation of CR or PR to the earlier of the first documentation of definitive disease progression or death from any cause • Percent change in lymph node area – defined as the percent change from baseline in the SPD of index lymph nodes • Splenomegaly response rate – defined as the proportion of subjects with baseline splenomegaly who achieve an on-study normalization or a 50% decrease (minimum 2 cm) from baseline in the enlargement of the splenic LVD (by imaging)

- Hepatomegaly response rate – defined as the proportion of subjects with baseline hepatomegaly who achieve an on-study normalization or a 50% decrease (minimum 2 cm) from baseline the hepatic longest vertical dimension (LVD) (by imaging)
- ALC response rate – defined as the proportion of subjects with baseline lymphocytosis (ALC≥4 x 10^9/L) who achieve an on-study ALC <4 x 10^9/L or demonstrate a ≥50% decrease in ALC from baseline (ALC values within 4 weeks post-baseline will be excluded from the ALC response rate evaluation)
- Platelet response rate – defined as the proportion of subjects with baseline thrombocytopenia (platelet count <100 x 10^9/L) who achieve an on-study platelet count ≥100 x 10^9/L or demonstrate a ≥50% increase in platelet count from baseline without need for exogenous growth factors (Platelet values within 4 weeks post-baseline or within 8 days post transfusion will be excluded from the platelet response rate evaluation)
- Hemoglobin response rate – defined as the proportion of subjects with baseline anemia (hemoglobin <110 g/L [11.0 g/dL]) who achieve an on-study hemoglobin ≥110 g/L (11.0 g/dL) or demonstrate a ≥50% increase in hemoglobin from baseline without red blood cell transfusions or need for exogenous growth factors (eg erythropoietin)
- Neutrophil response rate – defined as the proportion of subjects with baseline neutropenia (absolute neutrophil count [ANC] ≤1.5 x 10^9/L) who achieve an ANC >1.5 x 10^9/L or demonstrate a ≥50% increase in ANC from baseline without need for exogenous growth factors (eg, G-CSF)

Patient Well-Being

- Overall survival (OS) – defined as the interval from start of study therapy to death from any cause
- Change from baseline in HRQL domain and symptom scores based on the Functional Assessment of Cancer Therapy: Leukemia (FACT-Leu) (See Appendix 2)
- Changes from baseline in Karnofsky performance status (See Appendix 3)

Pharmacodynamic Markers of Drug Activity and Resistance

- Changes from baseline in PI3K/AKT/mTOR pathway activation as a measure of PI3Kδ pathway activity
- Changes from baseline in the plasma concentrations of disease-associated chemokines and cytokines

Exposure

- Study drug administration as assessed by prescribing records and compliance as assessed by quantification of used and unused drug
- Trough (pre-dose) and peak (~1.5-hour samples) of idelalisib plasma concentrations as assessed by a validated bioanalytical method

Safety

- Overall safety profile of each regimen characterized by the type, frequency, severity, timing of onset, duration, and relationship to study therapy of any adverse events or abnormalities of laboratory tests; serious adverse events; or adverse events leading to discontinuation of study drug

Pharmacoeconomics

- Change in health status – defined as the change from baseline in overall health and single-item dimension scores as assessed using the EuroQoL Five-Dimension (EQ-5D) utility measure
- Health resource measures, including resource utilization, total costs, and measures of cost per unit of benefit (eg, cost per additional progression-free month, cost per quality-adjusted life-year)

Statistical Methods: Appropriate data analysis sets will be defined. The intent-to-treat (ITT) analysis set will include data from all subjects who receive ≥1 dose of any study therapy on this study; in this data set, study drug assignment (high-dose or standard-dose idelalisib) will be designated according to the planned allocation to this study. A safety analysis set will comprise data from subjects in the ITT analysis set with treatment assignments designated according to the actual study drug (high-dose or standard-dose idelalisib) received. Other analysis sets [per-protocol (PP) and pharmacodynamic/pharmacokinetic analysis sets] 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 independent review committee (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 endpoints relating to tumor control, patient well-being, and biomarkers, analyses will be done based on ITT, PP or pharmacodynamic data sets, as appropriate. Blinded portion of the study analyses will be presented in the following two groups:

- IDELA 300 mg BID: Subjects who have PD per IRC confirmation in Arm A of Study GS-US-312-0116 and subsequently enroll into Study GS-US-312-0117 to receive IDELA 300 mg BID during the double-blind portion of the study
- Placebo in GS-US-312-0116 + IDELA 150 mg BID in GS-US-312-0117: Subjects who have PD per IRC confirmation in Arm B of Study GS-US-312-0116 and subsequently enroll in Study GS-US-312-0117 to receive IDELA 150 mg BID during the double-blind portion of the study.

After unblinding, open-label extension study analyses will be presented in the following 4 groups:

- IDELA 150 mg BID: Subjects who are randomized to Arm A in Study GS-US-312-0116 and transition to Study GS-US-312-0117 during the open-label portion of the study to continue IDELA 150 mg BID
- Placebo in GS-US-312-0116 + IDELA 150 mg BID (open-label): Subjects who are randomized to Arm B in Study GS-US-312-0116 and transition to receive IDELA 150 mg BID during the open-label portion of the study
- IDELA 300 mg BID: Subjects who have PD per IRC confirmation in Arm A of Study GS-US-312-0116 and subsequently enroll Study GS-US-312-0117 to receive IDELA 300 mg BID during the double-blind portion of the study
- Placebo in GS-US-312-0116 + IDELA 150 mg BID in GS-US-312-0117: Subjects who have PD per IRC confirmation in Arm B of Study GS-US-312-0116 and subsequently enroll Study GS-US-312-0117 to receive IDELA 150 mg BID during the double-blind portion of the study. Analyses will focus on evaluation of outcomes within each treatment arm and will be descriptive in nature; formal comparisons of outcomes between arms are not planned. Time-to-event endpoints will be summarized using Kaplan-Meier methods; medians, ranges, and the corresponding 95% CI will be presented. Continuous and categorical variables will also be summarized as appropriate. Changes from baseline in categorical variables and changes from baseline in continuous endpoints will be analyzed using appropriate methods.

Efficacy outcomes among subjects receiving rituximab alone in Study GS-US-312-0116 will be evaluated relative to those same outcomes among the same subjects receiving standard-dose idelalisib alone in Study GS-US-312-0117.

Based on the safety analysis set, information 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

The sample size for this extension study is not based upon a formal statistical hypothesis. The upper bound of the sample size in this study is determined by the sample size of the preceding primary clinical trial (Study GS-US-312-0116) in which ~180 subjects (~90 per arm) are expected to be enrolled. Assuming a ~10% dropout rate during Study GS-US-312-0116 and a further ~10% dropout rate in the transition from the primary study to the extension study, ~180 subjects are expected to be enrolled into Study GS-US-312-0117.

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
CAL-101	Former name for GS-1101
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 Sciences Department of 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
PFS	progression-free survival
PI3K	phosphatidylinositol 3-kinase
PI3Kδ	phosphatidylinositol 3-kinase p110δ isoform
PJP	Pneumocystis jiroveci 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
PVC/PCTFE	polyvinyl chloride/polychlorotrifluoroethylene
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

SPD	sum of the products of the perpendicular diameters of measured lymph nodes
SSC	study steering committee
SJS	Stevens-Johnson Syndrome
SUSAR	suspected, unexpected, serious adverse reaction
SYK	spleen tyrosine kinase
$t_{1/2}$	half-life
TEN	Toxic Epidermal Necrolysis
T_{max}	time of maximum concentration
TTR	time to response
UGT	uridine 5'-diphospho-glucuronosyltransferase
ULN	upper limit of normal
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 neoplasia 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 Europe and the United States {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 younger and relatively healthy patients with CLL, chemoimmunotherapy regimens that include the anti-CD20 monoclonal antibody, rituximab, are commonly employed to control disease manifestations {Gribben 2011}. Such combination therapies are effective in providing durable remissions {Byrd 2005, Fischer 2011, Hallek 2010, Iannitto 2011, Robak 2010}. However, while rituximab is usually well tolerated {Gentile 2010}, the chemotherapeutic agents (typically fludarabine, cyclophosphamide, or bendamustine) in such regimens are acutely cytotoxic, induce permanent bone marrow compromise, and can cause secondary malignancies {Carney 2010, Kyasa 2004, Tam 2008}. Furthermore, in elderly patients or in those with comorbid conditions, such regimens are associated with less efficacy and greater toxicity {Eichhorst 2009b, Goede 2011, Tam 2008}.

Increasing attention has been paid to the problem of treating patients with CLL who have comorbidities. Because of the relatively late age of diagnosis, a large proportion (~90%) of patients with CLL have co-morbidities and a substantial proportion (~45%) have major chronic conditions such as coronary artery disease, diabetes, or chronic obstructive pulmonary disease {Thurmes 2008}. At the time the disease is first identified, ~25% of patients with CLL do not meet conventional criteria for participation in clinical studies containing cytotoxic agents {Thurmes 2008}. By the time treatment is necessary or during treatment for CLL, patients continue to advance in age and have new or worsening chronic conditions; as a result, the proportion of patients with comorbidities increases during the course of the illness. Such patients have been substantially underrepresented in clinical trials due to concerns regarding the ability of such patients to tolerate intensive chemoimmunotherapy {Eichhorst 2009a, Thurmes 2008}. Instruments such as the Cumulative Illness Rating Scale (CIRS) {Linn 1968} are now being applied in order to categorize patient populations as fit or relatively unfit and to evaluate regimens tailored to these groups of patients {Del Giudice 2011, Eichhorst 2009a, Hallek 2010}.

Health constraints in older or compromised patients have prompted noncytotoxic approaches to therapy. Alternative immunotherapeutics, such as the monoclonal antibodies, alemtuzumab {Keating 2002a} or ofatumumab {Wierda 2010}, have been developed. However the therapeutic

utility of these drugs is modest; median progression-free survival (PFS) values in patients with recurrent CLL have been 4.7 months and 5.8 months, respectively. Moreover, these treatments can have clinical liabilities. Alemtuzumab causes extreme immunosuppression that leads to frequent opportunistic infection. Administration of the large amounts of protein recommended in ofatumumab product labeling results in frequent infusion reactions and cumbersome infusion schedules.

In view of these issues, repeated use of rituximab monotherapy or rituximab-corticosteroid combinations have been advocated in treatment guidelines for older or frail patients with recurrent CLL {Eichhorst 2010, Zelenetz 2011}. While single-agent rituximab use can offer palliative benefit with good tolerability in some patients with previously treated CLL, tumor control is not lasting, especially in patients with bulky adenopathy {Gentile 2010}. Addition of high-dose corticosteroids to rituximab can extend median PFS up to 12 months, but this combination is commonly associated with severe hyperglycemia and frequent life-threatening or fatal infections {Bowen 2007, Dungarwalla 2008}. New, noncytotoxic, well-tolerated, and convenient therapies that can successfully be combined with rituximab or given as single-agent therapy are needed in order to enhance and prolong tumor control in patients with comorbid conditions.

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/mTOR 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 (also known as GS-1101), 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 (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 (the major 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 (only circulating metabolite and 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), (KI = 0.18 μM, kinact = 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).

Any potential clinical implications of these metabolism studies were evaluated in a formal drug-drug interaction study (GS-US-313-0130) which evaluated the effect of idelalisib on cytochrome P450 3A and the drug transporters P-gp, OATP1B1, and OATP1B3.
Study GS-US-313-0130 also evaluated the impact of an inducer of metabolizing enzymes and transporters (rifampin) on the PK of idelalisib in healthy human subjects. 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 were 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 metabolized in humans primarily 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, which is not considered to be clinically relevant and suggesting that idelalisib is a weak CYP3A substrate. 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, the only circulating metabolite observed in human plasma, 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 of 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

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]). Subject 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 x 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 analyses indicated that the increase in C_{max} and AUC_{0-6h} with dose was less than dose-proportional, with modest 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 a 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. The median DOR has not been reached in subjects with iNHL; 19 subjects continued to receive idelalisib in a long-term extension study. The median [range] DOR was 2.7 months [1 month to 8 months] in subjects with MCL; 6 MCL subjects continued to receive idelalisib in a long-term extension study.

In subjects with CLL, idelalisib reduced lymphadenopathy in almost all subjects; 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 in some subjects; increases were maximal during the first 2 cycles and decreased thereafter; the pattern suggested drug-mediated lymphocyte redistribution. In 54 subjects with CLL, 39/54 (72%) achieved a PR (includes PR with lymphocytosis). The median DOR was not reached; 23 subjects continued to receive idelalisib in a long-term extension study.

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 rituximab to subjects with recurrent iNHL or CLL {Brown 2011, Leonard 2011}.

In this study, rituximab was administered at a standard dose of 375 mg/m^2 per infusion weekly for 8 weeks in all subjects. Idelalisib was started simultaneously with the rituximab, first at a dose level of 100 mg/dose BID (n=13) and then at a dose level of 150 mg/dose BID (n=12) and was administered continuously to both subjects with CLL (n=13) and subjects with iNHL (n=12) 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 63 and ranged to 85 years. Bulky tumors (≥1 lymph node ≥5 cm in diameter) were present in 63% of the subjects. The median number of prior therapies by disease was 2 and ranged up to 8 prior treatments. All had received prior rituximab and the majority had received prior fludarabine or alkylating agents. Approximately one-third 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 5 cycles, ranging up to 12 cycles (ie, 48 weeks).

No idelalisib-related dose-limiting toxicities were observed within the tested subject cohorts. Grade 3-4 adverse events largely comprised background events resulting from pre-existing disease- or treatment-related conditions or from intercurrent illness. Among subjects with CLL, 2 (15%) developed pneumonia. For subjects receiving idelalisib together with rituximab, Grade 3-4 elevations in ALT/AST were not observed in those with CLL, although 3 subjects (25%) of those with iNHL had such events.

