CLINICAL STUDY PROTOCOL

Study Title:	A Phase 3, Randomized, Controlled Study Evaluating the Efficacy and Safety of Idelalisib (GS-1101) in Combination with Ofatumumab 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:	2012-001236-65	
Indication:	Chronic Lymphocytic Leukemia	
Gilead Protocol ID:	GS-US-312-0119	
Gilead Sciences Medical Monitor:	Name: Office Telephone: Office Fax: Mobile Telephone: E-mail:	PPD PPD PPD PPD PPD
Protocol Version/Date:	Version 1.0 (Original): Version 2.0: Version 3.0: Version 4.0: Version 5.0: Version 6.0: Version 7.0: Version 8.0: Version 9.0: Version 10.0: Version 11.0	02 July 2012 09 November 2012 17 October 2013 13 January 2014 04 March 2014 26 September 2014 17 December 2014 28 March 2016 04 August 2016 24 October 2016 30 August 2017

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PROTOCOL SYNOPSIS

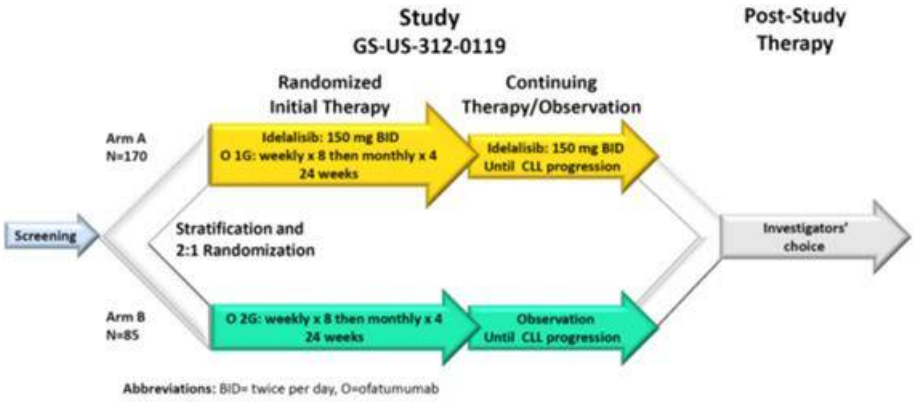
Gilead Sciences, Inc.
199 East Blaine Street
Seattle, WA 98102, USA

Study Title:	A Phase 3, Randomized, Controlled Study Evaluating the Efficacy and Safety of Idelalisib (GS-1101) in Combination with Ofatumumab for Previously Treated Chronic Lymphocytic Leukemia
Study Centers Planned:	Approximately 115 centers in the United States, Canada, Australia, and Europe
IND Number:	101254
EudraCT Number:	2012-001236-65
Primary Objective:	• To evaluate the effect of the addition of idelalisib (GS-1101) to ofatumumab on progression-free survival (PFS) in subjects with previously treated chronic lymphocytic leukemia (CLL)
Secondary Objectives:	• To evaluate the effect of the addition of idelalisib to ofatumumab on the onset, magnitude, and duration of tumor control • To evaluate the effect of the addition of idelalisib to ofatumumab on the onset, magnitude, and duration of tumor control for subjects with 17p deletion and/or TP53 mutation • To assess the effect of the addition of idelalisib to ofatumumab on measures of subject well-being, including overall survival (OS), health-related quality of life (HRQL) and performance status • To assess the effects of the addition of idelalisib to ofatumumab on disease-associated biomarkers and to evaluate potential mechanisms of resistance to idelalisib • To characterize the effect of ofatumumab on idelalisib exposure through evaluation of idelalisib plasma concentrations over time • To describe the safety profile observed with the addition of idelalisib to ofatumumab • To estimate health resource utilization associated with the addition of idelalisib to ofatumumab

Study Design:

Study GS-US-312-0119 is a Phase 3, multicenter, 2-arm, randomized, controlled, parallel-group, clinical trial.

Study Schema



Treatment Groups

- Arm A: idelalisib + ofatumumab (1000-mg dosing regimen)
- Arm B: Ofatumumab (2000-mg dosing regimen)

Randomization and Stratification

- 2:1 allocation to Arm A vs Arm B with implementation through an interactive web response system (IWRS)
- Fixed-block centralized randomization with allocation of subjects within the 8 strata as defined by the intersection of 3 binary stratification factors:
- 17p deletion and/or TP53 mutation in CLL cells: either vs neither (or indeterminate)
- Immunoglobulin heavy chain variable region (IgHV) mutation: unmutated (or IgHV3-21) vs mutated (or indeterminate)
- Disease status: refractory (CLL progression < 6 months from completion of prior therapy) vs relapsed
  (CLL progression ≥6 months from completion of prior therapy)

Number of Subjects Planned:

Total of ~255 subjects (~170 subjects in Arm A and ~85 subjects in Arm B)

Target Population:	The target population comprises adults with previously treated CLL who have measurable lymphadenopathy, require treatment for CLL, have disease that is not refractory to ofatumumab, and might benefit from a change in therapy because they have experienced CLL progression < 24 months since the completion of the last prior treatment.
Duration of Treatment:	Idelalisib will be taken continuously until the earliest of subject withdrawal from study, definitive progression of CLL, intolerable study drug-related toxicity, pregnancy, substantial noncompliance with study procedures, or study discontinuation. Idelalisib administration should be continued in subjects with a positive benefit-risk profile assessment as per the investigator. Ofatumumab will be administered until the earliest of a maximum of 12 infusions, subject withdrawal from study, definitive progression of CLL, intolerable ofatumumab-related toxicity, pregnancy, substantial noncompliance with study procedures, or study discontinuation. Subjects in Arm A will continue with idelalisib or ofatumumab, even if the other drug must be discontinued due to toxicity.
Diagnosis and Main Eligibility Criteria:	<u>Inclusion Criteria</u> Subjects must meet all of the following inclusion criteria to be eligible for participation in this study: 1) Male or female ≥18 years of age. 2) Diagnosis of B-cell CLL, with diagnosis established according to International Workshop on Chronic Lymphocytic Leukemia (IWCLL) criteria and documented within medical records. 3) CLL that warrants treatment (consistent with accepted IWCLL criteria for initiation of therapy). Any of the following conditions constitute CLL that warrants treatment: a) Evidence of progressive marrow failure as manifested by the onset or worsening of anemia and/or thrombocytopenia, or b) Massive (ie, lower edge of spleen ≥ 6 cm below the left costal margin), progressive, or symptomatic splenomegaly, or c) Massive (ie, ≥ 10 cm in the longest diameter), progressive, or symptomatic lymphadenopathy, or d) Progressive lymphocytosis in the absence of infection, with an increase in blood absolute lymphocyte count (ALC) ≥ 50% over a 2-month period or lymphocyte doubling time of < 6 months (as long as initial ALC was ≥ 30,000/L), or

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

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

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

ii) Significant fatigue (≥ Grade 2), or

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

iv) Night sweats for >1 month

4) Presence of measurable lymphadenopathy (defined as the presence of ≥ 1 nodal lesion that measures ≥ 2.0 cm in the longest diameter [LD] and ≥ 1.0 cm in the longest perpendicular diameter [LPD] as assessed by computed tomography [CT] or magnetic resonance imaging [MRI]).

5) Prior treatment for CLL comprising therapy with either of the following types of drugs given alone or in combination:

a) A purine analog (eg, fludarabine, pentostatin, cladribine) administered for ≥ 2 cycles of cytotoxic treatment

b) Bendamustine administered for ≥ 2 cycles of treatment

Note: Prior drugs may have been administered as single agents or as components of combination therapies. Subjects may also have received other commercially available therapies (eg, rituximab, alemtuzumab, ofatumumab, lenalidomide, corticosteroids, or others) or non-excluded investigational therapies. Each repeated but separated therapeutic application of the same single-agent or combination is considered an independent regimen.

6) Documentation of CLL progression < 24 months since the completion of the last prior therapy for CLL.

7) Discontinuation of all therapy (including radiotherapy, chemotherapy, immunotherapy, or investigational therapy) for the treatment of CLL ≥ 6 weeks before randomization.
Note: Subjects may be receiving corticosteroids to manage CLL manifestations.

8) All acute toxic effects of any prior antitumor therapy resolved to Grade ≤ 1 before randomization (with the exception of alopecia [Grade 1 or 2 permitted], neurotoxicity [Grade 1 or 2 permitted], or bone marrow parameters Grade 1, 2, 3, or 4 permitted]).

9) Karnofsky performance score of ≥ 60.