The idelalisib plus rituximab combination showed a high level of antitumor activity in both subjects with CLL and those with iNHL. Altogether 92% of subjects with CLL receiving the combination of idelalisib and rituximab had reductions in nodal size and 77% showed a lymph node response (≥50% reduction in index nodal lesions). Although concomitant administration of rituximab did not eliminate the redistribution lymphocytosis that is associated with idelalisib, it blunted the magnitude of the change. As a result, the overall response rate (ORR) was also 77% among subjects participating in this study. At the time of last data analysis, PFS through 48 weeks was 70% and a median PFS had not yet been observed.

Collectively, the emerging data from this study support further evaluation of idelalisib together with rituximab in subjects with CLL and indicate that co-administration of idelalisib with 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 program to evaluate the efficacy and safety of idelalisib in patients with previously treated, recurrent CLL. Collectively the data derived from the primary clinical trial (Study GS-US-312-0116) and from this extension trial (Study GS-US-312-0117) address the activity of idelalisib together with rituximab, the activity of idelalisib when given alone, and the potential for dose-dependent restoration of drug activity in subjects who have disease that appears to be drug resistant.

The design and conduct of this clinical trial program 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 of older patients that requires sequential treatment with agents that provide alternative mechanisms of tumor control. Existing cytotoxic agents have serious acute and chronic toxicities, making them less suitable for frail or unfit patients. Single-agent rituximab can offer disease palliation with good tolerability in some patients with relapsed CLL but tumor control is not lasting, especially in patients with bulky adenopathy. Development of a non-cytotoxic combination therapy of idelalisib with rituximab or a monotherapy regimen of idelalisib that can address disease pathogenesis with a new mechanism of action and might offer complementary nodal and peripheral blood activity would address an unmet medical need, particularly when applied in patients with substantial comorbidities or myelosuppression from prior chemotherapies.

- 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 monotherapy or of idelalisib plus rituximab in patients with relapsed or refractory CLL is supported by the observed antitumor activity of idelalisib - given alone or in combination with rituximab - in patients with heavily pretreated CLL and iNHL.

- The safety of advancing development of the idelalisib monotherapy and of a regimen of idelalisib plus rituximab in this Phase 3 clinical trial program 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 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 program, subjects will be continued on therapy until the occurrence of definitive disease progression, ie, disease progression that is manifest by worsening CLL-related signs or symptoms 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 program.

- 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 program.

- 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 program is justified.

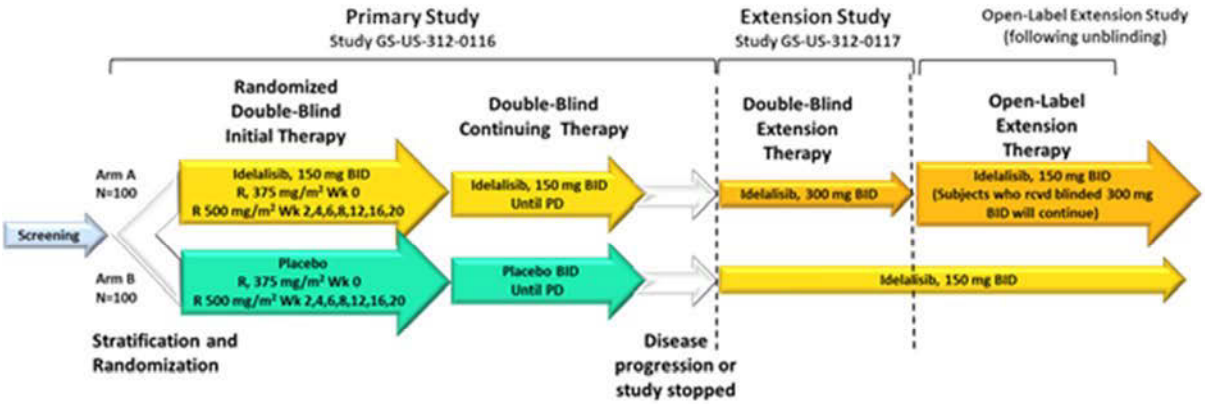
The rationale for specific design features is provided in relevant sections of the protocol, including Section 3.2 (Endpoint Selection Rationale), Section 2.2 (Design Rationale), Section 4.3 (Enrollment Criteria Rationale), Section 5.10 (Study Treatment Rationale), and Section 6.5 (Study Procedure Rationale).

2. STUDY DESIGN

2.1. Design Overview and Study Schema

This study is being conducted as part of an overall-clinical program that is evaluating the efficacy and safety of idelalisib in the therapy of patients with previously treated CLL (see Figure 2-1). Within this program, the primary clinical trial (Study GS-US-312-0116) is a Phase 3, multicenter, 2-arm, randomized, double-blind, placebo-controlled, parallel-group study. This clinical trial (Study GS-US-312-0117) is a separate, multicenter, 2-arm, double-blind, parallel-group extension study that is a companion study to the primary study.

Figure 2-1. Study Design



Candidates for the primary study will be adults with previously treated recurrent CLL who have measurable lymphadenopathy, require therapy for CLL, have experienced CLL progression <24 months since the completion of the last prior therapy, and are currently not sufficiently fit to receive cytotoxic therapy because of chemotherapy-induced bone marrow damage or comorbidities.

Primary study 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 any prior therapy with an anti-CD20 therapeutic monoclonal antibody (yes vs no) and randomized in a 1:1 ratio to receive 1 of the 2 treatment arms.

In the primary study, subjects will be administered rituximab intravenously in the clinic starting at a dose of 375 mg/m^2 on Day 1 (Week 0) and will continue with a dose of 500 mg/m^2 on Day 15 (Week 2), Day 29 (Week 4), Day 43 (Week 6), Day 57 (Week 8), Day 85 (Week 12), Day 113 (Week 16), Day 141 (Week 20) (for a total of 8 infusions). Rituximab will be administered until the earliest of subject withdrawal from study, definitive progression of CLL, intolerable rituximab-related toxicity, pregnancy, substantial noncompliance with study procedures, study discontinuation, or a maximum of 8 infusions.

Idelalisib or placebo will be taken orally, BID continuously. Subjects will continue whichever study drug (idelalisib/placebo or rituximab) continues to be tolerated, even if the other drug has been discontinued due to toxicity.

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.

Compliant subjects who are tolerating therapy but who develop definitive disease progression in the primary clinical trial (Study GS-US-312-0116) can consider enrollment in this separate companion extension trial (Study GS-US-312-0117). In the extension trial, subjects will take active blinded idelalisib therapy, either at a higher starting dose or at the standard starting dose, with allocation based on the original primary study randomization. Following unblinding of Study GS-US-312-0116, subjects will be allowed to enter Study GS-US-312-0117 in the absence of evidence of disease progression and will take 150 mg BID idelalisib regardless of treatment assignment in Study GS-US-312-0116.

The primary objective of Study GS-US-312-0116 will be to evaluate the effect of the addition of idelalisib to rituximab on PFS. Secondary and tertiary objectives will focus on determining the effect of the addition of idelalisib to 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. In Study GS-US-312-0117, the same endpoints will be assessed as in Study GS-US-312-0116; the focus of the analysis will be largely descriptive except for the within-subject assessment of treatment effects among subjects receiving first rituximab alone and then idelalisib alone on Arm B of each trial. No formal comparisons of outcomes in Arm A vs Arm B are planned within Study GS-US-312-0117.

2.2. Design Rationale

The randomized, add-on design for the primary trial (Study GS-US-312-0116) 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 a companion antineoplastic agent, 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.

This separate extension trial (Study GS-US-312-0117) enhances subject acceptance of randomization in the primary study and provides further information regarding idelalisib efficacy, resistance, and safety. Among subjects in Arm A, escalation to a higher dose level allows evaluation of dose-dependent resistance and a determination if a higher dose can reestablish disease control. The safety data obtained in these subjects will add to the overall safety database. Among subjects randomized to Arm B in the primary study, evaluation of idelalisib at a starting dose of 150 mg/dose BID in the extension study may permit a within-subject assessment of the treatment effects with single-agent idelalisib relative to the effects previously observed with rituximab alone. Of importance, the extension study maintains

the partial blinding of the primary study, thus minimizing the bias that might occur if the overall design entailed only a 1-way crossover to open-label idelalisib among subjects who had received placebo on Arm B of the primary study. To ensure confirmation of disease progression, tumor size data collected from the primary study will be subjected to independent review by an independent review committee (IRC) (see Section 10.4.2); subjects will continue with study therapy pending confirmation of progression status by the sponsor working in collaboration with the IRC. Subjects must have confirmation that the disease has progressed on the primary study before being permitted to receive secondary idelalisib therapy on the extension study, or in the event the primary study is stopped, subjects who have not yet progressed may enroll on the extension study to receive 150 mg BID idelalisib.

3. OBJECTIVES AND ENDPOINTS

- To evaluate the effect of idelalisib on the onset, magnitude, and duration of tumor control
- To compare tumor control in subjects receiving rituximab alone in Study GS-US-312-0116 to that observed in the same subjects when receiving the standard dose of idelalisib alone in Study GS-US-312-0117
- To assess the effect of idelalisib on measures of subject well-being, including overall survival (OS), health-related quality of life (HRQL), and performance status
- To assess the effects of idelalisib on disease-associated biomarkers and to evaluate potential mechanisms of resistance to idelalisib
- To characterize exposure to idelalisib as determined by treatment administration and evaluation of idelalisib plasma concentrations over time
- To describe the safety profile observed with idelalisib
- To estimate health resource utilization associated with administration of idelalisib

3.1. Endpoints

3.1.1. Tumor Control

- Progression-free survival (PFS) – defined as the interval from the start of study therapy 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
- 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 lymph nodes
- CR rate – defined as the proportion of subjects who achieve a CR
- Time to response (TTR) – defined as the interval from start of study therapy to the first documentation of CR or PR
- Duration of response (DOR) – defined as the interval from the first documentation of CR or PR to the earlier of the first documentation of definitive disease progression or death from any cause

- Percent change in lymph node area – defined as the percent change from baseline in the sum of the products of the greatest perpendicular diameters (SPD) of index lymph nodes

- Splenomegaly response rate – defined as the proportion of subjects with baseline splenomegaly who achieve an on-study normalization or a 50% decrease (minimum 2 cm) from baseline in the enlargement of the splenic LVD (by imaging)

- Hepatomegaly response rate – defined as the proportion of subjects with baseline hepatomegaly who achieve an on-study normalization or a 50% decrease (minimum 2 cm) from baseline in the hepatic longest vertical dimension (LVD) (by imaging)

- ALC response rate – defined as the proportion of subjects with baseline lymphocytosis (ALC≥4 x 10^9/L) who achieve an on-study ALC <4 x 10^9/L or demonstrate a ≥50% decrease in ALC from baseline; ALC values within 4 weeks post-baseline will be excluded from the ALC response rate evaluation

- Platelet response rate – defined as the proportion of subjects with baseline thrombocytopenia (platelet count <100 x 10^9/L) who achieve an on-study platelet count ≥100 x 10^9/L or demonstrate a ≥50% increase in platelet count from baseline; platelet values within 4 weeks post-baseline or after 8 days post transfusion will be excluded from the platelet response rate evaluation

- Hemoglobin response rate – defined as the proportion of subjects with baseline anemia (hemoglobin <110 g/L [11.0 g/dL]) who achieve an on-study hemoglobin ≥110 g/L (11.0 g/dL) or demonstrate a ≥50% increase in hemoglobin from baseline; hemoglobin values within 4 weeks post-baseline or after 4 weeks of receiving packed cell/whole blood transfusion or after 6 weeks of receiving exogenous growth factors (e.g., Darbepoetin alfa) will be excluded for the hemoglobin response evaluation

- Neutrophil response rate – defined as the proportion of subjects with baseline neutropenia (absolute neutrophil count [ANC] ≤1.5 x 10^9/L) who achieve an ANC >1.5 x 10^9/L or demonstrate a ≥50% increase in ANC from baseline; ANC values within 4 weeks of post-baseline or after 2 weeks of receiving exogenous growth factors (e.g., Filgrastim, G-CSF, Lenograstim) or after 4 weeks of receiving Neulasta were excluded for response evaluation

3.1.2. Patient Well-Being

- Overall survival (OS) – defined as the interval from start of study therapy to death from any cause

- Change from baseline in HRQL domain and symptom scores based on the Functional Assessment of Cancer Therapy: Leukemia (FACT-Leu) (see Appendix 2)

- Changes from baseline in Karnofsky performance status – defined as the change from baseline in the performance status (see Appendix 3)

3.1.3. Pharmacodynamic Markers of Drug Activity and Resistance

- Changes from baseline in PI3K/AKT/mTOR pathway activation as a measure of PI3Kδ pathway activity
- Changes from baseline in the plasma concentrations of disease-associated chemokines and cytokines

3.1.4. Exposure

- Study drug administration as assessed by prescribing records and compliance as assessed by quantification of used and unused drug
- Trough (pre-dose) and peak (1.5-hour samples) of idelalisib plasma concentrations as assessed by a validated bioanalytical method

3.1.5. Safety

- Overall safety profile of each study treatment regimen characterized by the type, frequency, severity, timing of onset, duration, and relationship to study therapy of any adverse events or abnormalities of laboratory tests; serious adverse events; or adverse events leading to discontinuation of study drug

3.1.6. Pharmacoeconomics

- Change in health status – defined as the change from baseline in overall health and single-item dimension scores as assessed using the EuroQoL Five-Dimension (EQ-5D) utility measure (Appendix 4)
- Health resource measures, including resource utilization, total costs, and measures of cost per unit of benefit (eg, cost per additional progression-free month, cost per quality-adjusted life-year)

3.2. 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.

3.2.1. 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.

Endpoints of overall tumor control as evaluated in this trial are customarily assessed and reported in studies of new therapies in patients with cancer. PFS offers a well established outcome measure that directly measures treatment effect, conveys important longitudinal information regarding tumor control, can be characterized in all subjects using intention-to-treat (ITT) principles, and is readily analyzed using statistical methods such as Kaplan-Meier techniques. 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. TTR and DOR are important in characterizing the rapidity of achieving tumor shrinkage and the duration of tumor control. 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}. Thus, changes in lymph node area and in the proportion of subjects having a lymph node response will be analyzed. In addition, among subjects who enter the study with splenomegaly or hepatomegaly, the proportion of subjects who achieve substantial (≥50%) reductions in spleen or liver size will be assessed. Similarly, the proportions of subjects who experience improvements in ALC, platelets, hemoglobin, and neutrophil counts will be characterized in order to provide specific insight into the degree to which therapy alters these individual parameters.

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, progressive cytopenias, appearance of new disease, or transformation to an 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 are 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. In addition, the risk is offset by the fact that the trial subjects will primarily be patients who have already received more potent mutagens (eg, purine analogs, alkylating agents), and all of whom have advanced cancer and limited treatment options at study entry. Based on published data {Keating 2002a, Wierda 2010}, median OS for patients with comparably advanced CLL is <18 months, 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 assess 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. To avoid duplication, the CT scan documenting CLL progression in Study GS-US-312-0116 will serve as the baseline CT scan for Study GS-US-312-0117. Among patients receiving idelalisib in Phase 1b/2 studies who experienced a nodal response (≥50% regression in tumor area), such responses were observed with the first 16 week of therapy {Coutre 2011, Leonard 2011}; the planned timing of tumor assessments (at Weeks 8, 16, 24, 36, 48 and then every 12 weeks thereafter) in this study fits with this known timing of changes in lymph node size during idelalisib therapy. Scans at 8-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 or after 24 weeks cumulative treatment with idelalisib across Study GS-US-312-0116 and Study GS-US-312-0117, the reduction in the frequency of CT scans (to 12-week intervals) reduces the overall protocol burden for subjects while still allowing characterization of the expected median PFS in this trial. As outlined in Section 7.3, iodine-containing or gadolinium contrast material may be omitted in subjects for whom use of a contrast agent would be medically contraindicated.

3.2.2. Measures of Patient Well-Being

3.2.2.1. 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 {Keating 2002a, Wierda 2010}. Evaluation of OS in this study continues the survival assessment from the primary study (Study GS-US-312-0116). The study program as a whole (considering both the primary randomized trial and secondary extension study) offers the potential to better understand OS and causes of death in a frail population of patients with both CLL, considering the consequences of the disease and comorbidities.

3.2.2.2. 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 study, it is postulated that 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 (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.

3.2.2.3. 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.

3.2.3. 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 using a clinically validated assay {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}. Clinically validated assays (eg, enzyme-linked immunosorbent assays [ELISAs]) will be used to measure circulating concentrations of chemokines and cytokines 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.

3.2.4. Assessments of Exposure

3.2.4.1. 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 kept. The compliance of the subject will be verified by accounting for used and unused drug.

3.2.4.2. Pharmacokinetics

Given the intent of this protocol to assess longer-term dosing, collection of plasma for idelalisib concentrations is important for evaluating exposure 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. Plasma samples will be retained for potential later analyses of idelalisib metabolites.

3.2.5. 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 idelalisib, and to serious adverse events.

In addition, the protocol will evaluate for potential adverse idelalisib effects on laboratory parameters of immune function; the absolute number of CD4+, CD5+,CD8+, CD16/CD56+, CD19+, and CD20+ cells will be assessed by flow cytometry. Serum concentrations of IgA, IgE, IgG, and IgM will be obtained.

For consistency of interpretation, adverse events will be coded using the standard Medical Dictionary for Regulatory Activities (MedDRA) [http://www.meddramsso.com]), 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 (*http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf).* Standard definitions for seriousness will be applied (see Section 8.1.2).

3.2.6. 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 idelalisib administration, 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} (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. The costs will be described relative to the health care findings as measured by duration of tumor control, the symptom-free survival period, and/or utility outcomes or some other appropriate measure of clinical benefits.

4. SUBJECT POPULATION

4.1. Number of Subjects

The planned sample size is ~160 subjects but will be bounded by the number of subjects enrolled to the primary clinical trial (Study GS-US-312-0116).

4.2. Subject Selection Criteria

Subjects in the primary Phase 3 study (GS-US-312-0116) who are compliant, are tolerating primary study therapy, and 1) have definitive progression of CLL while receiving primary study drug therapy (idelalisib /placebo) or 2) are actively participating in Study GS-US-312-0116 at the time the study is stopped, including if stopped early due to overwhelming efficacy following an interim analysis are eligible to enroll in the extension study. 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) Participation in Study GS-US-312-0116.

2) Occurrence of confirmed, definitive CLL progression while receiving study drug therapy (idelalisib/placebo) in Study GS-US-312-0116. ***Note: Definitive disease progression is CLL progression based on standard criteria and occurring for any reason (ie, increasing lymphadenopathy, organomegaly, or bone marrow involvement; decreasing platelet count, hemoglobin, or neutrophil count; or worsening of disease-related symptoms) other than lymphocytosis***. ***Subjects must have confirmation by the sponsor working in collaboration with an independent review committee (IRC) that the disease has progressed on the clinical trial (Study GS-US-312-0116) before receiving secondary idelalisib therapy on this extension trial (Study GS-US-312-0117).***

3) Presence of radiographically 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).

4) Permanent cessation of Study GS-US-312-0116 treatment (rituximab and idelalisib/placebo) and no intervening or continuing therapy (including radiotherapy, chemotherapy, immunotherapy, or investigational therapy) for the treatment of CLL. ***Note: Subjects may receive corticosteroids to manage CLL manifestations.***

5) The time from permanent cessation of Study GS-US-312-0116 treatment (rituximab and/or idelalisib/placebo) and the initiation of Study GS-US-312-0117 therapy is ≤12 weeks. ***Note: Study procedures performed as part of Study GS-US-312-0116 need not be repeated and can be used as screening procedures for Study GS-US-312-0117 if performed within 4 weeks prior to initiation of study drug therapy on Study GS-US-312-0117.***

6) Karnofsky performance score of ≥40.

7) Required baseline laboratory data (within 4 weeks prior to initiation of study treatment) as shown in the table below. ***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. Subjects with any degree of neutropenia, thrombocytopenia, or anemia due to CLL or prior therapy may enroll.***

Table 4-1. Required Screening Laboratory Values

Organ System	Parameter	Required Value
Hepatic	Serum total bilirubin	≤1.5 x ULN (unless elevated due to Gilbert's syndrome)
	Serum ALT	≤2.5 x ULN
	Serum AST	
Renal	eCCra	>30 ml/min
Pregnancy	β-HCGb	Negative

a As calculated by the Cockcroft-Gault formula (see Appendix 5) {Cockcroft 1976}
b 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 start of study treatment (Visit 2)
Abbreviations: β-HCG= beta human chorionic gonadotropin, ALT=alanine aminotransferase, AST=aspartate aminotransferase, eC_{Cr}=estimated creatinine clearance, ULN=upper limit of normal

8) For female subjects of childbearing potential, willingness to use a protocol-recommended method of contraception (as outlined in Section 5.6.4) from the screening visit (Visit 1) throughout the study and for 30 days following the last dose of study drug. ***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 (age ≥54 with amenorrhea for >12 months or amenorrhea for >6 months with serum estradiol and FSH levels within the institutional postmenopausal range).***

9) For male subjects of childbearing potential having intercourse with females of childbearing potential, willingness to use a protocol-recommended method of contraception (as outlined in Section 5.6.4) from the start of study drug (Visit 2) throughout the study and for 90 days following the last dose of study drug and to refrain from sperm donation from the start of study drug (Visit 2) throughout the study and for 90 days following the last dose of study drug. ***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®]).

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

11) 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.

12) 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) Evidence of ongoing systemic bacterial, fungal, or viral infection at the time of the start of study treatment (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; anti-pneumocystis prophylaxis is encouraged. 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.***

3) Pregnancy or breastfeeding.

4) Intentional breaking of the blind in Study GS-US-312-0116 by the investigator or the study subject.

5) Concurrent participation in another therapeutic clinical trial.

6) 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

The eligibility criteria are designed to limit enrollment to subjects who participated in the primary clinical trial (Study GS-US-312-0116), are compliant, have been generally able to tolerate study therapy and study procedures, and have experienced definitive CLL progression while receiving study treatment (rituximab and/or idelalisib/placebo) in the primary study or who are actively participating in Study GS-US-312-0116 at the time the study is stopped, including if stopped early due to overwhelming efficacy.

The requirement of measurable lymphadenopathy to enter the blinded portion of the study ensures that subjects have disease that can adequately be assessed for evidence of drug activity. Prior therapy provisions are intended to ensure that subjects are transitioning directly from Study GS-US-312-0116 to Study GS-US-312-0117 without receiving intervening treatments. The stipulation of ≤12-week interval from Study GS-US-312-0116 treatment until Study GS-US-312-0117 treatment precludes excessively protracted intervals between participation in the 2 studies but also permits sufficient time for clinicians and subjects to determine whether participation is appropriate.

In the blinded portion of the study, to ensure that subjects are not so acutely ill from life-threatening comorbidities that they require hospitalization and stabilization, subjects with Karnofsky performance scores <40 (ie, those who are bed-bound or hospitalized) will not be enrolled. Baseline laboratory evaluations are designed to limit participation to subjects who have not developed serious organ compromise that would pose a safety risk or confound the interpretation of adverse effects. Pregnancy testing and restrictions on eligibility relating to reproduction, pregnancy, and nursing are important because idelalisib is a new chemical entity with teratogenic effects in rats 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.

5. TREATMENT OF SUBJECTS

5.1. Enrollment

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 enrollment, 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. Treatment Assignment

After a subject has completed the necessary documentation of definitive CLL progression in the primary clinical trial (GS-US-312-0116) and has been confirmed to be eligible, the subject can be entered into this trial (Study GS-US-312-0117). In order to obtain a treatment arm allocation for a subject, a site representative will access the IWRS and supply the system with the required information.

Subjects will be assigned to either of the following treatment assignments with allocation based on the original primary study randomization:

Treatment Groups

Blinded Portion

- Arm A: Idelalisib + rituximab (Study GS-US-312-0116)
  ⇒high-dose idelalisib (300 mg BID) (Study GS-US-312-0117)

- Arm B: Placebo + rituximab (Study GS-US-312-0116)
  ⇒standard-dose idelalisib (150 mg BID) (Study GS-US-312-0117)

Open-Label Extension Portion (following unblinding)

- Arm A: subjects already on 300 mg BID will continue, and newly enrolled subjects will receive 150 mg BID

- Arm B: subjects already on 150 mg BID will continue, and newly enrolled subjects will receive 150 mg BID

Note: At the Investigator's discretion, subjects who were randomized to placebo on Study GS-US-312-0116 may delay initiation of idelalisib following enrollment on Study GS-US-312-0117 until the time of disease progression or until the investigator determines that the subject would benefit from initiation of idelalisib treatment.

Treatment Assignment

- Assignment to Arm A or Arm B with allocation based on the original primary study randomization

- Implementation through an interactive web response system (IWRS)

The IWRS will assign blister card, or bottle numbers and instructions for dispensing of blinded study drug (high-dose or standard-dose idelalisib). It is anticipated that subjects will usually begin study drug immediately at Visit 2 of the study.

5.1.3. Blinding

During the blinded portion of the study, 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). 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) or in the event the study is discontinued by the Sponsor, a Regulatory Agency, or an IRB or EC (see Section 5.9). Where required by local regulation, expedited reporting of serious adverse events to specific regulatory authorities will include information regarding the study drug treatment assignment (high-dose or standard-dose idelalisib); 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 unblinded analysis of the study will be performed when the database is completed and locked following unblinding of Study GS-US-312-0116 and Study GS-US-312-0117. The final analysis of the open label portion of the study will occur once the open label portion is stopped. 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 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.

5.2. Investigational Study Drug (Idelalisib/Placebo)

5.2.1. Description

Subjects allocated to Arm A in the blinded portion of the study will be provided with 2 tablets of active idelalisib for oral administration at each dose. 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 Table 5-1).

Subjects allocated to Arm B in the blinded portion of the study will be provided with 1 tablet of active idelalisib and 1 tablet of placebo for oral administration at each dose. Each active tablet contains 150 mg or 100 mg of active idelalisib. The 150-mg tablets (and matching placebo) will be used for initial therapy; the 100-mg tablets (and matching placebo) are provided for use by those subjects who require a dose reduction.

In the open-label portion of the study, subjects will be provided with 150 mg tablets of idelalisib.

The 150-mg tablets are pink, oval-shaped film-coated, 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 orange, oval shaped film-coated, and include the following inactive excipients: microcrystalline cellulose, hydroxypropyl cellulose, croscarmellose sodium, sodium starch glycolate, magnesium stearate, FD&C Yellow #6/Sunset Yellow FCF aluminum lake, polyethylene glycol, talc, PVA, and titanium dioxide.

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.

5.2.2. Source

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

5.2.3. Packaging and Labeling

During the blinded portion of the study, study drug (idelalisib or idelalisib/placebo) will be provided in blister cards. The blister cards are made of polyvinyl chloride/ polychlorotrifluoroethylene (PVC/PCTFE) film and have aluminum foil lidding materials. Each blister card contains 120 tablets (4-week supply plus a modest overage) of one of the relevant dose strengths. The 100-mg or 150-mg and matching placebo tablets will be combined in order to obtain the daily doses to be used in this study. Thus, in Arm A, the 300-mg idelalisib dose will

be obtained by administering two 150-mg tablets and the 200-mg idelalisib dose will be obtained by administering two 100-mg tablets. In Arm B, the 150-mg idelalisib dose will be obtained by administering one 150-mg tablet and one placebo tablet and the 100-mg idelalisib dose will be obtained by administering one 100-mg tablet and one placebo tablet.

Each blister card will have a unique number. Labeling for blister cards dispensed to subjects in Arm A will appear identical to blister cards dispensed to subjects in Arm B, and may include either idelalisib or placebo.

When the primary study (GS-US-312-0116) is stopped including if early after an interim analysis, GS-US-312-0116 active study subjects will become eligible for participation on Study GS-US-312-0117. Active GS-US-312-0117 study subjects will be transitioned to open-label idelalisib at this time. Each bottle contains 60 tablets (4 week supply plus a modest overage) of one of the relevant dose strengths (150 mg, 100 mg) and a polyester coil. 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.