10) Required baseline laboratory data (within 4 weeks prior to randomization) 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 syndrome or hemolysis)
	Serum ALT	≤ 2.5 x ULN
	Serum AST	
Renal	eC_{Cr}[a]	> 30 ml/min
Pregnancy	β-HCG[b]	Negative
Infection	HIV	Negative HIV antibody
	HBV	Negative HBsAg and negative HBc antibody or positive HBc and negative for HBV DNA by quantitative PCR
	HCV	Negative viral RNA (if HCV antibody is positive)

a As calculated by the Cockcroft-Gault formula {Cockcroft 1976} (see Appendix 5)
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, DNA=deoxyribonucleic acid, eCCr=estimated creatinine clearance, HBc antibody=anti-hepatitis B core antibody, HBsAg=hepatitis B surface antigen, HBV=hepatitis B virus, HCV=hepatitis C virus, HIV=human immunodeficiency virus, Ig=immunoglobulin, PCR=polymerase chain reaction, RNA=ribonucleic acid, ULN=upper limit of normal

11) For female subjects of child-bearing potential, willingness to use a protocol-recommended method of contraception from the screening visit (Visit 1) throughout the study treatment period and to 30 days from the last dose of study drug or 12 months from the last dose of ofatumumab (whichever is later). Note: A female subject is considered to be of child-bearing 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 years with amenorrhea for ≥ 6 months).

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

13) 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.

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

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

Exclusion Criteria

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

1) Known histological transformation from CLL to an aggressive lymphoma (ie, Richter transformation). ***Note: Biopsy documentation of the absence or presence of transformation is not required.***

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

3) History of a non-CLL malignancy except for the following: adequately treated local basal cell or squamous cell carcinoma of the skin, cervical carcinoma in situ, superficial bladder cancer, asymptomatic prostate cancer without known metastatic disease and with no requirement for therapy or requiring only hormonal therapy and with normal prostate-specific antigen for ≥ 1 year prior to randomization, other adequately treated Stage 1 or 2 cancer currently in complete remission, or any other cancer that has been in complete remission for ≥ 2 years.
4) Known hypersensitivity or intolerance to any of the active substances or excipients in the formulations for either idelalisib or ofatumumab.
5) Evidence of ongoing systemic bacterial, fungal, or viral infection at the time of randomization (Visit 2). ***Note: Subjects with localized fungal infections of skin or nails are eligible. Subjects may be receiving prophylactic antiviral or antibacterial therapies at the discretion of the investigator; 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.***
6) Ongoing drug-induced liver injury, chronic active hepatitis C (HCV), chronic active hepatitis B (HBV), alcoholic liver disease, non-alcoholic steatohepatitis, primary biliary cirrhosis, extrahepatic obstruction caused by cholelithiasis, cirrhosis of the liver, or portal hypertension.
7) Ongoing drug-induced pneumonitis.
8) Ongoing inflammatory bowel disease.
9) Ongoing alcohol or drug addiction.
10) Pregnancy or breastfeeding.
11) History of prior allogeneic bone marrow progenitor cell or solid organ transplantation.
12) Ongoing immunosuppressive therapy other than corticosteroids. ***Note: Subjects may use topical, enteric, inhaled, or systemic corticosteroids as therapy for manifestations of CLL, comorbid conditions, or autoimmune anemia and/or thrombocytopenia. During study participation, subjects may receive systemic or other corticosteroids as pretreatment for ofatumumab infusions or as needed for treatment-emergent comorbid conditions.***

	13) In a subject with a history of prior ofatumumab therapy, the time from the last dose of ofatumumab to documented CLL progression is < 6 months. 14) History of prior therapy with any inhibitor of AKT, Bruton tyrosine kinase (BTK), Janus kinase (JAK), mammalian target of rapamycin (mTOR), phosphatidylinositol 3-kinase (PI3K) (including idelalisib), or spleen tyrosine kinase (SYK). 15) Prior participation in an idelalisib clinical trial. 16) Concurrent participation in another therapeutic clinical trial. 17) Prior or ongoing clinically significant illness, medical condition, surgical history, physical finding, electrocardiogram (ECG) finding, or laboratory abnormality that, in the investigator's opinion, could adversely affect the safety of the subject or impair the assessment of study results.
Study Procedures/ Frequency:	Subjects will be randomized with a 2:1 ratio into Arm A or Arm B of the study. In Arm A, subjects will take idelalisib orally BID continuously and will receive 12 infusions of ofatumumab over ~24 weeks. In Arm B, subjects will receive 12 infusions of ofatumumab over ~24 weeks. Clinic/laboratory visits will occur weekly for Weeks 1 through 8, every 4 weeks at Weeks 12, 16, 20, and 24, and every 6 weeks between Weeks 24 and 48. Subjects continuing on study drug(s) past Week 48 will have clinic visits every 12 weeks. Subjects will be assessed for safety at each visit. Subjects in Arm A will require monthly CMV testing. Subjects will be assessed for CLL disease status by physical and/or laboratory examinations at each visit and by CT or MRI at Weeks 8, 16, 24, 36, 48 and every 12 weeks thereafter until the primary endpoint is met.
Test Therapy, Dose, and Mode of Administration:	• Arm A: Idelalisib: 150 mg taken orally BID starting on Day 1 and administered continuously thereafter
Study Drug, Dose, and Mode of Administration:	• Arm A: Ofatumumab: 300 mg intravenously on Day 1 (Week 1); thereafter 1,000 mg intravenously on Day 8 (Week 2), Day 15 (Week 3), Day 22 (Week 4), Day 29 (Week 5), Day 36 (Week 6), Day 43 (Week 7), Day 50 (Week 8), Day 78 (Week 12), Day 106 (Week 16), Day 134 (Week 20), Day 162 (Week 24) (for a total of 12 infusions)

- Arm B: Ofatumumab: 300 mg intravenously on Day 1 (Week 1); thereafter 2,000 mg intravenously on Day 8 (Week 2), Day 15 (Week 3), Day 22 (Week 4), Day 29 (Week 5), Day 36 (Week 6), Day 43 (Week 7), Day 50 (Week 8), Day 78 (Week 12), Day 106 (Week 16), Day 134 (Week 20), Day 162 (Week 24) (for a total of 12 infusions)

Criteria for Evaluation:

Primary Endpoint

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

Secondary and Exploratory Endpoints

- Five endpoints are designated as secondary endpoints for which sequential testing will be performed to control Type I error rate. Secondary endpoints will be ORR, lymph node response rate, OS, PFS in the subgroup of 17p deleted and/or TP53 mutated subjects, and CR rate. All other endpoints will be considered exploratory.

Tumor Control

- Overall response rate (ORR) – defined as the proportion of subjects who achieve a complete response (CR) or partial response (PR) response for at least 8 weeks
- 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
- PFS in the subgroup of subjects with 17p deletion and/or TP53 mutation
- CR rate – defined as the proportion of subjects who achieve a confirmed CR

[redacted]

[redacted]

Patient Well-Being

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

[redacted]

Pharmacodynamic Markers of Drug Activity and Resistance

[redacted]

Exposure

[redacted]

Safety

[redacted]

Pharmacoeconomics

[redacted]

Statistical Methods: Analysis Methods

Appropriate data analysis sets will be defined. The intent-to-treat (ITT) analysis set will be used in the analyses of the primary efficacy endpoint, PFS. The ITT analysis set will include data from all subjects who are randomized, with study drug assignment designated according to initial randomization, regardless of whether subjects receive any study drug(s) or receive a different regimen from that to which they were randomized. A safety analysis set will comprise data from subjects who receive ≥ 1 dose of study drug, with treatment assignment designated according to the actual study drug(s) 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 the primary efficacy analysis, the difference in PFS between the treatment arms will be assessed in the ITT analysis set using Kaplan-Meier methods and the stratified log-rank test. Medians, ranges, the proportions of subjects who are progression-free at 24 and 48 weeks from randomization (based on Kaplan-Meier estimates), hazard ratios, and the corresponding 95% CIs (as calculated using a Cox proportional hazards regression model) will be presented.

Secondary endpoints will be ORR, lymph node response rate, OS, PFS in the subgroup of subjects with 17p deletion and/or TP53 mutation, and CR rate. The primary efficacy hypothesis relating to PFS must be rejected at the pre-specified significance level before the efficacy hypotheses for these secondary efficacy endpoints are tested. These 5 secondary endpoints will be tested at the 2-sided 0.03 significance level in the order listed at an interim or final analysis when the primary endpoint is rejected. If a null hypothesis is not rejected, formal sequential testing will be stopped and only nominal significance will be cited for the remaining secondary endpoints.

For secondary or exploratory endpoints relating to tumor control, patient well-being, and biomarkers, analyses will be done based on the ITT, PP, or pharmacodynamic data sets, as appropriate. Time-to-event efficacy endpoints will be analyzed in a similar manner as PFS. Categorical variables will be compared using the Cochran Mantel-Haenszel test adjusted for stratification factors. Continuous endpoints will be assessed using analysis of covariance (ANCOVA) with baseline values and stratification factors as covariates. Changes from baseline in HRQL parameters and in performance status will be compared between the treatment groups using the Wilcoxon rank-sum test, considering subjects' disease progression status.

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

Based on data from prior studies, it is reasonable to assume that administration of ofatumumab to subjects with previously treated CLL in Arm B of this trial will result in a median PFS of ~8 months. An improvement in median PFS from 8 months to 14 months resulting from the addition of idelalisib to ofatumumab in Arm A of the study would correspond to a benefit ratio of 1.75 (hazard ratio 0.57).