All labels for study drugs to be distributed to centers in the United States, the EU, and other countries will meet all applicable requirements of the United States Food and Drug Administration (FDA), the EU Annex 13 of Current Good Manufacturing Practice (cGMP) (Manufacture of Investigational Medicinal Products, July 2010), and/or other local regulations as applicable.

5.2.4. Storage and Handling

Blister cards or bottles containing tablets of study drug (idelalisib or idelalisib/placebo) should be stored at controlled room temperature (ie, ~25 °C, with a range of 15 to 30 °C). While the stability of study drug tablets stored at controlled room temperature has been confirmed, brief excursions to temperatures as low as -20 °C or as high as 40 °C (eg, during shipping) will not adversely affect the drug. Updated stability data will be provided to the sites, as appropriate.

5.2.5. Dispensing

The clinic staff (eg, pharmacist or other qualified person) will be responsible for dispensing study drug according to the IWRS directions. It is planned that drug will be dispensed at 4-week intervals through the first 24 weeks of treatment and at 12-week intervals thereafter, or on a frequency consistent with the subject's visit schedule. Sufficient study drug will be provided for each study period at the beginning of the period. Multiple blister cards or bottles may be dispensed at a single visit. Tablets should be kept in the original blister cards or bottles provided until they are self-administered by the subject.

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

5.2.6. Return

The study drug 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. When possible, 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.

5.2.7. Accountability

The disposition of all study drug 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.

5.2.8. Overdose Precautions

In Phase 1 studies, an MTD for idelalisib was not reached when the drug was administered continuously at dose levels through 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, >600 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 overdose will result in specific reporting requirements (see Section 8.8).

5.2.9. 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.

5.3. Study Drug Administration

5.3.1. Premedication

No specific premedications or supporting medications are required in conjunction with study drug administration.

5.3.2. Administration Instructions

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.

5.3.3. Dosing Schedule

Study drug should be taken on a BID schedule 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, especially in the clinic.

At specified clinic visits, the 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 idelalisib administration information, including the exact clock time of each dose, for doses of study drug administered in the clinic or hospital. Thereafter, subjects will be given an adequate supply of tablets to take at home.

5.3.4. Dose Levels

Study drug dose levels for Arm A and Arm B are described in Table 5-1. The lower dose level (Dose Level -1) is provided in case a subject requires a study drug dose modification.

Table 5-1. Study Drug Dose Levels

Treatment Arm	Starting Dose	Dose Level -1
Arm A	300 mg/dose BID	200 mg/dose BID
Arm B	150 mg/dose BID	100 mg/dose BID

Abbreviation: BID=twice per day

When the primary study (GS-US-312-0116) is stopped, and GS-US-312-0116 active study subjects become eligible for participation on Study GS-US-312-0117 subjects will be enrolled into Study GS-US-312-0117 at open label 150 mg BID. Subjects already participating in Study GS-US-312-0117 will remain on the same dose.

5.3.5. Dose Schedule Interruptions and Vomited Doses

Subjects who have a delay in administration of a dose of the 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.

5.3.6. Safety Monitoring and Study Drug 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.

Recommendations and requirements for modifications of the dosing regimens based on the drug and the type and severity of adverse events or laboratory abnormalities are provided in Table 5-2 below. The dose modification instructions focus on the types of events most commonly attributed to each of the study agents. Required dose modifications and actions provided in Table 5-2 must be followed based on the type and severity of adverse avent. The recommendations provided in Table 5-2 comprise only guidelines; variations from these recommendations 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 5-2, if a subject experiences an adverse event that is suspected to be related to study drug and requires a dose modification during the course of study therapy, then study drug administration should be held, as necessary, until the adverse event resolves or stabilizes to an acceptable degree Thereafter, study drug may be reinstituted, but the dose should be modified per(Table 5-1 and Table 5-2). If the adverse event occurs again, reinitiation of therapy may be attempted if the investigator feels that a second rechallenge is medically appropriate. If the subject cannot tolerate idelalisib at Dose Level -1 after 2 rechallenges, then the subject should be discontinued from study drug therapy unless continued therapy is discussed with the Gilead Sciences medical monitor.

After the study drug dose is reduced, 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 level may be increased to the starting dose level (see Table 5-1) 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 should not intentionally be exceeded in this study.

Whenever possible, any dose adjustment of study drug should be discussed between the investigator and the Gilead Sciences medical monitor prior to implementation. To implement either a dose reduction or a dose reescalation, the investigator/study staff member will call the IWRS, enter the subject number, and inform the IWRS of the need for dose titration. The IWRS will provide details regarding the study drug to be dispensed to the subject. The appropriate clinic staff should instruct the subject/caregiver about the change in dose.

Recommendations for dose modification based on the type and severity of adverse events or laboratory abnormalities are provided in Table 5-2 below.

Table 5-2. Recommendations and Requirements for Study Drug Dose Modifications Based on Type and Severity of Treatment-Related Adverse Events or Laboratory Abnormalities

	Recommendation
NCI CTCAE Grade[a]	**Idelalisib**
HEMATOLOGICAL ADVERSE EVENTS	
Neutropenia	
Grade ≤2 neutropenia	Recommended Action: Maintain current dose level and schedule.
Grade ≤3 neutropenia	Required Action: Blood counts should be monitored at least weekly until ANC ≤ Grade 2. Recommended Action: Maintain current idelalisib dose level and schedule.
Grade 4 neutropenia (or occurrence of neutropenic fever or infection)	Required Action: Withhold idelalisib. Required Action:Monitor blood counts at least weekly until ANC ≤ Grade 2 Recommended Action: May resume idelalisib at lower dose level at investigator discretion. Neutropenia should be managed according to established clinical guidelines.
Thrombocytopenia	
Grade ≤3	Recommended Action: Maintain current dose level and schedule.
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.
NON-HEMATOLOGICAL ADVERSE EVENTS	
Rash	
Grade ≤1	Recommended Action: Maintain current dose level and schedule.
Grade 2	Recommended Action: Maintain current dose level and schedule.

NCI CTCAE Grade[a]	Recommendation Idelalisib
Grade ≥3	Required Action: Withhold idelalisib until Grade ≤1. Recommended Action: Resume at lower dose level or discontinue idelalisib at investigator discretion.
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.
Gastrointestinal Inflammation/Diarrhea	
Grade ≤1	Required Action: Obtain history of onset and duration of diarrhea, including description, number of stools, stool composition (e.g., 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 (e.g., evaluate for sepsis, bowel obstruction, dehydration). Recommended Action: Provide anti-diarrheal (eg, loperamide) and maintain current idelalisib dose level and schedule.
Grade 2 diarrhea or colitis (unless clinical diagnosis is established from medical history and physical examination)	Required Action: Obtain history of onset and duration of diarrhea, including description, number of stools, and stool composition (e.g., 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 (e.g., evaluate for sepsis, bowel obstruction, dehydration). 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, Clostridium difficile toxin, Rotavirus, Cytomegalovirus, 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 (clostridium difficile enterocolitis), endoscopy with biopsy[b] is strongly recommended to assess by immunohistochemistry (IHC) and PCR for CMV, Adenovirus. (Optional: If ileal biopsy is performed, consider Acid Fast Bacillus staining.) Recommended Action: Provide anti-diarrheal (eg, loperamide). Consider addition of anti-inflammatory agent (eg, sulfasalazine, budesonide). Maintain current idelalisib dose level and schedule.

NCI CTCAE Grade[a]	Recommendation Idelalisib
Grade ≥ 3 diarrhea or colitis or persistent grade 2 diarrhea or colitis without clear etiology	Required Action: Withhold idelalisib. Required Action: Obtain history of onset and duration of diarrhea, including description, number of stools, stool composition (e.g., 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 (e.g., evaluate for sepsis, bowel obstruction, dehydration). 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, Clostridium difficile toxin, Rotavirus, Cytomegalovirus, Adenovirus), ova and parasites (Cryptosporidium parvum, Isospora belli, Enterocytozoon bieneusi, Septata intestinalis, Strongyloides, Microsporidia, Entamoeba histolytica, Cyclospora), and Giardia antigen. Recommended Action: For Grade 3 colitis or diarrhea without clear etiology (eg, clostridium difficile enterocolitis), endoscopy with biopsy[b] isstrongly recommended to assess by immunohistochemistry (IHC) and PCR for CMV, Adenovirus. . (Optional: If ileal biopsy is performed, consider Acid Fast Bacillus staining.) Recommended Action: At Grade ≤1, may resume idelalisib at lower dose level or discontinue at investigator discretion. Recommended Action: Provide anti-diarrheal (eg, loperamide) and/or addition of anti-inflammatory agent (eg, sulfasalazine, budesonide).
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.
Grade 2 (ALT/AST>3-5xULN) (Bilirubin>1.5-≤3xULN)	Recommended Action: Monitor ALT, AST, ALP, and bilirubin at least 1x per week until all abnormalities are Grade ≤ 1; thereafter maintain current dose level.
Grade 3 (ALT/AST>5-20xULN) (Bilirubin>3-10xULN)	Recommended Action: Withhold idelalisib. Monitor ALT, AST, ALP, and bilirubin at least 1x per week until all abnormalities are Grade ≤1. Recommended Action: If bilirubin abnormality was Grade <3, resume idelalisib at same dose level. If bilirubin abnormality was Grade >3, resume at lower dose level.
Grade 4 (ALT/AST>20xULN) (Bilirubin>10xULN)	Required Action: Withhold idelalisib. Required Action: Monitor ALT, AST, ALP, and bilirubin at least 1x per week until all abnormalities are Grade ≤1. Required Action: If bilirubin abnormality was Grade 4, discontinue idelalisib. Required Action: If bilirubin abnormality was Grade <4, if drug is restarted then resume idelalisib at lower dose level.

NCI CTCAE Grade[a]	Recommendation Idelalisib
Pneumonitis (with new onset or worsening 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 idelalisib at investigator discretion.
Grade ≥ 2	Required Action: Discontinue idelalisib permanently in subjects with any severity of symptomatic pneumonitis and institute therapy as clinically appropriate.
Pneumocystis jirovecci pneumonia (PJP)	
Any Grade	Required Action: Discontinue idelalisib
Organizing Pneumonia	
Any Grade	Required Action: Discontinue idelalisib permanently
Unequivocal CMV infection[c]	
Any Grade	Required Action: Interrupt idelalisib upon unequivocal clinical or laboratory evidence of CMV infection. Required Action: Treat according to established clinical guidelines. Required Action: 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.
Grade ≥3	Recommended Action: Withhold idelalisib until Grade ≤1. May resume idelalisib at initial or lower dose level or discontinue idelalisib 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, AST= aspartate aminotransferase, CTCAE=Common Terminology Criteria for Adverse Events, CMV=cytomegalovirus, 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

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

For subjects who develop Grade ≥3 rash for which an underlying etiology cannot be identified (e.g., infection, co suspect drug), study drug must be interrupted.

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 (e.g., bendamustine, rituximab) and/or other concomitant medications known to be associated with SJS or TEN (e.g., 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 should 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. Upon recovery, rituximab may be resumed.

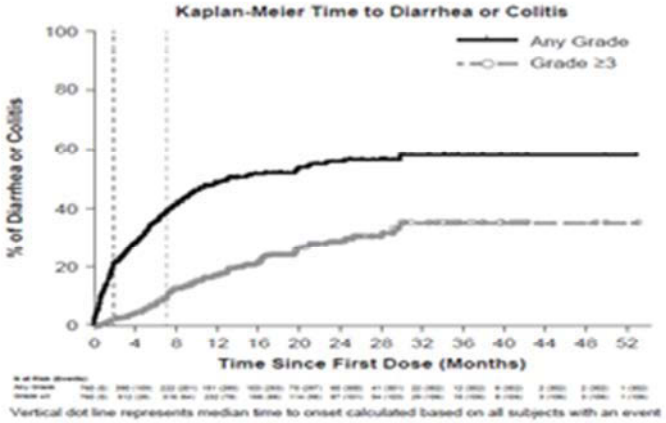
Among patients receiving rituximab in combination with chemotherapy, rare instances of life-threatening bowel obstruction or perforation has been observed {Ram 2009}, primarily in patients with NHL. In post-marketing reports, the mean time to documented gastrointestinal perforation was 6 (range 1–77) 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-Meler 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

Differentiate between small-bowel and large-bowel diarrhea on a clinical basis if recommended. If unclear, consider upper and lower tract endoscopy with biopsy.

- Small bowel diarrhea is characterized by large volume diarrhea (more than one per day), possibly 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 and start appropriate treatment for HBV. In the event of HBV reactivation, please contact the Medical Monitor regarding continuation of idelalisib.

5.4.4. Hematological and Immunological Events

In the Phase 1 experience with idelalisib in 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 therapy were largely due to minor fluctuations in these parameters among patients 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 weekly. For subjects who develop Grade 4 neutropenia , idelalisib must be interrupted and blood counts monitored weekly until ANC is ≥ 0.5 Gi/L, at which point, idelalisib dosing may be resumed at 100 mg BID. Neutropenia should be managed according to established clinical guidelines.

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, and must continue for 2 to 6 months after the last dose of idelalisib. Prophylaxis must continue until the CD4+ T-cell count is documented to be >200 cells/mcL 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.

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. 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 or worsening neurologic manifestations, especially weakness or paralysis, vision loss, impaired speech, or cognitive deterioration. Evaluation of PML should include consultation with a neurologist, brain MRI, and lumbar puncture. In subjects diagnosed with PML, study drug should also be permanently discontinued.

5.4.7. 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}.

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

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

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

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.

5.4.8. 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.

5.4.9. Tumor Lysis Syndrome

Tumor lysis syndrome has not been observed with idelalisib monotherapy.

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.

5.4.10. 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 in rats and dogs indicated dose-dependent reductions in testicular weights, with persistent minimal to mild degeneration of the seminiferous tubules and decreased spermatozoa in rats and hypospermatogenesis in dogs. The implications of these testicular changes for animal or human fertility are unknown.

Given the preliminary nature of data regarding 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 must be discontinued.

5.4.10.1. PJP Prophylaxis

Trimethoprim sulfamethoxazole is rated a Pregnancy category C. 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. 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. 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. 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.