It is assumed that PFS times are exponentially distributed in each of the 2 arms. With a hazard ratio equal to 1 under the null hypothesis of no difference between the 2 treatment arms and a hazard ratio of 0.57 under the alternative hypothesis of superiority of the idelalisib containing combination, 129 events (definitive CLL progressions or deaths) are required to achieve a power of > 0.85 based on a log-rank test with a 2-sided significance level of 0.05. Further assuming a planned accrual period of 12 months (with approximately half of the subjects enrolled during the initial 60% of the accrual period, and the remaining half of the subjects enrolled during the last 40% of the accrual period), a minimum follow-up period of 12 months, and an expectation that 10% of subjects will be lost to follow-up (5% during the accrual period and 5% during the follow-up period), and to ensure the primary analysis on PFS will be performed before or at the planned minimum 12-month follow-up period, 170 subjects will be enrolled into Arm A and 85 subjects will be enrolled into Arm B in order to achieve the expected number of events by the end of the planned minimum 12-month follow-up period.

It is expected that there will be approximately 65 deaths at the time of final analysis. This would provide ~ 85% power to detect a HR of 0.45 for overall survival based on a log-rank test on a 2-sided alpha level of 0.03.

Interim Efficacy Analyses

Two formal interim efficacy analyses for PFS are planned. The first interim analysis will be performed when ~50% of the planned 129 events occur. The second interim will be performed when ~75% of the expected events occur. Type I error rate for testing PFS will be controlled by using the O'Brien-Fleming boundaries. Based on the planned number of PFS events (50% and 75%) for the 2 interim analyses, the 2-sided alpha for the interim and the final analyses are 0.003, 0.018, 0.044. The significant levels will be recalculated based on the actual observed number of events at the time of the interim and final analyses.

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)
ADCC	antibody-dependent cellular cytotoxicity
AE	adverse event
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 idelalisib
CCL	chemokine (C-C motif) ligand
CDC	complement-dependent cytotoxicity
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
DLBCL	Diffuse large B-cell lymphoma
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
GCP	Good Clinical Practice
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
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
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
MDR	multi-drug resistance
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
mTOR	mammalian target of rapamycin
ND	no disease
NHL	non-Hodgkin lymphoma
OAT	occluded artery trial
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
Pgp	P-glycoprotein
PI3K	phosphatidylinositol 3-kinase
PI3Kδ	phosphatidylinositol 3-kinase p110δ isoform
PJP	*Pneumocystis jirovecii* pneumonia
PFS	progression-free survival
PML	progressive multifocal leukoencephalopathy
PP	per protocol
PPD	product of the perpendicular diameters
PRO	patient-reported outcome
PR	partial response
PT	prothrombin time
PVA	polyvinyl alcohol

QD	once per day
QT (interval)	measure of time between start of Q wave and end of T wave in electrical cycle of heart
RNA	ribonucleic acid
SAE	serious adverse event
SADR	serious adverse drug reaction
SD	stable disease
SJS	stevens-johnson syndrome
SPD	sum of the products of the perpendicular diameters of measured lymph nodes
SUSAR	suspected, unexpected, serious adverse reaction
SYK	spleen tyrosine kinase
$t_{1/2}$	half-life
T_{max}	time of maximum concentration
TEN	toxic epidermal necrolysis
TTR	time to response
UGT	uridine 5'-diphospho-glucuronosyltransferase
ULN	upper limit of normal
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 patients with treatment-naïve CLL, chemotherapy or chemoimmunotherapy are commonly employed to control disease manifestations {Gribben 2011}. Such therapies typically contain some combination of a purine analog, an alkylating agent, and the anti-CD20 monoclonal antibody, rituximab, and can be effective in providing durable remissions {Byrd 2005, Hallek 2010, Knauf 2009, Robak 2010}, particularly when administered in fit patients. However, these treatments are not curative; the disease will eventually relapse and further intervention is required to obtain and maintain tumor control. If the interval from prior therapy has been long (≥ 24-36 months), retreatment with the previous regimen is advocated {Eichhorst 2010, Zelenetz 2011}. However, if the interval from prior therapy has been shorter (<24 months), it is presumed that resistance to the previously administered cytotoxic agent is likely and that a change in therapy is warranted.

Among alternative treatments considered for such patients is alemtuzumab, a humanized IgG1γ monoclonal antibody directed against the CD52 antigen that is expressed on the cell surface of both B and T cells. The drug was initially approved as therapy for patients with previously treated CLL after failure of fludarabine-based treatment. However, alemtuzumab showed only modest activity in the pivotal study; the overall response rate (ORR) was 33% and the median progression-free survival (PFS) was 4.7 months {Keating 2002a}. In addition, the drug proved highly immunosuppressive, leading to frequent opportunistic infections.

A new alternative is ofatumumab, an IgG1κ, fully humanized CD20 monoclonal antibody that targets B cells. Ofatumumab binds to an epitope on CD20 that is distinct from the epitope recognized by rituximab and is closer to the cell membrane {Teeling 2006}. Its antibody-dependent cellular cytotoxicity (ADCC) has been reported to be similar to that of rituximab {Li 2009}, but ofatumumab delivers stronger complement-dependent cytotoxicity (CDC) in in vitro models, including malignant B cells lines with low CD20 expression levels and fresh CLL cells that are considered relatively resistant to rituximab {Li 2009, Pawluczkowycz 2009, Teeling 2004}. Ofatumumab also binding exhibits a slower off-rate than rituximab {Teeling 2004}.

Ofatumumab has recently received approval in Europe and in the United States for the treatment of patients with previously treated CLL {Gravanis 2010, Lemery 2010, Wierda 2010}. In the pivotal Phase 2 trial, all patients received 8 weekly infusions of ofatumumab followed by 4 monthly infusions during a 24-week period; the dose of the initial infusion was 300 mg and the dose of the remaining 11 infusions was 2,000 mg. The primary efficacy population comprised 59 patients with CLL refractory to fludarabine and alemtuzumab. Also accrued was a population of 79 patients who had fludarabine-refractory disease and bulky lymphadenopathy (ie, ≥ 1 nodal mass > 5 cm in diameter). The overall response rates were 58% and 47% and the median PFS values were 5.7 months and 5.9 months for the 2 groups. Median neutrophil counts were stable during treatment and improvements in thrombocytopenia and anemia were observed. The most frequent adverse events were infusion reactions and infections. Infusion reactions were common during the first 2 doses, typically subsiding with subsequent drug administrations. The rates of infection were consistent with historical data {Perkins 2002, Tam 2007} when considering the extent of CLL, the amount of prior therapy, and the level of pre-existing immunosuppression among the study participants.

The 2000-mg dose selected for the Phase 2 study was based on data indicating that the mass of CLL tumor affected the clearance of the drug, with high elimination rates in patients with bulky lymphadenopathy {Coiffier 2008, Coiffier 2010}. The data suggested that the 2000-mg dose offered necessary target coverage in patients with high-volume CLL. In patients with lower tumor burden, drug concentrations were better maintained. The data supported use of lower ofatumumab doses in patients receiving concomitant therapy that could reduce tumor volume. Nonclinical data have indicated that exposure values consistent with a 1000-mg clinical dose are sufficient to provide saturation of the CD20 target {Bleeker 2008}. Based on these collective data, current trials for patients with previously treated CLL use a 1000-mg dose of ofatumumab when giving the drug as a component of combination therapy.

Ofatumumab offers an active, non-myelotoxic option for patients with recurrent CLL, particularly when the disease requires intervention with a new mechanism of action. However, while treatment with single-agent ofatumumab offers benefit, tumor response is not universal and the duration of PFS is often limited. Moreover, the large amounts of protein necessary for single-agent ofatumumab treatment result in frequent infusion reactions and cumbersome infusion schedules. Combining ofatumumab with other therapies may generate better efficacy while allowing for reductions in ofatumumab dose that may minimize infusion reactions and avoid protracted infusion times. Novel, non-myelosuppressive, well-tolerated, and convenient therapies are needed that can be successfully combined with ofatumumab to achieve these goals.

1.2. Phosphatidylinositol 3-Kinase in Lymphoid Malignancies

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

PI3K signaling is mediated by 4 catalytic isoforms of the p110 subunit of the enzyme - α, β, γ, and δ. While potentially important in multiple cell types, PI3K p110δ (PI3Kδ) shows an expression pattern that is particularly prominent in cells of hematopoietic origin {Vanhaesebroeck 2005}. Mice deficient in PI3Kδ have no gross abnormalities, are fertile, fecund, and live a normal life span without an increased susceptibility to infections {Okkenhaug 2003a}. However, the B-lymphocyte population in these animals shows a decrease in maturation, diminished receptor-induced proliferation, and increased susceptibility to apoptotic cell death. Conversely, mice with aberrantly elevated PI3K signaling develop lymphadenopathy and have an increased incidence of lymphoma {Donahue 2004}. In CLL, sustained activation of the PI3K/AKT pathway has been shown to promote malignant B-cell survival through mechanisms that are dependent on the PI3Kδ isoform {Cuni 2004, Herman 2010, Lannutti 2011}.

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

1.3. Idelalisib

1.3.1. General Information

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

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 a therapeutic antibody eg, rituximab, alemtuzumab) has not impaired antibody-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 transporers (eg, human P-glycoprotein MDR1 and breast cancer resistance protein (BCRP)); idelalisib is a substrate for the efflux transporters MDR1 and BCRP; however, the permeability increases in a concentration-dependent manner, resulting in a lower efflux ratio at higher, clinically relevant concentrations of idelalisib.

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

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

In hepatic tissues from nonclinical species, idelalisib is primarily metabolized by aldehyde oxidase, CYP3A, and UGT1A4. In vitro metabolism in dog and human yields 3 primary oxidative metabolites and 5 primary glucuronides. Of these, the oxidative product GS-563117 is the predominant metabolite in vitro and in vivo. In preclinical species, plasma levels of GS-563117 are below those of idelalisib. However, in humans GS-563117 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 (IC50 = 13 μM), CYP2C19 (IC50 = 76 μM), and CYP3A (IC50 = 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 (IC50 = 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 (IC50 = 7.7 μM), OATP1B1 (IC50 = 10.1 μM), OATP1B3 (IC50 = 7.0 μM), and, at concentrations above those observed clinically, of glucuronosyltransferase UGT1A1 (IC50 = 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 (IC50 = 16.8 μM).

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

Potential clinical implications of these metabolism studies have been evaluated in a formal drug-drug interaction study (GS-US-313-0130) which examined 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 thie 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

Three studies in healthy subjects (Studies 101-01, 101-04, and 101-05) have provided information regarding drug safety, pharmacokinetics, food effects, and the potential for drug interactions with CYP3A4 inhibitors {Webb 2010}. One of these trials also included a preliminary evaluation of absorption, metabolism and excretion in healthy volunteers; in this trial, unlabeled idelalisib was co-administered with a trace amount of [^{14}C]idelalisib given either orally or intravenously and biological samples were assessed by accelerator mass spectrometry.

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 BID (the highest dose level tested). Dosing with 200 mg 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 receivingidelalisib, but have not typically proved dose- or treatment-limiting.

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. C_{max} and AUC increased in a less-than-dose-proportional manner and mean $t_{1/2}$ values across the dose range were 6.5 to 9.8 hours.

Idelalisib dosing after a high-fat, high-calorie meal delayed median time of maximum concentration (T_{max}) from 0.75 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 was the only circulating metabolite observed in human plasma, and was also observed in urine and feces.

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

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

Pharmacodynamic results showed that an 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 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 BID to 350 mg 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]), Patient 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, pneumonia 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, n=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 AUC0-6h 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 idelalisb 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 (72%) subjects achieved a PR (includes PR with lymphocytosis). The median DOR was not reached; 23 subjects continued to receive idelalisb 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 ofatumumab to subjects with recurrent CLL {Barrientos 2012, Furman 2012}.

In this study, idelalisib (150 mg BID) was co-administered with a total of 12 infusions of ofatumumab given over 24 weeks (300-mg initial dose followed 1 week later by 1,000 mg weekly for 7 doses, followed 4 weeks later by 1,000 mg every 4 weeks for 4 doses). Thereafter, subjects continued to receive single-agent idelalisib as long as the subject was safely benefiting from therapy. Subjects were evaluated in 4-week cycles; response and progression assessments were based on standard criteria {Hallek 2008}.

At the time of the data analysis, accrual of the cohorts was complete with 21 subjects enrolled and evaluable. Median [range] age was 66 [43-79] years. The majority (14/21; 67%) of patients had bulky adenopathy (≥1 lymph node ≥5 cm in diameter). The median [range] number of prior therapies was 3 [1-6], including prior exposure to alkylating agents (18/21; 86%), rituximab (20/21; 95%), purine analogs (16/21; 76%), alemtuzumab (4/21; 19%), and/or ofatumumab (3/21; 14%). The median [range] idelalisib treatment duration was 36+ [0-48+] week.

No idelalisib-related dose-limiting toxicities were observed within the tested subject cohorts. Ofatumumab infusion reactions were manageable. One patient developed corticosteroid-related hyperglycemia and sepsis. No clinically significant myelosuppression was observed.

Almost all subjects (17/21, 84%) experienced marked and rapid reductions in lymphadenopathy within the first 2 cycles**.** The lymphocyte mobilization that is expected with PI3Kδ inhibition was significantly reduced in magnitude and duration and persisted past Cycle 1 in only 1 patient. The ORR was 16/21 (76%) with 2/21 (10%) subjects showing evidence of complete response (CR), as reported by the investigators. Elevated baseline levels of CCL3, CCL4, CXCL13, and TNFα were significantly reduced after 28 days of treatment. At the time of the data analysis, overall PFS through 48 weeks was >75% and a median PFS had not yet been observed.

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

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

1.4. Summary and Justification for the Current Study

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

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

- CLL is a serious, disabling, and potentially life-threatening disorder that requires sequential treatment with agents that provide alternative mechanisms of tumor control. Single-agent ofatumumab can offer disease palliation with good tolerability in some patients with relapsed CLL but tumor control is not lasting. Development of a non-cytotoxic combination therapy of idelalisib with ofatumumab 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.

- 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 idelalisibplus ofatumumab in patients with relapsed or refractory CLL is supported by the observed antitumor activity of idelalisib given alone or in combination with ofatumumab or other anti-CD20 antibodies in patients with heavily pretreated CLL.

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

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

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

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

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

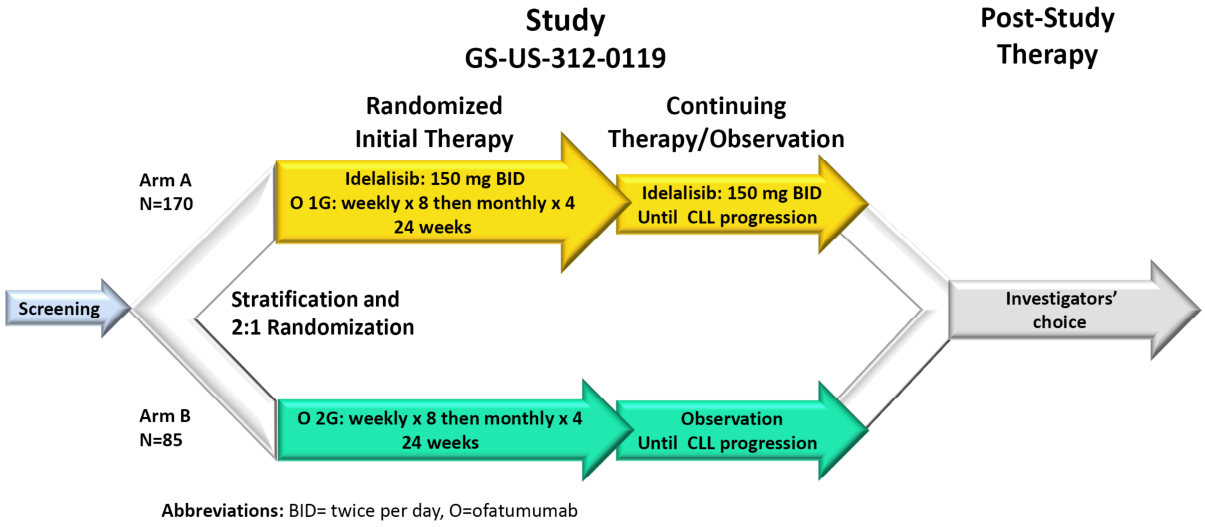
The rationale for specific design features is provided in relevant sections of the protocol, including Section 3.5 (Endpoint Selection Rationale), Section 2.2 (Design Rationale), Section 4.3 (Enrollment Criteria Rationale), Section 5.10 (Study Treatment Rationale), and Section 6.5 (Study Procedure Rationale).

2. STUDY DESIGN

2.1. Design Overview and Study Schema

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
Study GS-US-312-0119 is a Phase 3, multicenter, 2-arm, randomized, controlled, parallel-group, clinical trial (see Figure 2-1) that will be conducted internationally.

Figure 2-1. Study Design



The target population comprises adults with previously treated CLL who have measurable lymphadenopathy, require treatment for CLL, have disease that is not refractory to ofatumumab, and might benefit from a change in therapy because they have experienced CLL progression < 24 months since the completion of the last prior treatment.

Subjects will be stratified based on 17p deletion and/or a TP53 mutation status (either vs neither), immunoglobulin heavy chain variable region (IgHV) mutation status (unmutated vs mutated), and disease status (refractory vs relapsed), and randomized in a 2:1 ratio to receive either idelalisib/ofatumumab combination therapy or ofatumumab single-agent therapy.

Subjects receiving combination therapy in Arm A will take idelalisib orally, BID continuously.

All subjects will also receive 12 ofatumumab infusions. Ofatumumab will be administered intravenously in the clinic starting at a dose of 300 mg on Day 1 (Week 1) (Arms A and B) and will continue with a dose of either 1,000 mg (Arm A) or 2,000 mg (Arm B) on Day 8 (Week 2),

Day 15 (Week 3), Day 22 (Week 4), Day 29 (Week 5), Day 36 (Week 6), Day 43 (Week 7), Day 50 (Week 8) followed 4 weeks later by 1,000 mg (Arm A) or 2,000 mg (Arm B) given every 4 weeks for 4 doses on Day 78 (Week 12), Day 106 (Week 16), Day 134 (Week 20), and Day 162 (Week 24).