5.4.11. 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.

5.4.12. Further Safety Information

Further safety information regarding the study drug may be found in the investigator brochure for idelalisib.

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 corticosteroids (see Section 5.6.5), no other systemic anticancer therapies (including but not limited to chemotherapy, radiation, antibody therapy, immunotherapy, or other experimental therapies) of any kind are permitted. 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.

For subjects who develop an infection, appropriate medical therapy (with antibiotics, antifungals, or antiviral) or other interventions should be instituted. Whenever appropriate, subjects may continue with study drug 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 in prior studies. However, 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 (age ≥54 years with 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 during heterosexual intercourse throughout the study treatment period and for 30 days following the last dose of the study drug. The investigator should counsel subjects on the most effective methods for avoiding pregnancy during the trial. Protocol-recommended contraceptive methods are described in Table 5-3.

Table 5-3. 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[a] • Male condom(with spermicide[a])

a If available/approved for use in the specific country
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 accept continuous heterosexual abstinence as a lifestyle choice; limit intercourse to female partners who are surgically sterile, post-menopausal, or using effective contraception (as noted in Table 5-3); or agree to use a protocol-recommended method of contraception during heterosexual intercourse throughout the study treatment period and for 90 days following discontinuation of the study drug (as noted in Table 5-3).

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 therapy. However, 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 5-2).

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 a ~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 5-4:

Table 5-4. 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 CYP3A-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.

The specific clinical relevance of these findings with idelalisib 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 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 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 may be taken with or without food.

5.7. Duration of Study Drug

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

5.8. Discontinuation of Study Drug

All study participants may receive study drug indefinitely; however:

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

- Any subject unable to tolerate a second rechallenge with protocol-described, dose-modified idelalisib at Dose Level –1 (see Section 5.2) should discontinue study drug.
- Any subject who becomes pregnant or begins breastfeeding should 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 (only applicable to the blinded portion of the study).
- The investigator, in consultation with the Gilead Sciences medical monitor, may discontinue study drug, if, it is not in the subject's best interest to continue.
- 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.
- 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.

Any subject whose benefit-risk profile is not deemed positive by the investigator should discontinue study drug.

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

5.9. Discontinuation from Study

Subject study participation will 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 treatment.
- 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

Subjects will be assigned to treatment (Arm A or Arm B) in this study based on their randomization in the primary study. The 1:1 randomization in the primary trial (GS-US-312-0116) ensures that sufficient Arm B subjects will cross over from rituximab alone to single-agent idelalisib at the 150-mg/dose BID starting dose level in this extension trial (GS-US-312-0117) to allow an adequate evaluation of efficacy and safety in this trial. The randomization and allocation processes will be established and performed through an IWRS; the intent is to maximize the integrity and security of the subject disposition and to ensure appropriate access and convenience-of-use by the investigational sites.

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.

Selection of the idelalisib treatment regimen (including starting dose level, dose-modifications and supportive care, schedule, duration, and conditions of administration) for this study program 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, Kahl 2011, Webb 2010}. The following information was considered in selecting the study drug dosing regimen for the primary study and this companion extension 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 are tolerable, the starting dose of 150 mg/dose BID appears to appropriately balance safety with efficacy in idelalisib-naïve subjects. The starting dose of 300 mg/dose BID in this study also appears appropriate for evaluation; it is lower than the dose level of 350 mg/dose BID that has been tolerable in prior studies and is likely to be suitable in subjects who have already been tolerating idelalisib therapy at ≥100 mg/dose BID.

- Upon disease progression, permitting escalation from 150 mg/dose BID to 300 mg/dose BID among subjects allocated to Arm A offers a systematic evaluation of higher doses in subjects who are tolerating idelalisib treatment and might benefit from increased PI3Kδ inhibition. The pharmacological basis for considering such an intervention is based on the concept that some individuals might have lower-than-expected plasma exposures or dose-dependent resistance to the compound at 150 mg/dose BID and might benefit from a higher dose.

The intent is to determine if the higher dose can reestablish disease control or whether absolute resistance to PI3Kδ inhibition has been acquired. The safety data obtained in these subjects would add to the overall safety database.

- 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 the dose-levels to be used in this 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 and the dose level of 300 mg/dose BID may provide additional benefit in patients with disease resistance as systematically evaluated in this trial.

- 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 starting doses 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.

- In both the primary and extension studies, study treatment 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 is likely to extend treatment effect. In addition, this design permits collection of further single-agent safety information and thus is likely to enhance understanding of the overall safety profile of idelalisib.

6. STUDY PROCEDURES

6.1. Enrollment and Study Management Procedures

6.1.1. Subject Recruitment

Study candidates are limited to those subjects who participated in the primary clinical trial (Study GS-US-312-0116) and meet the entry criteria for this trial (Study GS-US-312-0117). Subjects will be enrolled from investigational sites in the United States and Europe. The site principal investigator, designated sub-investigators, or other designees will discuss the possibility of participation directly with subjects who participated in the primary study.

The study sponsor will post a description of the study on the ClinicalTrials.gov website. Any 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 the subject number as already assigned in Study GS-US-312-0116.

Any consented subject who is excluded from the study before initiation of study treatment 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 treatment on this study.

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 and 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 visit designated as a laboratory-only visit (Visit 7), 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.

Local lab results may be requested in the event central laboratory results are not available for assessment of disease response, progression, 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 3.2.1.

Following unblinding of the study:

- Subjects who were randomized to idelalisib on Study GS-US-312-0116 and who received ≥ 24 weeks idelalisib will complete Visit 16+ twelve weeks from the date of their last radiology assessment (CT/MRI) and study visits will continue every 12 weeks thereafter. Visits 3 through 15 will not be required.

- Subjects who have received < 24 weeks of idelalisib will have all Study GS-US-312-0117 assessments completed per the Schedule of Procedures until they have received idelalisib for 24 weeks cumulative across both studies. After completion of 24 weeks of cumulative idelalisib treatment, Visit 16+ will be conducted 12 weeks from the date of their last radiology assessment (CT/MRI), after which time study visits will occur every 12 weeks.

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.

In order to optimize scheduling convenience for the subject and for the investigational staff, study procedures performed as part of Study GS-US-312-0116 need not be repeated and can be used as screening procedures for Study GS-US-312-0117 if performed within 4 weeks prior to initiation of study drug therapy on Study GS-US-312-0117. In addition, screening procedures may be performed over as many days as necessary provided that screening is completed within 4 weeks prior to initiation of study drug therapy on Study GS-US-312-0117.

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

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

Assessment or Procedure	Explanation[a]
Informed consent	To be obtained before any screening procedures are initiated
IWRS access	Access IWRS to document that subject is in screening and provide the subject number from Study GS-US-312-0116
CIRS assessment	Recording of current 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 height, weight, evidence of palpable lymphadenopathy, hepatomegaly, and/or splenomegaly
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 β2 microglobulin
PPD	PPD
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 absolute number 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
Radiology assessment	CT or MRI imaging of neck, chest, abdomen, and pelvis, to be scheduled with 4 weeks prior to initiation of study treatment at Visit 2
Bone marrow biopsy and aspirate	To be performed at investigator discretion to determine extent of CLL involvement and bone marrow cellularity.

a Study procedures performed as part of Study GS-US-312-0116 need not be repeated and can be used as screening procedures for Study GS-US-312-0117 if performed within 4 weeks prior to initiation of study drug therapy on Study GS-US-312-0117.

Abbreviations: β-HCG=beta human chorionic gonadotropin, ALP=alkaline phosphatase, ALT=alanine aminotransferase, AST=aspartate aminotransferase, CIRS=cumulative illness rating scale, CLL=chronic lymphocytic leukemia, CT=computed tomography, DNA=deoxyribonucleic acid, FISH= fluorescence in-situ hybridization, GGT=gamma--glutamyltransferase, Ig=immunoglobulin, IgHV=immunoglobulin heavy chain variable region, IWRS=interactive web response system, LDH=lactate dehydrogenase, MRI=magnetic resonance imaging, RNA=ribonucleic acid, ZAP-70=zeta-associated protein 70

6.2.2. Visit 2 (Day 1) (Clinic Visit)

Subjects will be assessed to determine if they still meet eligibility criteria and can initiate study treatment. Study drug holds from primary study GS-US-312-0116 may continue as medically appropriate. The procedures outlined in Table 6-2 will be performed at Visit 2 (Day 1).

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

Assessment or Procedure	Explanation
Pre-Dose 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 any other procedures are performed and before any 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 weight, evidence of palpable lymphadenopathy, hepatomegaly, and/or splenomegaly
β-HCG	For women of child-bearing potential only; serum β-HCG or urine dipstick pregnancy test must be negative prior to initial study treatment
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
Idelalisib pharmacokinetics	Pre-dose collection of plasma sample for idelalisib pharmacokinetics (with recording of the date and actual clock time of blood collection)
IWRS access	Access of IWRS to obtain study drug blister card number
Study Therapy Administration	
Study drug administration[a]	First dose of study drug to be administered to the subject (with recording of the date and actual clock time of the study drug administration)
Post-Therapy Procedures and Assessments	
Idelalisib pharmacokinetics[a]	Post-dose collection of plasma sample for idelalisib pharmacokinetics at 1.5 hours ± 15 mins after study drug administration (with recording of the date and actual clock time of blood collection)
Study drug dispensing[a]	Dispensing of 4-week supply of study drug to the subject with instructions for self-administration at home
Instruction regarding study drug dosing at next full clinic visit[a]	Instruction to the subject that the morning dose of study drug should not be taken on the day of Visit 3.

a Subjects who were randomized to placebo on Study GS-US-312-0116 and enroll on Study GS-US-312-0117 following unblinding may have idelalisib treatment (and associated PK testing) delayed at the Investigator's discretion until the time of disease progression or until the investigator determines the subject may benefit by the initiation of idelalisib treatment

Abbreviations: β-HCG=beta human chorionic gonadotropin, 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, IWRS=interactive web response system, LDH=lactate dehydrogenase, RNA=ribonucleic acid

6.2.3. Visit 3 (Day 15) (Clinic Visit)

The procedures outlined in Table 6-3 will be performed at Visit 3 (Day 15 [±2 days]).

Table 6-3. Procedures and Assessments at Visit 3 (Day 15)

Assessment or Procedure	Explanation
Pre-Dose 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 any other procedures are performed and before any 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
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 absolute number 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)
IWRS access	Access of IWRS to document subject visit
Study Therapy Administration	
Study drug administration	Study drug to be administered to the subject (with recording of the date and actual clock time of the study drug administration)
Post-Therapy Procedures and Assessments	
Idelalisib pharmacokinetics	Post-dose collection of plasma sample for idelalisib pharmacokinetics at 1.5 hours ± 15 mins after study drug administration (with recording of the date and actual clock time of blood collection)
Instruction regarding study drug dosing at next full clinic visit	Instruction to the subject that the morning dose of study drug should not be taken on the day of Visit 4.

Abbreviations: 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, IWRS=interactive web response system, LDH=lactate dehydrogenase

6.2.4. Visit 4 (Day 29) (Clinic Visit)

The procedures outlined in Table 6-4 will be performed at Visit 4 (Day 29 [±2 days]).

Table 6-4. Procedures and Assessments at Visit 4 (Day 29)

Assessment or Procedure	Explanation
Pre-Therapy 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 any other procedures are performed and before any study-related information is communicated to the subject
Adverse events	Recording of adverse events occurring since Visit 3
Concomitant medications	Recording of concomitant medication used since Visit 3
Study drug return/ accounting	Counting returned study drug. Recording of the date and actual clock time of the last prior subject self-administration of study drug (should be the prior evening dose)
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 weight, evidence of palpable lymphadenopathy, hepatomegaly, and/or splenomegaly
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 absolute number 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, IgM
Idelalisib pharmacokinetics	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)
IWRS access	Access of IWRS to obtain study drug blister card number
Study Therapy Administration and Dispensing	
Study drug administration	Dose of study drug to be administered to the subject (with recording of the date and actual clock time of the study drug administration)

Assessment or Procedure	Explanation
Post-Therapy Procedures and Assessments	
Idelalisib pharmacokinetics	Post-dose collection of plasma sample for idelalisib pharmacokinetics at 1.5 hours ± 15 mins after study drug administration (with recording of the date and actual clock time of blood collection)
Study drug dispensing	Dispensing of 4-week supply of study drug to the subject with instructions for self-administration at home
Instruction regarding dosing at next full clinic visit	Instruction to the subject that the morning dose of study drug should not be taken on the day of Visit 5.

Abbreviations: 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, GGT=gamma-glutamyltransferase, HRQL=health-related quality of life, Ig=immunoglobulin, LDH=lactate dehydrogenase, MRI=magnetic resonance imaging

6.2.5. Visit 5 (Day 43) (Clinic Visit)

The procedures outlined in Table 6-5 will be performed at Visit 5 (Day 43 [±2 days]).

Table 6-5. Procedures and Assessments at Visit 5 (Day 43)

Assessment or Procedure	Explanation
Pre-Dose 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 any other procedures are performed and before any 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
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
IWRS access	Access of IWRS to document subject visit
Post-Therapy Procedures and Assessments	
Instruction regarding study drug dosing at next full clinic visit	Instruction to the subject that the morning dose of study drug should not be taken on the day of Visit 6.
Scheduling of Visit 6 radiology assessment	CT or MRI imaging of neck, chest, abdomen, and pelvis to be scheduled for Visit 6.

Abbreviations: 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, IWRS=interactive web response system, LDH=lactate dehydrogenase

6.2.6. Visit 6 (Day 57) (Clinic and Radiology Visit)

The procedures outlined in Table 6-6 will be performed at Visit 6 (Day 57 [±2 days]).

Table 6-6. Procedures and Assessments at Visit 6 (Day 57)

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-Therapy 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 any other procedures are performed and before any study-related information is communicated to the subject
Adverse events	Recording of adverse events occurring since Visit 5
Concomitant medications	Recording of concomitant medication used since Visit 5
Study drug return/ accounting	Counting returned study drug. Recording of the date and actual clock time of the last prior subject self-administration of study drug (should be the prior evening dose)
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 weight, evidence of palpable lymphadenopathy, hepatomegaly, and/or splenomegaly
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 absolute number of CD4+, CD5+, CD8+, CD16/CD56+, CD5+, 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	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)
IWRS access	Access of IWRS to obtain study drug bottle number

Assessment or Procedure	Explanation
Study Therapy Administration	
Study drug administration	Dose of study drug to be administered to the subject (with recording of the date and actual clock time of the study drug administration)
Post-Therapy Procedures and Assessments	
Idelalisib pharmacokinetics	Post-dose collection of plasma sample for idelalisib pharmacokinetics at 1.5 hours ± 15 mins after study drug administration (with recording of the date and actual clock time of blood collection)
Study drug dispensing	Dispensing of 4-week supply of study drug to the subject with instructions for self-administration at home
Instruction regarding dosing at next full clinic visit	Instruction to the subject that the morning dose of study drug should not be taken on the day of Visit 8.

Abbreviations: ALP=alkaline phosphatase, ALT=alanine aminotransferase, AST=aspartate aminotransferase, CR=complete response, CT=computed tomography, EQ-5D=EuroQoL Five-Dimension, FACT-Leu=Functional Assessment of Cancer Therapy-Leukemia, GGT=gamma-glutamyltransferase, HRQL=health-related quality of life, Ig=immunoglobulin, LDH=lactate dehydrogenase, MRI=magnetic resonance imaging

6.2.7. Visit 7 (Day 71) (Laboratory Visit)

The procedures outlined in Table 6-7 will be performed at Visit 7 (Day 71 [±2 days]).

Table 6-7. Procedures and Assessments at Visit 7 (Day 71)

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

Abbreviations: ALP=alkaline phosphatase, ALT=alanine aminotransferase, AST=aspartate aminotransferase, GGT=gamma-glutamyltransferase, LDH=lactate dehydrogenase

6.2.8. Visit 8 (Day 85) (Clinic Visit)

The procedures outlined in Table 6-8 will be performed at Visit 8 (Day 85 [±2 days]).

Table 6-8. Procedures and Assessments at Visit 8 (Day 85)

Assessment or Procedure	Explanation
Pre-Therapy 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 any other procedures are performed and before any study-related information is communicated to the subject
Adverse events	Recording of adverse events occurring since Visit 6
Concomitant medications	Recording of concomitant medication used since Visit 6
Study drug return/ accounting	Counting returned study drug. Recording of the date and actual clock time of the last prior subject self-administration of study drug (should be the prior evening dose)
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 weight, evidence of palpable lymphadenopathy, hepatomegaly, and/or splenomegaly
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 absolute number 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	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)
IWRS access	Access of IWRS to obtain study drug blister card number
Study Therapy Administration and Dispensing	
Study drug administration	Dose of study drug to be administered to the subject (with recording of the date and actual clock time of the study drug administration)

Assessment or Procedure	Explanation
Post-Therapy Procedures and Assessments	
Idelalisib pharmacokinetics	Post-dose collection of plasma sample for idelalisib pharmacokinetics at 1.5 hours ± 15 mins after study drug administration (with recording of the date and actual clock time of blood collection)
Study drug dispensing	Dispensing of 4-week supply of study drug to the subject with instructions for self-administration at home
Instruction regarding dosing at next full clinic visit	Instruction to the subject that the morning dose of study drug should not be taken on the day of Visit 9.
Scheduling of Visit 9 radiology assessment	CT or MRI imaging of neck, chest, abdomen, and pelvis to be scheduled for Visit 9.

Abbreviations: 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, GGT=gamma-glutamyltransferase, HRQL=health-related quality of life, Ig=immunoglobulin, LDH=lactate dehydrogenase, MRI=magnetic resonance imaging

6.2.9. Visit 9 (Day 113) (Clinic and Radiology Visit)

The procedures outlined in Table 6-9 will be performed at Visit 9 (Day 113 [±3 days]).

Table 6-9. Procedures and Assessments at Visit 9 (Day 113)

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-Therapy 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 any other procedures are performed and before any study-related information is communicated to the subject
Adverse events	Recording of adverse events occurring since Visit 8
Concomitant medications	Recording of concomitant medication used since Visit 8
Study drug return/ accounting	Counting returned study drug. Recording of the date and actual clock time of the last prior subject self-administration of study drug (should be the prior evening dose)
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 weight, evidence of palpable lymphadenopathy, hepatomegaly, and/or splenomegaly
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 absolute number of CD4+, CD5+, CD8+, CD16/CD56+, CD5+, 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	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)
IWRS access	Access of IWRS to obtain study drug blister card number

Assessment or Procedure	Explanation
Study Therapy Administration	
Study drug administration	Dose of study drug to be administered to the subject (with recording of the date and actual clock time of the study drug administration)
Post-Therapy Procedures and Assessments	
Idelalisib pharmacokinetics	Post-dose collection of plasma sample for idelalisib pharmacokinetics at 1.5 hours ± 15 mins after study drug administration (with recording of the date and actual clock time of blood collection)
Study drug dispensing	Dispensing of 4-week supply of study drug to the subject with instructions for self-administration at home
Instruction regarding dosing at next full clinic visit	Instruction to the subject that the morning dose of study drug should not be taken on the day of Visit 10.

Abbreviations: ALP=alkaline phosphatase, ALT=alanine aminotransferase, AST=aspartate aminotransferase, CR=complete response, CT=computed tomography, EQ-5D=EuroQoL Five-Dimension, FACT-Leu=Functional Assessment of Cancer Therapy-Leukemia, GGT=gamma-glutamyltransferase, HRQL=health-related quality of life, Ig=immunoglobulin, LDH=lactate dehydrogenase, MRI=magnetic resonance imaging

6.2.10. Visit 10 (Day 141) (Clinic Visit)

The procedures outlined in Table 6-10 will be performed at Visit 10 (Day 141 [±3 days]).

Table 6-10. Procedures and Assessments at Visit 10 (Day 141)

Assessment or Procedure	Explanation
Pre-Therapy 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 any other procedures are performed and before any study-related information is communicated to the subject
Adverse events	Recording of adverse events occurring since Visit 9
Concomitant medications	Recording of concomitant medication used since Visit 9
Performance status	Using Karnofsky performance status criteria (see Appendix 3)
Study drug return/ accounting	Counting returned study drug. Recording of the date and actual clock time of the last prior subject self-administration of study drug (should be the prior evening dose)
Physical examination	Including weight, evidence of palpable lymphadenopathy, hepatomegaly, and/or splenomegaly
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 absolute number 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	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)
IWRS access	Access of IWRS to obtain study drug blister card number
Study Therapy Administration	
Study drug administration	Dose of study drug to be administered to the subject (with recording of the date and actual clock time of the study drug administration)

Assessment or Procedure	Explanation
Post-Therapy Procedures and Assessments	
Idelalisib pharmacokinetics	Post-dose collection of plasma sample for idelalisib pharmacokinetics at 1.5 hours ± 15 mins after study drug administration (with recording of the date and actual clock time of blood collection)
Study drug dispensing	Dispensing of 4-week supply of study drug to the subject with instructions for self-administration at home
Instruction regarding dosing at next full clinic visit	Instruction to the subject that the morning dose of study drug should not be taken on the day of Visit 11.
Scheduling of Visit 11 radiology assessment	CT or MRI imaging of neck, chest, abdomen, and pelvis to be scheduled for Visit 11.

Abbreviations: 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, GGT=gamma-glutamyltransferase, HRQL=health-related quality of life, Ig=immunoglobulin, LDH=lactate dehydrogenase, MRI=magnetic resonance imaging

6.2.11. Visit 11 (Day 169) (Clinic and Radiology Visit)

The procedures outlined in Table 6-11 will be performed at Visit 11 (Day 169 [±3 days]).

Table 6-11. Procedures and Assessments at Visit 11 (Day 169)

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-Therapy 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 any other procedures are performed and before any study-related information is communicated to the subject
Adverse events	Recording of adverse events occurring since Visit 10
Concomitant medications	Recording of concomitant medication used since Visit 10
Study drug return/ accounting	Counting returned study drug. Recording of the date and actual clock time of the last prior subject self-administration of study drug (should be the prior evening dose)
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 weight, evidence of palpable lymphadenopathy, hepatomegaly, and/or splenomegaly
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 absolute number 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, 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	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)
IWRS access	Access of IWRS to obtain study drug blister card numbers

Assessment or Procedure	Explanation
Study Therapy Administration	
Study drug administration	Dose of study drug to be administered to the subject (with recording of the date and actual clock time of the study drug administration)
Post-Therapy Procedures and Assessments	
Idelalisib pharmacokinetics	Post-dose collection of plasma sample for idelalisib pharmacokinetics at 1.5 hours ± 15 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 to the subject with instructions for self-administration at home.

Abbreviations: ALP=alkaline phosphatase, ALT=alanine aminotransferase, AST=aspartate aminotransferase, CR=complete response, CT=computed tomography, EQ-5D=EuroQoL Five-Dimension, FACT-Leu=Functional Assessment of Cancer Therapy-Leukemia, GGT=gamma-glutamyltransferase, HRQL=health-related quality of life, Ig=immunoglobulin, LDH=lactate dehydrogenase, MRI=magnetic resonance imaging

6.2.12. Visit 12 (Day 211) (Clinic Visit)

The procedures outlined in Table 6-12 will be performed at Visit 12 (Day 211 [±3 days]).

Table 6-12. Procedures and Assessments at Visit 12 (Day 211)

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 any other procedures are performed and before any study-related information is communicated to the subject
Adverse events	Recording of adverse events occurring since Visit 11
Concomitant medications	Recording of concomitant medication used since Visit 11
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 weight, evidence of palpable lymphadenopathy, hepatomegaly, and/or splenomegaly
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 absolute number 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
IWRS access	Access of IWRS to document subject visit
Study drug administration	Subject to continue with study drug as prescribed.
Scheduling of Visit 13 radiology assessment	CT or MRI imaging of neck, chest, abdomen, and pelvis to be scheduled for Visit 13.

Abbreviations: 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, GGT=gamma-glutamyltransferase, HRQL=health-related quality of life, Ig=immunoglobulin, LDH=lactate dehydrogenase, MRI=magnetic resonance imaging

6.2.13. Visit 13 (Day 253) (Clinic and Radiology Visit)

The procedures outlined in Table 6-13 will be performed at Visit 13 (Day 253 [±3 days]).

Table 6-13. Procedures and Assessments at Visit 13 (Day 253)

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.
During-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 any other procedures are performed and before any study-related information is communicated to the subject
Adverse events	Recording of adverse events occurring since Visit 10
Concomitant medications	Recording of concomitant medication used since Visit 10
Study drug return/ accounting	Counting returned study drug.
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 weight, evidence of palpable lymphadenopathy, hepatomegaly, and/or splenomegaly
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 absolute number 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.
IWRS access	Access of IWRS to obtain study drug blister card numbers
Study drug administration	Subject to continue with study drug as prescribed.
Study drug dispensing	Dispensing of 12-week supply of study drug to the subject with instructions for self-administration at home.

Abbreviations: ALP=alkaline phosphatase, ALT=alanine aminotransferase, AST=aspartate aminotransferase, CR=complete response, CT=computed tomography, EQ-5D=EuroQoL Five-Dimension, FACT-Leu=Functional Assessment of Cancer Therapy-Leukemia, GGT=gamma-glutamyltransferase, HRQL=health-related quality of life, Ig=immunoglobulin, LDH=lactate dehydrogenase, MRI=magnetic resonance imaging

6.2.14. Visit 14 (Day 295) (Clinic Visit)

The procedures outlined in Table 6-14 will be performed at Visit 14 (Day 295 [±3 days]).

Table 6-14. Procedures and Assessments at Visit 14 (Day 295)

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 any other procedures are performed and before any study-related information is communicated to the subject
Adverse events	Recording of adverse events occurring since Visit 10
Concomitant medications	Recording of concomitant medication used since Visit 10
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 weight, evidence of palpable lymphadenopathy, hepatomegaly, and/or splenomegaly
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 absolute number 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
IWRS access	Access of IWRS to document subject visit
Study drug administration	Subject to continue with study drug as prescribed.
Scheduling of Visit 15 radiology assessment	CT or MRI imaging of neck, chest, abdomen, and pelvis to be scheduled for Visit 15.

Abbreviations: 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, GGT=gamma-glutamyltransferase, HRQL=health-related quality of life, Ig=immunoglobulin, LDH=lactate dehydrogenase, MRI=magnetic resonance imaging

6.2.15. Visit 15 and Subsequent Visits (Day 337 and Every 12 Weeks) (Clinic and Radiology Visits)

The procedures outlined in Table 6-15 will be performed at Visit 15 (Day 337 [±3 days]) and every 12 weeks thereafter [±7 Days]).