Subjects in Arm A will continue whichever study drug (idelalisib or ofatumumab) continues to be tolerated, even if the other drug has been discontinued due to toxicity.

Following permanent discontinuation of study drug(s), subjects shall remain on study until definitive progression of CLL or withdrawal from the study for reasons specified in Section 5.8.

The primary objective of Study GS-US-312-0119 will be to evaluate the effect of the addition of idelalisib to ofatumumab on PFS. Secondary objectives will focus on determining the effect of the addition of idelalisib to ofatumumab on the onset, magnitude, and duration of tumor control; overall survival (OS); health-related quality of life (HRQL); changes in subject performance status; disease-associated biomarkers and potential mechanisms of resistance; treatment administration; safety; and health resource utilization.

2.2. Design Rationale

The randomized, add-on design 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.

Randomization is an accepted means to reduce bias and allows for the highest standard of evidence in documenting a treatment effect. A centralized, standard block randomization should be sufficient to preclude site personnel from making inferences regarding future treatment assignments based on existing treatment assignments. A 2:1 randomization is planned in order to generate a larger safety database with the idelalisib combination and to enhance study accrual. The randomization process will be established and performed through an interactive web response system (IWRS); the intent is to maximize the integrity and security of the randomization and ensure appropriate access and convenience-of-use by the investigational sites.

Stratification will be used to balance allocation by potentially important parameters. The selected stratification factors are those that are likely to have a substantial influence on prognosis based on historical information regarding the therapy of CLL {Cramer 2011, Gonzalez 2011}, considering published data regarding use of ofatumumab in patients with CLL {Wierda 2010}, or based on information derived from the Phase 1 experience involving the idelalisib treatment of CLL {Coutre 2011}. Available data suggest that each of the selected stratification factors may divide the population relatively evenly, with > 30% of the subjects having one or the other levels of each of the strata. Further stratification factors could be considered, but it is problematic to overstratify a trial of this size given the potential loss of statistical power associated with expenditure of further degrees of freedom in the analysis.

The differences in ofatumumab doses between the arms of the study are considered acceptable because less ofatumumab is being administered in the investigational combination arm (Arm A) than is being administered in the control single-agent arm (Arm B). If the treatment effect is better in Arm A than in Arm B despite this difference, the results will provide particularly convincing testament to the merits of the idelalisib/ofatumumab combination.

Because of the difference in ofatumumab doses between the arms, both idelalisib and ofatumumab placebos would be required to blind the study. Centralized blinding is not possible because an ofatumumab placebo is not available. Attempting to blind the trial at the level of the pharmacist or nurse would be procedurally insufficient for maintaining the ofatumumab blind. In addition, there would be a high likelihood of breaking the blind due to expected differences in infusion times between the arms. In view of these constraints, the investigational site and sponsor study teams will have knowledge of the treatment assignments for individual subjects. However, several steps will be taken to minimize potential bias:

- Investigational sites will not be presented with any summary data or analyses during the course of the study.
- Efficacy results will be subjected to review by an independent review committee (IRC) that will be blinded as to treatment arm (see Section 10.4.2).
- An independent data monitoring committee (DMC) will be established to review accumulating study results in closed data review sessions and provide recommendations regarding study conduct.

3. OBJECTIVES AND ENDPOINTS

3.1. Primary Objective

- To evaluate the effect of the addition of idelalisib to ofatumumab on progression-free survival (PFS) in subjects with previously treated chronic lymphocytic leukemia (CLL)

3.2. Secondary Objectives

- To evaluate the effect of the addition of idelalisib to ofatumumab on the onset, magnitude, and duration of tumor control for subjects with 17p deletion and/or TP53 mutation
- To evaluate the effect of the addition of idelalisib to ofatumumab on the onset, magnitude, and duration of tumor control for subjects with 17p deletion and/or TP53 mutation
- To assess the effect of the addition of idelalisib to ofatumumab on measures of subject well-being, including overall survival (OS), health-related quality of life (HRQL) and performance status
- To assess the effects of the addition of idelalisib to ofatumumab on disease-associated biomarkers and to evaluate potential mechanisms of resistance to GS-1101
- To characterize the effect of ofatumumab on idelalisib exposure through the evaluation of idelalisib plasma concentrations over time
- To describe the safety profile observed with the addition of idelalisib to ofatumumab
- To estimate health resource utilization associated with the addition of idelalisib to ofatumumab

3.3. Primary Endpoint

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

3.4. Secondary and Exploratory Endpoints

The following secondary and exploratory endpoints will be defined and analyzed in this study. Five endpoints are designated as secondary endpoints for which sequential testing will be performed to control Type I error rate (see Section 9.4.1.6). Secondary endpoints will be ORR, lymphadenopathy response rate, OS, PFS in the subgroup of subjects with 17p deletion and/or TP53 mutation, and CR rate. All other endpoints will be considered exploratory.

3.4.1. Tumor Control

- Overall response rate (ORR) – defined as the proportion of subjects who achieve a complete response (CR) or partial response (PR) and maintain their response for at least 8 weeks

- 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

[redacted]

3.4.2. Patient Well-Being

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

[redacted]

[redacted]

3.4.3. Pharmacodynamic Markers of Drug Activity and Resistance

[redacted]

[redacted]

3.4.4. Exposure

[redacted]

[redacted]

3.4.5. Safety

[redacted]

3.4.6. Pharmacoeconomics

[redacted]

[redacted]

3.5. Endpoint Selection Rationale

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

3.5.1. Tumor Control Endpoints

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

In CLL, disease-related nodal enlargement is a major cause of patient discomfort and can cause organ dysfunction {Dighiero 2008}. Extensive lymphadenopathy constitutes a reason to treat CLL and controlling the size of pathologically enlarged lymph nodes is an important therapeutic goal for improving patient well-being and relieving obstructive symptoms {Hallek 2008}. Given that the natural history of recurrent CLL is inexorable nodal growth, enhancing tumor shrinkage and prolonging tumor control provides strong evidence of pharmacological activity. In assessing PFS as the primary outcome measure, this study builds on a past precedent in randomized, pivotal trials supporting the approval of rituximab or bendamustine in CLL

{Hallek 2010, Knauf 2009, Robak 2010}. PFS offers a well-established primary outcome measure that directly measures treatment effect, conveys important longitudinal information regarding tumor control, can be characterized in all subjects using intent-to-treat (ITT) principles, and is readily analyzed using statistical methods such as Kaplan-Meier techniques, log-rank tests, and Cox regression models.

Other endpoints of overall tumor control as evaluated in this trial are customarily assessed and reported in studies of new therapies in patients with cancer. In CLL, ORR provides an integrated assessment of the magnitude and extent of changes in lymphadenopathy, organomegaly, bone marrow infiltration, and bone marrow function that conveniently categorizes and describes treatment effects. 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 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 a more aggressive lymphoid malignancy histology (eg, Richter syndrome) will be considered to have progressed. Subjects with lymphocytosis without any of these other events will not be considered to have progressed. Given that lymphocytosis has no prognostic significance in patients with relapsed/refractory disease {Silverman 2002, Tsimberidou 2007} and is not generally considered a reason to treat in patients with CLL {Eichhorst 2010, Hallek 2008, Zelenetz 2011}, this approach does not jeopardize subject safety or subsequent therapy. Furthermore, it will allow complete collection of all response and progression data (both considering lymphocytosis and ignoring lymphocytosis) with the intent of providing complete information for regulatory authority review.

The current IWCLL guidelines indicate that physical examination is generally sufficient to evaluate nodal response and progression in patients with CLL {Hallek 2008} but that radiographic assessments may be appropriate in clinical trials. Computed tomography (CT) is considered the preferred imaging method unless patients have contraindications that require use of magnetic resonance imaging (MRI). Given the low fluorodeoxyglucose (FDG) avidity of

CLL, positron emission tomography (PET) does not have a role in evaluation of this disease. The incremental benefits of using radiographic imaging is limited in patients undergoing long-term follow-up following first-line therapy {Blum 2007, Eichhorst 2011}. However, in the patients with advanced CLL and bulky adenopathy such as those who will be enrolled to this trial, it is known that CT scans commonly detect bulky intra-abdominal lymphadenopathy and splenomegaly that would be missed by palpation alone and that the presence of large-volume, intra-abdominal disease of the nodes and spleen is associated with a poor prognosis {Norin 2010}. Thus, while use of CT confers greater radiation exposure, subjects have the chance to benefit from radiographic imaging because it will offer more accurate information regarding their response to protocol therapy and the appropriate duration of protocol treatment. Having this information is particularly important in this trial because PI3Kδ inhibition precludes use of lymphocyte counts as evidence for disease progression. Based on published data {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 compare the treatment arms for radiographic evidence of drug-induced lung changes {Maroto 2011, White 2010}. Furthermore, CT measurements have greater accuracy and reproducibility than palpation, are subject to independent expert review, and can be audited against electronic case report form (eCRF) information.

The timing of radiographic tumor assessments has been carefully considered. Among subjects receiving idelalisib in Phase 1b/2 studies who experienced a nodal response (≥ 50% regression in tumor area), such responses were observed with the first 16 weeks of therapy {Coutre 2011, Sharman 2011}; the planned timing of tumor assessments (at Weeks 8, 16, 24, 36, and 48 and every 12 weeks thereafter) in this study fits with this known timing of changes in lymph node size during idelalisib therapy. Scans at 8-week intervals during the first 24 weeks allow initial documentation of response (at Week 8 or 16) and follow-up confirmation of response 8 weeks later (at Week 16 or 24) consistent with current response criteria {Hallek 2008}. During this period, early documentation of disease progression allows subjects who are not benefiting from Study GS-US-312-0119 therapy to move rapidly to alternative treatments. After 24 weeks on study, the reduction in the frequency of CT scans (to 12-week intervals) reduces the overall protocol burden for subjects while still allowing detection of the incremental ≥ 6-month improvement in PFS (from a median of 8 months to 14 months) that is targeted in this comparative trial. As outlined in Section 7.2, iodine-containing or gadolinium contrast material may be omitted in subjects for whom use of a contrast agent would be medically contraindicated.

3.5.2. Measures of Patient Well-Being

3.5.2.1. Overall Survival

While OS provides an ultimate measure of patient well-being, it has not routinely been used as the primary endpoint in CLL clinical trials. Unlike PFS, it does not specifically measure drug-mediated tumor control, and thus provides only an indirect assessment of treatment effect. Depending upon the treatment setting, long OS times in patients with CLL can preclude use of

this endpoint as an efficient method for understanding drug benefits. In both the front-line and recurrent disease settings, post-study treatments can influence OS in unpredictable ways, potentially confounding differences between treatment groups.

However, given the life-threatening nature of systemic malignancy, documentation of OS is customary in oncology therapeutic clinical trials, including those evaluating subjects with recurrent CLL {Keating 2002a, Wierda 2010}. Evaluation of OS in this study has the potential to ensure that no unexpected, early adverse effect on the likelihood of death occurs as a consequence of the addition of idelalisib to ofatumumab in the Phase 3 trial.

CCI [redacted]

[redacted]

[redacted]

CCI [redacted]

CCI [redacted]

3.5.3. Pharmacodynamic Markers of Drug Activity and Resistance

CCI [redacted]

CCI [redacted]

[redacted]

[redacted]

3.5.4. Assessments of Exposure

CCI [redacted]

[redacted]

[redacted]

CCI [redacted]

[redacted]

CCI

[redacted]

[redacted]

3.5.5. Evaluations of Safety

CCI

[redacted]

[redacted]

[redacted]

[redacted]

CCI [redacted]

3.5.6. Pharmacoeconomic Measures

CCI [redacted]

[redacted]

[redacted]

CCI [redacted]

[redacted]

4. SUBJECT POPULATION

4.1. Number of Subjects

The planned sample size is 255 subjects. However, as many as 270 subjects may be enrolled in order to permit study participation by eligible subjects who have already signed the informed consent document and entered screening at the time that study enrollment is closed.

4.2. Subject Selection Criteria

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

4.2.1. Inclusion Criteria

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

1) Male or female ≥ 18 years of age.

2) Diagnosis of B-cell CLL, with diagnosis established according to IWCLL criteria {Kessenbrock 2010} and documented within medical records.

3) CLL that warrants treatment (consistent with accepted IWCLL criteria for initiation of therapy {Hallek 2008}). Any of the following conditions constitute CLL that warrants treatment:

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

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

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

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

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

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

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

ii) Significant fatigue (≥Grade 2), or

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

iv) Night sweats for >1 month.

4) Presence of 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).

5) Prior treatment for CLL comprising therapy with either of the following given alone or in combination:

a) A purine analog (eg, fludarabine, pentostatin, cladribine) administered for ≥ 2 cycles of cytotoxic treatment, or

b) Bendamustine administered for ≥ 2 cycles of treatment

Note: Prior drugs may have been administered as single agents or as components of combination therapies. Subjects may also have received other commercially available therapies (eg, rituximab, alemtuzumab, ofatumumab, lenalidomide, corticosteroids, or others) or non-excluded investigational therapies. Each repeated but separated therapeutic application of the same single-agent or combination is considered an independent regimen.

6) Documentation of CLL progression <24 months since the completion of the last prior therapy for CLL.

7) Discontinuation of all therapy (including radiotherapy, chemotherapy, immunotherapy, or investigational therapy) for the treatment of CLL ≥ 6 weeks before randomization.
Note: Subjects may be receiving corticosteroids to manage CLL manifestations.

8) All acute toxic effects of any prior antitumor therapy resolved to Grade ≤ 1 before randomization (with the exception of alopecia [Grade 1 or 2 permitted], neurotoxicity [Grade 1 or 2 permitted], or bone marrow parameters [Grades 1, 2, 3, or 4 permitted).

9) Karnofsky performance score of ≥ 60.

10) Required baseline laboratory data (within 4 weeks prior to randomization) 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 syndrome or hemolysis)
	Serum ALT	≤ 2.5 x ULN
	Serum AST	
Renal	eCCr[a]	> 30 ml/min
Pregnancy	β-HCG[b]	Negative
Infection	HIV	Negative HIV antibody
	HBV	Negative HBsAg and negative HBc antibody or positive HBc and negative for HBV DNA by quantitative PCR
	HCV	Negative viral RNA (if HCV antibody is positive)

a As calculated by the Cockcroft-Gault formula {Cockcroft 1976} (see Appendix 5)
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, DNA=deoxyribonucleic acid, eCCr=estimated creatinine clearance, HBc antibody=anti-hepatitis B core antibody, HBsAg=hepatitis B surface antigen, HBV=hepatitis B virus, HCV=hepatitis C virus, HIV=human immunodeficiency virus, Ig=immunoglobulin, PCR=polymerase chain reaction, RNA=ribonucleic acid, ULN=upper limit of normal

11) For female subjects of child-bearing potential, willingness to use a protocol-recommended method of contraception from the screening visit (Visit 1) throughout the study treatment period and to 30 days from the last dose of study drug or 12 months from the last dose of ofatumumab (whichever is later). ***Note: A female subject is considered to be of child-bearing 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 years with amenorrhea for ≥ 6 months). See Section 5.5.3 for information regarding recommendations for contraception.***

12) For male subjects of child-bearing potential and having intercourse with females of child-bearing potential, willingness to use a protocol-recommended method contraception from the randomization visit (Visit 2) throughout the study treatment period and for 90 days following the last dose of study drug and to refrain from sperm donation from randomization (Visit 2) throughout the study treatment period 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®]). See Section 5.5.3 for information regarding recommendations for contraception.

13) 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.

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

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

4.2.2. Exclusion Criteria

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

1) Known histological transformation from CLL to an aggressive lymphoma (ie, Richter transformation). ***Note: Biopsy documentation of the absence or presence of transformation is not required.***

2) Known presence of intermediate- or high-grade myelodysplastic syndrome (ie, subjects are excluded who have ≥ 5% bone marrow blasts; karotypic abnormalities other than normal, Y deletion, 5q deletion, or 20q deletion; or ≥ 2 lineages of cytopenias due to myelodysplasia) {Greenberg 1997}.

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

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

5) Evidence of ongoing systemic bacterial, fungal, or viral infection at the time of initiation of randomization (Visit 2). ***Note: Subjects with localized fungal infections of skin or nails are eligible. Subjects may be receiving prophylactic antiviral or antibacterial therapies at the discretion of the investigator; 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.***

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

7) Ongoing drug-induced pneumonitis.

8) Ongoing inflammatory bowel disease.

9) Ongoing alcohol or drug addiction.

10) Pregnancy or breastfeeding.

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

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

13) In a subject with a history of prior ofatumumab therapy, the time from the last dose of ofatumumab to documented CLL progression is < 6 months.

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

15) Prior participation in an idelalisib clinical trial.

16) Concurrent participation in another therapeutic clinical trial.

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

4.3. Enrollment Criteria Rationale

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

To maximize the likelihood that therapeutic intervention is appropriately matched to disease risk, subjects must have CLL that is sufficiently severe to justify therapy as determined by accepted criteria {Hallek 2008}. The requirement of measurable lymphadenopathy ensures that subjects have disease that can adequately be assessed for evidence of drug activity. Prior therapy provisions are intended to identify subjects who have already received appropriate therapies with well-defined activity. Exclusion of patients who have experienced CLL recurrence within 6 months of prior ofatumumab avoids treating those with disease known to be refractory to such therapy. Ensuring participation of only patients who are <24 months from prior therapy limits enrollment to subjects who require a change in therapy based on current guidelines {Eichhorst 2010, Zelenetz 2011}.