Table 6-15. Procedures and Assessments at Visit 15 and Subsequent Visits (Day 337 and Every 12 Weeks)

Assessment or Procedure	Explanation
Pre-Visit Tumor Assessment	
Radiology assessment[a]	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.
During-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 any other procedures are performed and before any study-related information is communicated to the subject
Adverse events	Recording of adverse events occurring since prior visit
Concomitant medications	Recording of concomitant medication used since prior visit
Study drug return/ accounting	Counting returned study drug.
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 weight, evidence of palpable lymphadenopathy, hepatomegaly, and/or splenomegaly
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 absolute number of CD4+, 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

Assessment or Procedure	Explanation
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.
IWRS access	Access of IWRS to obtain study drug blister card numbers
Study drug administration	Subject to continue with study drug as prescribed.
Study drug dispensing	Dispensing of 12-week supply of study drug to the subject with instructions for self-administration at home
PJP prophylaxis	Subjects must receive trimethoprim-sulfamethoxazole or other established prophylaxis for PJP throughout the course of idelalisib treatment. Subjects must permanently discontinue idelalisib upon diagnosis of PJP.
Scheduling of next visit radiology assessmenta	CT or MRI imaging of neck, chest, abdomen, and pelvis to be scheduled for next clinic visit (every 12 weeks).

a As of Amendment 9, Version 10, 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: ALP=alkaline phosphatase, ALT=alanine aminotransferase, AST=aspartate aminotransferase, CMV=cytomegalovirus, CR=complete response, CT=computed tomography, EQ-5D=EuroQoL Five-Dimension, FACT-Leu=Functional Assessment of Cancer Therapy-Leukemia, GGT=gamma-glutamyltransferase, HRQL=health-related quality of life, Ig=immunoglobulin, LDH=lactate dehydrogenase, MRI=magnetic resonance imaging, PJP= *Pneumocystis jirovecii pneumonia*

6.2.16. 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 6-16. 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 6-16. Procedures and Assessments at End-of-Study Visit

Assessment or Procedure	Explanation
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.
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 weight, evidence of palpable lymphadenopathy, hepatomegaly, and/or splenomegaly
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 β2 microglobulin
PPD	PPD
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

Assessment or Procedure	Explanation
Circulating cells	Including cells for analysis of PI3K/AKT/mTOR pathway activation and quantitation of absolute number of CD4+, 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
PJP prophylaxis	Subjects must receive trimethoprim-sulfamethoxazole or other established prophylaxis for PJP after completion of idelalisib treatment until the CD4+ T-cell count is > 200 cells/mcL, at which point PJP prophylaxis may be discontinued.
IWRS	Access IWRS to document that subject has permanently discontinued study therapy and to indicate whether subject agrees to continue to undergo long-term follow-up

a An end-of-study CT/MRI tumor assessment should be performed unless the subject has had a CT/MRI assessment ≤4 weeks prior to end-of-study discontinuation.

Abbreviations: β-HCG=beta human chorionic gonadotropin, ALP=alkaline phosphatase, ALT=alanine aminotransferase, AST=aspartate aminotransferase, CLL=chronic lymphocytic leukemia, CT=computed tomography, FISH= fluorescence in-situ hybridization, GGT=gamma-glutamyltransferase, IgHV=immunoglobulin heavy-chain variable-region, IWRS=interactive web response system, LDH=lactate dehydrogenase, MRI=magnetic resonance imaging, PJP= *Pneumocystis jirovecii pneumonia,* RNA=ribonucleic acid, ZAP-70=zeta-associated protein 70

6.2.17. 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 will be requested of all subjects who withdraw from study for any reason.

The 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

PPD

6.4. Blood Collection

The maximum amount of blood to be drawn at a visit ~115 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 ~560 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 ~1.6 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.

PPD

6.5. Study Procedure Rationale

The planned study assessments and timing have been selected as appropriate for screening of subjects, for determination of idelalisib-related 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 3.2.

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}. Treatment decisions by the investigator in this study will be based on these assessments. Radiographic and clinical tumor assessments will be subject to independent confirmation by the IRC (see Section 10.4.2).

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.

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 10.4.2).

7.3. Timing of Assessments

All baseline clinical and CT/MRI tumor assessments should be performed within 4 weeks prior to initiation of study drug therapy. In order to optimize scheduling convenience for the subject and for the investigational staff, clinical and CT/MRI tumor assessments performed as part of Study GS-US-312-0116 need not be repeated and can be used as baseline tumor assessments for Study GS-US-312-0117 if performed within 4 weeks prior to initiation of study drug therapy on Study GS-US-312-0117. Clinical tumor assessments should be performed at each clinical visit. On-study CT/MRI tumor assessments should be performed at ~8- to 12-week intervals as dictated by the study protocol. As of Amendment 9, Version 10, 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 has had a CT/MRI assessment ≤4 weeks prior.

7.4. Identification and Measurement 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. The cross-sectional dimensions (the largest cross-sectional diameter, ie, the LD × LPD) will be recorded (in cm) for each index lesion. The product of the perpendicular diameters (PPD) (in cm^2) for each index lesion and the sum of the products (SPDs) (in cm^2) for all index lesions will be calculated and recorded. The baseline SPDs will be used as references by which 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 centimenters 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

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

By imaging, the spleen will be considered enlarged if it is >12 cm in LVD {Asghar 2011, Bezerra 2005}.

For subjects with splenomegaly at baseline or at the splenic LVD nadir, respective response and progression evaluations of the spleen will consider only changes relative to the enlargement of the spleen at baseline or nadir, not changes relative to the total splenic LVD.

A 50% decrease (minimum 2 cm) from baseline in the enlargement of the spleen in its LVD or decrease to ≤12 cm in the LVD, is required for declaration of a splenomegaly response. Conversely, an increase in splenic enlargement by ≥50% from nadir (with a minimum 2 cm increase) is required for declaration of splenic progression.

By imaging, the liver will be considered enlarged if it is >18 cm in LVD {Erturk 2006}.

A 50% decrease (minimum 2 cm) from baseline in the enlargement of the liver in its LVD or decrease to ≤ 18 cm in the LVD is required for declaration of a hepatomegaly response. Conversely, an increase in liver enlargement by ≥50% from nadir (with a minimum 2 cm increase) is required for declaration of hepatic progression.

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, and 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 evaluable (NE) is provided for situations in which there is inadequate information to otherwise categorize response status. A response category of no disease (ND) is included for situations in which there is absence of tumor both at baseline and on treatment.

The best overall response will be determined. The best overall response is the best response recorded from the start of treatment until disease/recurrence progression (taking as a reference for disease progression the smallest measurements recorded since treatment started). Subjects with a best overall response of NE or ND will be counted in the denominators in calculations of tumor response rates.

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 or transfusions
  - 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
- A 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, defined as a ≥50% decrease (minimum 2 cm) from baseline in the enlargement of the spleen or decrease to ≤12 cm in the LVD by imaging
- In a subject with enlargement of the liver at baseline, a hepatomegaly response, defined as a ≥50% decrease (minimum 2 cm) from baseline in the enlargement of the liver or decrease to ≤18 cm in the LVD by imaging
- 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 or transfusions
  - 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 stable disease (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
- 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 by ≥50% from the nadir in the SPD of index lesions
  - Increase from the nadir by ≥50% in the LD of 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 lymph node or other tissue biopsy, or fluid cytology (with the biopsy or fluid cytology date being considered the date of CLL progression if the subject has no earlier objective documentation of CLL progression).
- Decrease in platelet count or hemoglobin that is attributable to CLL, is not attributable to an autoimmune phenomenon, and is confirmed by bone marrow biopsy showing an infiltrate of clonal CLL cells
  - The current platelet count is $<100 \times 10^9$/L and there has been a decrease by >50% from the highest on-study platelet count
  - 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: If there is uncertainty regarding whether there is true progression, the subject should continue study treatment and remain under close observation (eg, evaluated at 4-week intervals) 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 has experienced 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

7.5.7. 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, lymphocytosis alone will not preclude subjects from meeting the criteria for PR if other criteria for PR are met and will not be considered evidence of disease 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.

7.5.8. Documentation of Definitive CLL Progression

Of importance, CLL response and progression data collected from the primary study will be subjected to IRC review (see Section 10.4.2). ***Subjects must have confirmation by the sponsor working in collaboration with the IRC that the disease has progressed on the primary clinical trial (Study GS-US-312-0116) before being permitted to receive secondary idelalisib therapy on this extension trial (GS-US-312-0117).*** Subjects should continue study drug pending confirmation of progression status. CT/MRI should be attempted in order to document definitive disease progression by the IRC. The end-of study scan from the primary study can serve as the baseline scan for the extension study if obtained within the specific screening period for the extension study. If obtained within the specified screening period for the extension study, this scan can serve as the baseline scan for the extension study.

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; 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 (e.g., hospitalization for elective surgery, social and/or convenience admissions)
- Overdose without clinical sequelae (see Section 5.2.8)
- 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 5.4.10 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 defect

- A medically important event or reaction. Such events may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the subject or may require intervention to prevent 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 8.5. 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 Drug Safety and Public Health (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 4 weeks after last administration of study IMP must be reported to the CRF/eCRF 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 suspected unexpected serious adverse reactions (SUSARs). In accordance with the EU Clinical Trials Directive (2001/20/EC), Gilead or a specified designee will notify worldwide regulatory agencies and the relevant 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 for Study GS-US-312-0117. Any new adverse events occurring thereafter should not be reported within Study GS-US-312-0116, but instead should be reported within Study GS-US-312-0117. The end of the adverse-event-reporting period for Study GS-US-312-0117 occurs 30 days after the discontinuation from study drug 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 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:	PPDPPD
Gilead Sciences Medical Monitor	Name: Title: Telephone: Facsimile: E-mail:	PPD Medical Monitor, Clinical Research PPD PPD 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 following possible maternal or paternal exposure to the medicinal product.

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 the 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. Analysis Objectives

As described in Section 3, the objectives of this clinical trial will focus on determining the effect of idelalisib 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

The endpoints of the study are defined in Section 3.1, grouped in categories relating to tumor control, patient well-being, pharmacodynamic markers of drug activity and resistance, exposure, safety, and pharmacoeconomics.

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 receive ≥1 dose of any study treatment (high-dose idelalisib or standard-dose idelalisib). In the ITT analysis set, study drug assignment will be designated according to planned allocation in this study, regardless of whether subjects receive a different study therapy from that to which they were allocated.

This analysis set will be used in the analyses of subject characteristics and all the tumor control and patient well-being endpoints. 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 will be included in the denominators 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 designated 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 these tumor control and patient well-being endpoints: PFS, ORR, lymph node response rate, OS and CR rate.

9.3.1.3. Safety Analysis Set

A safety analysis set will include subjects in the ITT analysis set grouped for analyses with treatment assignments designated according to the actual study drug received.

This analysis set will be used in the analyses of safety variables as well as study treatment administration, and health economic variables.

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.

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.

9.3.2.2. Double-Blinded Portion of the Study Analyses

Efficacy and safety data collected during the blinded portion of Study GS-US-312-0117 will be presented in the following 2 groups:

- IDELA 300 mg BID: Subjects who have PD per IRC confirmation in Arm A of Study GS-US-312-0116 and subsequently enroll into Study GS-US-312-0117 to receive IDELA 300 mg BID during the double-blind portion of the study

- Placebo in Study GS-US-312-0116 + IDELA 150 mg BID in Study GS-US-312-0117: Subjects who have PD per IRC confirmation in Arm B of Study GS-US-312-0116 and subsequently enroll Study GS-US-312-0117 to receive IDELA 150 mg BID during the double-blind portion of the study

All analyses will be performed based on the data collected during the blinded-portion of the extension study. Time-to-event analyses will reference to the date of first treatment on this clinical trial (Study GS-US-312-0117). Similarly, evaluations of on-therapy changes will reference the baseline values obtained prior to treatment in this study. The baseline value used in each analysis will be the last (most recent) pre-treatment value. Analyses will be descriptive in nature and formal comparisons of outcomes in the 2 groups are not planned.

9.3.2.3. Open-Label Extension Study Analyses

GS-US-312-0117 will become an open-label study offering idelalisib 150 mg BID to GS-US-312-0116 subjects who were randomized to Arm B. Subjects randomized to Arm A will continue idelalisib at 150 mg BID. Efficacy and safety data collected during the primary and open-label extension studies will be presented in the following 4 groups:

- IDELA 150 mg BID: Subjects who are randomized to Arm A in Study GS-US-312-0116 and transition to Study GS-US-312-0117 during the open-label portion of the study to continue IDELA 150 mg BID

- Placebo in GS-US-312-0116 + IDELA 150 mg BID (open-label): Subjects who are randomized to Arm B in Study GS-US-312-0116 and transition to receive IDELA 150 mg BID during the open-label portion of the study

- IDELA 300 mg BID: Subjects who have PD per IRC confirmation in Arm A of Study GS-US-312-0116 and subsequently enroll Study GSUS-312-0117 to receive IDELA 300 mg BID during double-blind portion of the study

- Placebo in GS-US-312-0116 + IDELA 150 mg BID in GS-US-312-0117: Subjects who have PD per IRC confirmation in Arm B of Study GS-US-312-0116 and subsequently enroll Study GS-US-312-0117 to receive IDELA 150 mg BID during double-blind portion of the study.

Depending on the endpoints, analyses may be based on the combined data from both primary and extension studies or data from the extension study alone. Analyses will be descriptive in nature and formal comparisons of outcomes in the 4 groups are not planned. A separate statistical analysis plan will be created for the open-label portion of the study.

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

Tumor control assessments will be based on standardized IWCLL criteria {Cheson 2012, Hallek 2008}, as specifically modified for this study considering the pharmacology of idelalisib. The individual and composite endpoints of response and progression (considering changes in lymph node area, liver and spleen size, bone marrow, platelet counts, hemoglobin, neutrophil counts, and peripheral blood lymphocyte counts) will be determined. Tumor control will be documented at each assessment by response category (eg, CR, PR, SD, definitive PD, NE, ND) 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 relevant objective radiographic or laboratory data. Because of the characteristic redistribution lymphocytosis that is expected with PI3Kδ inhibition, lymphocyte count will be ignored in the evaluation of progression. Changes in tumor status as provided by the investigator and changes in tumor status as adjudicated by the IRC (see Section 10.4.2) will be described. The findings of the IRC will be considered primary for analyses of all tumor control endpoints.

The following censoring conventions will be applied:

- PFS and DOR: 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.

- OS: Data from surviving subjects will be censored at the last time that the subject was known to be alive.

9.4. Analysis Plan

9.4.1. Subject Disposition and Baseline Characteristics

A listing of all ITT analysis subjects will be generated to describe site, subject number, first screening date, first treatment date, allocated study drug assignment, actual study drug assignment, the longest duration of study drug treatment, and the reason for discontinuing study treatment. Available information on subjects who were screened or registered but 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 for the ITT analysis set. As appropriate for the specific variable, subject baseline characteristics acquired in Study GS-US-312-0116 will be referenced in Study GS-US-312-0117.

9.4.2. Efficacy Analyses

9.4.2.1. Time-to-Event Tumor Control and Survival Endpoints

PFS, DOR and OS will be described in the ITT analysis set using Kaplan-Meier methods by treatment group. Medians, ranges, and corresponding 95% CIs will be presented.

The Cox regression approach may be used to explore the influence of the primary study stratification factors and other baseline characteristics on PFS and OS. The stratification variables from the primary study and additional baseline subject characteristics may be included as covariates, focusing on those with expected prognostic significance.

9.4.2.2. Categorical Endpoints

Response rates, lymph node response rate, splenomegaly response rate, hepatomegaly response rate, ALC response rate, platelet response rate, hemoglobin response rate, and neutrophil response rate will be described. In the calculation of response rates, subjects who do not have sufficient baseline or on-study tumor assessment to characterize response will be included in the denominator. For all analyses, the corresponding 95% CIs will be presented.

The potential influence of subject baseline characteristics on response rates may be explored with multiple logistic regression modeling.

9.4.2.3. Continuous Endpoints

Changes in lymph node area and changes in performance status, PI3K/AKT/mTOR pathway activation, and plasma chemokines/cytokines will be assessed by treatment group. Both changes from baseline to each subsequent timepoint and best overall on-study changes will be analyzed using appropriate methods (eg, analysis of covariance [ANCOVA] or paired t-tests). Means and standard errors will be presented.

9.4.2.4. Health-Related Quality of Life and Performance Status

The FACT-Leu questionnaire data will be scored and processed according to the user manual. Missing items in a subscale will be imputed consistent 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.

As a baseline, the last value obtained prior to receiving the first idelalisib dose of 150 mg and 300 mg will be used, depending on the treatment group assigned.

The mean and change from baseline in mean scores to each subsequent assessment will be summarized for the FACT-Lym subscale and composite scores. The best change from baseline during the study, defined as the highest positive value among all post-baseline visits minus the baseline value, will also be summarized.

9.4.3. Exposure and Safety Analyses

9.4.3.1. Treatment Administration and Study Drug Compliance

Descriptive information will be provided by treatment arm regarding the number of doses of study therapy prescribed, the total number of doses taken, the percent of expected doses taken, the number of days of treatment, and the number and timing of prescribed dose reductions and interruptions.

Study drug 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).

9.4.3.2. Idelalisib Plasma Concentrations

Bioanalytical analyses will performed independently so that the study team and investigators will not have knowledge of data from individual subjects. 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.

9.4.3.3. 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. Information regarding CLL therapy that was administered prior to Study GS-US-312-0116 will be referenced in reporting the results of Study GS-US-312-0117. In addition, relevant treatment administration information collected during Study GS-US-312-0116 will be referenced in reporting the results of this study. As appropriate and if available, information on the sequencing, type, dose, schedule, timing, duration of use, and efficacy of prior regimens will be provided, focusing particularly on findings observed in Study GS-US-312-0116.

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.

The number, type, and timing of post-study-treatment regimens for CLL will be summarized by treatment arm, characterizing the disposition of all subjects who were eligible for post-study treatment and also those who were not eligible for post-study treatment (eg, subjects who are never treated at all, die while on study treatment, are still on study, are lost to follow-up, etc).

9.4.3.4. 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 to 30 days after the last dose of study treatment.

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 and by visit. 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 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)

Separate listings and summaries will be prepared for long-term follow-up safety data (see Section 6.2.17).

9.4.3.5. 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 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.

9.4.3.6. 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).

9.4.4. Other Analyses

9.4.4.1. Between-Study Comparisons

It is expected that patients with a progressive malignancy like CLL will normally fare better with an earlier therapy than with a later therapy. However, if the converse situation proves true – eg, if an investigational treatment (idelalisib) administered later shows similar or greater benefit than a standard treatment (rituximab) administered earlier – strong evidence of investigational drug effect is demonstrated. Evaluating data derived from the same study subjects during their sequential participation in 2 clinical trials offers unique analytical challenges. However, in this integrated Phase 3 study program, it is likely that comparing baseline characteristics and outcomes among Arm B subjects participating in Study GS-US-312-0116 and Study GS-US-312-0117 will be informative. Such an evaluation characterizes how the subjects and the CLL disease process change with time and treatment. In addition, such an analysis provides relevant supporting information documenting the benefits of single-agent idelalisib relative to single-agent rituximab in the same subjects.

Accordingly, baseline characteristics, time-to-event efficacy variables (eg, PFS, TTR, DOR), categorical variables (eg, ORR, lymph node response rate, splenomegaly response rate, hepatomegaly response rate), and continuous variables (eg, percentage changes in lymph node area; changes in performance status, PI3K/AKT/mTOR pathway activation and plasma chemokines/cytokines) may be evaluated between Study GS-US-312-0116 and Study GS-US-312-0117 for Arm B subjects.

9.4.4.2. Health Care Resource Utilization

The EQ-D5 questionnaire data will be scored, processed, and standardized according to the user manual. Change from baseline in EQ-5D visual analogue scale and EQ-5D index will be summarized. 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.

The perspective of this analysis will be that of the third-party payer(s) and the hospital over a lifetime horizon in the base case. The costs will be described relative to the health care findings as measured by duration of tumor control, the symptom-free survival period, life-years, utility outcomes, 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.

9.4.4.3. 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. 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).

9.5. Sample Size

The sample size for this extension study is not based upon a formal statistical hypothesis. The upper bound of the sample size in this study is determined by the sample size of the preceding primary study (Study GS-US-312-0116) in which ~220 subjects (~110 per arm) are expected to be enrolled. It is estimated that this extension study (Study GS-US-312-0117) will have a total idelalisib-treated N~180 (assuming a ~10% dropout rate during Study GS-US-312-0116 and a further ~10% dropout rate in the transition from the primary study to the extension study).

9.6. Timing of Analyses

The DMC will have access to serious adverse events requiring expedited reporting and will be provided with accumulating safety data on a regular basis. Interim safety reviews will be conducted by the DMC in conjunction with safety reviews of the primary clinical trial (Study GS-US-312-0116) if applicable. Thus, 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 trials are 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 interim efficacy analysis of this clinical trial (Study GS-US-312-0117) is planned to take place at the time of the final blinded analysis of the primary study (GS-US-312-0116). The intent is to provide the data from this extension study in support of regulatory review of data from the primary study. An analysis of efficacy and safety may be performed to satisfy regulatory requirements and to perform long-term efficacy, safety and OS follow-up. The timing of the final analysis is expected to occur within 48 months of accrual of the final subject to Study GS-US-312-0117.

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 United States) and to an IEC for sites enrolling outside of the United States). 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 United States, 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 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 the 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 section (see Section 5.2.7), 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 IRB/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 United States 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

Electronic data capture 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 this extension study (GS-US-312-0117) 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. 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. It is expected that the members of the DMC will be the same as those for the primary study (Study GS-US-312-0116).

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:

- Reviewing the general progress of the study as regards subject accrual, study conduct, and protocol violations
- Examining accumulated safety, efficacy, and other relevant data at prespecified points during the course of the study
- Reviewing major study design modifications prior to implementation of those modifications
- Making recommendations concerning continuation, modification, interruption, or termination of each study
- Advising the company on changes to informed consent documents
- Proposing updates to the DMC monitoring plan, changes in the DMC membership, actions to be taken relating to conflict of interest or confidentiality breaches, the need for additional expertise during DMC deliberations, revisions to the DMC charter, or alterations in the support provided to the DMC
- 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 appropriate actions (eg, continuation of the study unchanged, continuation of the study with modifications in design or monitoring plan, interruption of study accrual, study termination).

10.4.2. 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 until the primary analysis . 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 same organization that is providing IRC services for Study GS-US-312-0116 will provide IRC services for this study.

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12. APPENDICES

Appendix 1. Investigator Signature Page

GILEAD SCIENCES, INC.
199 EAST BLAINE STREET
SEATTLE, WA 98102

STUDY ACKNOWLEDGEMENT

A Phase 3, Double-Blind Extension Study Evaluating the Efficacy and Safety of Two Different Dose Levels of Single-Agent Idelalisib (GS-1101) for Previously Treated Chronic Lymphocytic Leukemia

GS-US-312-0117, Version 10 (Amendment 9), 21 September 2017

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

PPD

PPD
Gilead Sciences Medical Monitor

22 September 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)

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
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FACT-Leu (Version 4)

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

	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 ☐

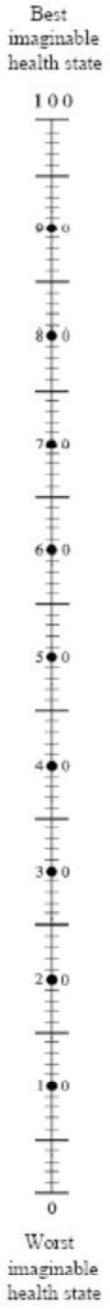
Anxiety/Depression

- 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.

Cockcroft-Gault Formulas for Calculating Estimated Creatinine Clearance

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. Cumulative Illness Rating Scale (CIRS)

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.

CIRS List of Comorbid Conditions

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	

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:

CIRS Rating Scale

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[a]**	**4[a]**	**5[a]**	**6[a]**	**7[a]**	**8[a]**	**9[a]**	**10[a]**	**11[a]**	**12[a]**	**13[a]**	**14[a]**	**15[a]**	**16+[e]**			
Week	**-4**	**0**	**2**	**4**	**6**	**8**	**10**	**12**	**16**	**20**	**24**	**30**	**36**	**42**	**48**			**30 days**	**Long-term**
Study Day	**Within -28 Days**	**1**	**15**	**29**	**43**	**57**	**71**	**85**	**113**	**141**	**169**	**211**	**253**	**295**	**337**	**Q12 Weeks**	**End of Study**	**Within +30 days**	**To +5 years**
Visit Window			**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±7**			
Informed consent	X																		
CIRS assessment	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																X		
CLL serology	X																X		
IWRS	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X		
PPD																			
HRQL/ healthy utility – FACT-Leu/EQ-5D		X	X	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	X	X	
Concomitant medications	X	X	X	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	X	X		
Physical exam (includes nodes, liver, spleen)	X	X		X		X		X	X	X	X	X	X	X	X	X	X		

Period	Screen	Treatment															Follow-up	
Visit	1	2	3[a]	4[a]	5[a]	6[a]	7[a]	8[a]	9[a]	10[a]	11[a]	12[a]	13[a]	14[a]	15[a]	16+[e]		
Week	-4	0	2	4	6	8	10	12	16	20	24	30	36	42	48		30 days	Long-term
Study Day	Within -28 Days	1	15	29	43	57	71	85	113	141	169	211	253	295	337	Q12 Weeks	End of Study	Within +30 days	To +5 years
Visit Window			±2	±2	±2	±2	±2	±2	±3	±3	±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	X	X		
Hematology	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Serum chemistry	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Circulating cells/ Immune monitoring[b]	X		X	X		X		X	X	X	X	X	X	X	X	X	X[b]		
Biomarkers	X		X	X		X		X	X	X	X	X	X	X	X	X	X		
Serum Igs[b]	X		X	X		X		X	X	X	X	X	X	X	X	X	X[b]		
Study drug administration in clinic		X	X	X		X		X	X	X	X								
Idelalisib pharmacokinetics [c]		X	X	X		X		X	X	X	X								
Study drug dispensing/ accounting [c]		X		X		X		X	X	X	X		X		X	X	X		
Radiology assessment (CT/MRI)	X					X[f]			X[f]		X[f]		X[f]		X[f]	X[f, k]	X [f,g]		
Bone marrow biopsy/ aspirate [d]	X					X			X		X		X		X	X	X		
CMV viral load[h]																X			
PJP prophylaxis[i, j]																X[i]	X[j]		

Period	Screen	Treatment															Follow-up	
Visit	**1**	**2**	**3[a]**	**4[a]**	**5[a]**	**6[a]**	**7[a]**	**8[a]**	**9[a]**	**10[a]**	**11[a]**	**12[a]**	**13[a]**	**14[a]**	**15[a]**	**16+[e]**			
Week	**-4**	**0**	**2**	**4**	**6**	**8**	**10**	**12**	**16**	**20**	**24**	**30**	**36**	**42**	**48**			**30 days**	**Long-term**
Study Day	**Within -28 Days**	**1**	**15**	**29**	**43**	**57**	**71**	**85**	**113**	**141**	**169**	**211**	**253**	**295**	**337**	**Q12 Weeks**	**End of Study**	**Within +30 days**	**To +5 years**
Visit Window			**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±7**			
CD4+ T-cell count[j] (related to PJP prophylaxis)																	X[j]		
Post-treatment CLL therapy																			X
Long-term follow-up																			X

a Following unblinding of the study, the visit schedule will be modified per Section 6.2 and Visits 3 – 15 may not be applicable for subjects who were randomized to idelalisib on Study GS-US-312-0116 or who were randomized to placebo on GS-US-312-0116 and have received 24 weeks cumulative treatment with idelalisib

b Circulating cells/Immune monitoring and Serum Igs should be performed at the the End of Study visit

c Subjects who were randomized to placebo on Study GS-US-312-0116 and enroll following unblinding, may have idelalisib treatment (and associated PK testing) delayed at the Investigator's discretion until the time of disease progression or until the investigator determines the subject may benefit by the initiation of idelalisib treatment

d At screening, to be performed 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; if the subject does not otherwise meet criteria for CR or if the nature of PD does not require bone marrow confirmations, it is not necessary to obtain a follow-up bone marrow biopsy/aspirate

e Following unblinding, Visit 16+ may be completed prior to 48 weeks as subjects transition to a Q12 week visit schedule

f 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

g An end-of-study CT/MRI tumor assessment should be performed unless the subject already has radiographic confirmation of definitive disease progression ≤ 4 weeks prior to study discontinuation

h CMV viral load should be performed approximately every 4 weeks throughout idelalisib treatment. 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.

i 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 after the last dose of idelalisib. Subjects must permanently discontinue idelalisib upon diagnosis of PJP. Prophylaxis will continue for 2 to 6 months after the last dose of idelalisib and until the CD4+ T-cell count is documented to be >200 cells/mcL after idelalisib treatment ends.

j CD4+ T-cell count[l] (related to PJP prophylaxis): PJP prophylaxis will continue until the CD4+ T-cell count is documented to be >200 cells/mcL after idelalisib treatment ends.

k As of Amendment 9, Version 10, 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, CMV=cytomegalovirus, CR=complete response, CT=computed tomography, 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.