This protocol focuses on establishing a noncytotoxic combination therapy alternative for previously treated fit or unfit CLL patients. Thus, the trial permits any degree of baseline myelosuppression and seeks to enroll a relatively broad population of subjects. However, to ensure that subjects are able to perform basic self-care functions and are not so ill from life-threatening comorbidities that they require hospitalization and stabilization, subjects with Karnofsky performance scores < 60 will not be enrolled. Subjects must not have serious prior or concomitant conditions or therapies that would compromise safety, compliance, or evaluation. Severe comorbid conditions (eg, myelodysplasia, other cancers {Luciani 2009}, active hepatitis, hepatic dysfunction, history of drug-induced pneumonitis) may mask, exacerbate, or confound the interpretation of adverse effects or efficacy of idelalisib and therefore subjects with such medical disorders are excluded.

Pregnancy testing and restrictions on eligibility relating to reproduction, pregnancy, and nursing are important 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 human fetal development, or on the health of a breast-feeding child. Ofatumumab is known to have effects on the immune system in the developing fetuses of drug-exposed female animals; whether similar effects could exist for a human fetus is uncertain.

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

While it will not be used to determine eligibility, the general health status of study subjects will be characterized at baseline using the Cumulative Illness Rating Scale (CIRS) instrument (see Appendix 6). The CIRS has a well-established history as a clinical tool for classifying patient comorbidities {Linn 1968}. Its utility is based on its validation as a predictor of clinical outcomes in older patient populations {Boulos 2006, Castle 2005, Conwell 1993, de Groot 2003, Extermann 2000, Extermann 1998, Miller 1992, Parmelee 1995, Salvi 2008, Zekry 2010}; its

value in predicting prognosis, appropriate patient selection, and treatment tolerability in patients with cancer {Firat 2006, Monfardini 2005, Ngeow 2010, Wedding 2007a, Wedding 2007b}, and its increasing use to categorize treatable fit ("GO-GO") vs treatable unfit ("SLOW-GO") patients with CLL {Eichhorst 2009}, {Hallek 2010}, {Goede 2012}.

5. TREATMENT OF SUBJECTS

5.1. Randomization

5.1.1. Interactive Web Response System

An IWRS will be employed to manage the conduct of the trial. The IWRS will be used to maintain a central log documenting screening, to implement stratification and randomization, to manage dose modifications, to assess current inventories of study drug, to initiate any necessary resupply of study drug, and to document discontinuation of study.

5.1.2. Randomization and Stratification

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

Subjects will be randomized in a 2:1 ratio to either of the following treatment assignments:

- Arm A: Idelalisib + ofatumumab (1,000-mg dosing regimen)
- Arm B: Ofatumumab (2,000-mg dosing regimen)

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

- 17p deletion and/or TP53 mutation in CLL cells: either vs neither (or indeterminate)
- Immunoglobulin heavy chain variable region (IgHV) mutation:
  unmutated (or IgHV3-21) vs mutated (or indeterminate)
- Disease status: refractory (CLL progression < 6 months from completion of prior therapy)
  vs relapsed (CLL progression ≥ 6 months from completion of prior therapy)

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

5.2. Study Drugs

5.2.1. Idelalisib

5.2.1.1. Description

For subjects allocated to Arm A of the study, idelalisib will be provided in tablets intended for oral administration. Each tablet contains 150 mg or 100 mg of active idelalisib. The 150-mg tablets will be used for initial therapy; the 100-mg tablets are provided for use by those subjects who require a dose reduction (see Table 5-2). The 150-mg tablets are pink, 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, film-coated, and include the following inactive excipients: microcrystalline cellulose, hydroxypropyl cellulose, croscarmellose sodium, sodium starch glycolate, magnesium stearate, yellow iron oxide, polyethylene glycol, talc, PVA, and titanium dioxide.

Details regarding the shape and size of each tablet dosage form will be provided in the pharmacy manual for the study.

5.2.1.2. Source

Idelalisib will be supplied free of charge by Gilead Sciences.

5.2.1.3. Packaging and Labeling

Idelalisib will be provided in bottles. Each bottle contains 60 tablets (4-week supply plus a modest overage) of one of the relevant dose strengths (150 mg or 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.

Each bottle will have a label with a unique number. All labels for study drugs to be distributed to centers in the United States and other countries will meet all applicable requirements of the United States Food and Drug Administration (FDA), Annex 13 of Current Good Manufacturing Practice (cGMP) (Manufacture of Investigational Medicinal Products, July 2003), and/or other local regulations as applicable.

5.2.1.4. Storage and Handling

Bottles containing tablets of idelalisib should be stored at controlled room temperature (ie, ~25 °C, with a range of 15 to 30 °C). While 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.

5.2.1.5. Dispensing

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

5.2.1.6. Return

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

5.2.1.7. Accountability

The disposition of all idelalisib should be documented from the time of receipt at the site through subject dispensing and return.

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

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

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

5.2.1.8. Overdose Precautions

In Phase 1 studies, an MTD for idelalisib was not reached when administering the drug continuously at dose levels of 350 mg 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.

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 8.6).

5.2.1.9. Inadvertent Exposure and Spill Precautions

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

5.2.2. Ofatumumab

5.2.2.1. Description

Ofatumumab (Arzerra®) is a human monoclonal IgG1 kappa antibody directed against the CD20 antigen found on pre-B and mature B cells. Ofatumumab is generated with hybridoma technology by using HCo7 and KM transgenic mice and is produced in a recombinant murine cell line (NS0) {Teeling 2004}. The protein has an approximate molecular weight of 149 kD.

For pharmaceutical use, the drug is provided as a sterile, colorless, preservative-free liquid concentrate containing 20 mg/mL for dilution and intravenous administration. Inactive ingredients include: 10 mg/mL arginine, diluted hydrochloric acid, 0.019 mg/mL edetate disodium, 0.2 mg/mL polysorbate 80, 6.8 mg/mL sodium acetate, 2.98 mg/mL sodium chloride and Water for Injection, USP. The pH of the solution is 5.5.

5.2.2.2. Packaging

Ofatumumab is supplied in single-use 100-mg/5-ml vials or 1,000-mg/50-mL vials.

5.2.2.3. Source

Ofatumumab will be supplied free of charge by Gilead Sciences and commercial ofatumumab may be supplied through a vendor, as needed.

5.2.2.4. Storage and Stability

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

Diluted ofatumumab solutions for infusion may be stored at 2 °C–8 °C (36 °F–46 °F). The infusion should be started within 12 hours of ofatumumab preparation. Prepared solution should be discarded after 24 hours from constitution.

5.2.2.5. Solution Preparation and Dispensing

The clinic staff (eg, pharmacist or other qualified person) will be responsible for preparing ofatumumab. A qualified person (eg, nurse or physician with experience in monitoring the administration of chemotherapeutic agents) will be responsible for infusing ofatumumab.

Before use, the ofatumumab vials should be visually inspected for particulate matter and discoloration. The solution should be colorless and may contain a small amount of visible translucent-to-white, amorphous, ofatumumab particles. The solution should not be used if discolored or cloudy, or if foreign particulate matter is present.

For the preparation of each 300-mg dose of ofatumumab, 15 ml should be withdrawn from a 1,000-mL polyolefin or PVC bag of 0.9% Sodium Chloride Injection, USP and discarded, and 5 mL from each of 3 vials containing 100 mg/5 mL of ofatumumab should be aseptically added to the bag.

For the preparation of each 1,000-mg dose of ofatumumab, 50 ml should be withdrawn from a 1,000-mL polyolefin or PVC bag of 0.9% Sodium Chloride Injection, USP and discarded, and 50 mL from a vial containing 1000 mg/50mL of ofatumumab should be aseptically added to the bag.

For the preparation of each 2,000-mg dose of ofatumumab, 100 ml should be withdrawn from a 1,000-mL polyolefin or PVC bag of 0.9% Sodium Chloride Injection, USP and discarded, and 50 mL from each of 2 vials containing 1000 mg/50 mL of ofatumumab should be aseptically added to the bag.

The diluted solution should be mixed by gentle inversion. The infusion solution should not be mixed or diluted with other drugs.

Using an infusion pump, ofatumumab should be administered via polyvinyl chloride administration sets and through an in-line filter. The intravenous line should be flushed with 0.9% Sodium Chloride Injection, USP before and after each dose.

5.2.2.6. Accountability

The disposition of all ofatumumab 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 and be readily available for review by Gilead Sciences and/or its designee. Records documenting the date of study drug shipping or destruction, relevant lot numbers, and amount shipped or destroyed should be maintained.

5.2.2.7. Overdose Precautions

Ofatumumab doses as high as 2,000 mg have been administered without inducing excessive toxicity {Coiffier 2008, Coiffier 2010, Wierda 2010}. Accordingly, for this protocol, an overdose is defined as infusion of >2,000 mg of ofatumumab in a single day. In a subject who experiences an overdose, any further ofatumumab infusion on that day should be interrupted. Observation for any symptomatic side effects should be instituted, and biochemical and hematological parameters should be followed closely (consistent with the protocol or more frequently, as needed). Appropriate supportive management to mitigate adverse effects should be initiated, as necessary.

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

5.2.2.8. Exposure and Spill Precautions

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

5.3. Study Drug Administration

5.3.1. Overview of Dosing Regimen

Table 5-1 provides information regarding the planned dosing regimen. All subjects will receive the recommended premedication ~30 to ~60 minutes (or per institution-specific standard) before the ofatumumab infusion. In Arm A, idelalisib will be administered together with the premedication ~30 to ~60 minutes before the ofatumumab infusions. For both treatment arms

(Arm A and Arm B) the first infusion of ofatumumab will be administered at a dose of 300 mg. At each of Visits 3 through 13, subjects on both arms will be given the recommended premedications, and ofatumumab will be infused at a dose of 1,000 mg (Arm A) or 2,000 mg (Arm B).

Table 5-1. Planned Dosing Regimen

Period		Screen	Initial Therapy												Continuing Therapy
Visit		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14+**
Week		**-4**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**12**	**16**	**20**	**24**	**30+**
Study Day		**-28 Days**	**1**	**8**	**15**	**22**	**29**	**36**	**43**	**50**	**78**	**106**	**134**	**162**	**204+**
Purpose		**Screening**	**Clinic Visit**	**Clinic Visit**	**Clinic Visit**	**Clinic Visit**	**Clinic Visit**	**Clinic Visit**	**Clinic Visit**	**Clinic Visit**	**Clinic Visit**	**Clinic Visit**	**Clinic Visit**	**Clinic Visit**	**Clinic Visit**
Idelalisib (Arm A)			|————150 mg BID or highest tolerated dose, taken continuously————→												
Pre-medications (Arms A and B)	Antipyretic		X	X	X	X	X	X	X	X	X	X	X	X	
	Antihistamine		X	X	X	X	X	X	X	X	X	X	X	X	
	Prednisolone		X[a]	X[a]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[a]	X[c]	X[c]	X[c]	
Ofatumumab, mg	Arm A		300	1000	1000	1000	1000	1000	1000	1000	1000	1000	1000	1000	
	Arm B		300	2000	2000	2000	2000	2000	2000	2000	2000	2000	2000	2000	

a Corticosteroid should be given at full dose (prednisolone 100 mg or equivalent).
b Corticosteroid may be given at gradually decreasing doses for successive infusions if a Grade ≥3 reaction did not occur with the preceding ofatumumab infusion.
c Corticosteroid dose (prednisolone doses of 50 mg to 100 mg or equivalent) may be given if a Grade ≥3 reaction did not occur with the preceding ofatumumab infusion.
Abbreviation: BID=twice per day

5.3.2. Investigational Study Drug (Idelalisib)

5.3.2.1. Premedication

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

In the absence of concomitant cytotoxic administration, tumor lysis syndrome is uncommon with either idelalisib or ofatumumab. However, investigators are at liberty to consider additional monitoring and prophylaxis for tumor lysis syndrome according to local practices.

5.3.2.2. Administration Instructions

The prescribed dose of idelalisib 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.

5.3.2.3. Dosing Schedule

Idelalisib will be started on a BID schedule beginning ~30 minutes prior to the initial ofatumumab infusion. Study drug should be taken 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.

5.3.2.4. Dose Levels

Idelalisibdose levels are shown in Table 5-2 below. The starting dose level will be 150 mg BID. The lower dose level (Dose Level -1) is provided in case a subject requires a study drug dose modification.

Table 5-2. Idelalisib Dose Levels

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

Abbreviation: BID=twice per day

5.3.2.5. Dose Schedule Interruptions and Vomited Doses

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

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

5.3.3. Ofatumumab

5.3.3.1. Premedications

Before administration of ofatumumab, subjects must be premedicated to reduce the incidence and severity of infusion reactions. Although institution-specific standards may be followed, a recommended regimen is an oral antipyretic (acetaminophen [paracetamol], 1,000 mg or equivalent); an oral or intravenous antihistamine (cetirizine, 10 mg or equivalent); and an intravenous corticosteroid (prednisolone, 100 mg or equivalent). All premedications should be given ~30 to ~60 minutes prior to each ofatumumab administration. Local practices may be followed.

For the 1st, 2nd, and 9th ofatumumab infusions, intravenous corticosteroid at full dose (prednisolone, 100 mg or equivalent) should be administered. For the 3rd through 8th ofatumumab infusions, the corticosteroid dose may be gradually reduced prior to successive infusions if a Grade ≥ 3 reaction did not occur with the preceding ofatumumab infusion. For the 10th through 12th ofatumumab infusions, reduced corticosteroid doses (prednisolone doses of 50 mg to 100 mg) may be administered if a Grade ≥3 reaction did not occur with the prior infusion.

In the absence of concomitant cytotoxic administration, tumor lysis syndrome is uncommon with either idelalisib or ofatumumab. However, investigators are at liberty to consider additional monitoring and prophylaxis for tumor lysis syndrome according to local practices.

Institution of antibiotic prophylaxis for *Pneumocystis (carinii) jiroveci* is required for all subjects, and should be continued for up to 12 months following treatment with ofatumumab, particularly in patients with multiple risk factors for pneumocystis infection {Green 2007}.

5.3.3.2. Administration Instructions

The recommended initial infusion rate for the first dose of ofatumumab is 12 mL/hour. Subsequent infusions can be initiated at 25 mL/hour. In the absence of infusion toxicity, the infusion rate can be increased as described in Table 5-3. Ofatumumab should not be administered as an intravenous push or bolus. Infusion rates should not exceed the indicated values.

Table 5-3. Study Drug (Ofatumumab) Infusion Rates

Interval After Start of Infusion, min	Arm A		Arm B		
	Infusion 1 (300 mg), ml/hr	Infusion 2-12 (1,000 mg), ml/hr	Infusion 1 (300 mg), ml/hr	Infusion 2 (2,000 mg), ml/hr	Infusion 3-12 (2,000 mg), ml/hr
0-30	12	25	12	12	25
31-60	25	50	25	25	50
61-90	50	100	50	50	100
91-120	100	200	100	100	200
> 120	200	400	200	200	400

5.3.3.3. Management of Infusion Toxicity

Ofatumumab can cause infusion reactions manifesting as bronchospasm, dyspnea, laryngeal edema, pulmonary edema, flushing, hypertension, hypotension, syncope, cardiac ischemia/infarction, back pain, rigors, abdominal pain, pyrexia, rash, urticaria, and angioedema {Coiffier 2008, Glaxo Group Limited 2011, Wierda 2010}. Reactions are typically more frequent and severe during the first infusion and are generally less frequent and less severe with subsequent infusions. In the Phase 2 pivotal trial {Wierda 2010}, infusion reactions occurred in 44% of patients on the day of the first infusion (300 mg), in 29% of patients on the day of the second infusion (2,000 mg), and less frequently during subsequent infusions. The time to onset of infusion toxicity may range from 30 to 120 minutes.

Subjects should be monitored (including vital signs approximately every 15 minutes) for infusion toxicity for ~1 hour following the administration of the first and second infusions, or until vital signs return to normal or baseline for subjects who experience infusion toxicity during any infusion. If a subject has not experienced infusion toxicity during the first 2 infusions, it is acceptable to perform a final vital signs check 15 to 30 minutes after the end of subsequent infusions.

Patients with pre-existing pulmonary or cardiac conditions, those who experienced prior cardiopulmonary adverse reactions to ofatumumab, and those with high numbers of circulating malignant cells ($\geq 25 \times 10^9$/L) may be at particular risk. For example, in a study of patients with moderate to severe chronic obstructive pulmonary disease, 2 of 5 patients developed Grade 3 bronchospasm during infusion {Glaxo Group Limited 2011}.

If an infusion reaction Grade ≤ 2 occurs, the infusion may be temporarily slowed or interrupted and then can be restarted when the subject's condition has stabilized. Upon restarting, the infusion rate should be half of the infusion rate at the time the infusion was paused but not less than 12 mL/hour. After resuming the infusion, the infusion rate may be increased consistent with Table 5-3 based on patient tolerance.

If an infusion reaction Grade ≥ 3 occurs, the infusion must be interrupted. Medical management (eg, oxygen, epinephrine, bronchodilators, and/or glucocorticoids) should be instituted, as needed. After the severity of the reaction has decreased to Grade ≤ 2 the investigator may restart the infusion at the initial rate for this ofatumumab dose (ie, at 12 mL/hour or 25 mL/hour).

If the severity of the infusion reaction does not rapidly resolve to Grade ≤ 2 despite adequate clinical intervention, or if infusion reactions of Grade ≥ 3 occur on 3 occasions during a single infusion, the subject may be withdrawn from ofatumumab treatment at the discretion of the investigator. If the subject is being treated on Arm A of the study, the subject should continue idelalisib if the subject is tolerating idelalisib therapy.

5.3.4. 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 agent as well as the type and severity of adverse events or laboratory abnormalities are provided in Table 5-4 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 (in bold and italic) provided in Table 5-4 must be followed based on the type and severity of adverse event.The recommendations provided in Table 5-4 (not italicized) 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 5-4, if a subject experiences an adverse event that is suspected to be related to idelalisib during the course of study, then study drug administration should be held, as outlined in Table 5-4, until the adverse event resolves or stabilizes to an acceptable degree (requirements vs recommendations defined in Table 5-4). Thereafter, study drug may be reinstituted at either the starting dose level (150 mg BID) or at Dose Level-1 (100 mg BID) consistent with the instructions in Table 5-4. One further attempt at reinitiation of therapy at Dose Level -1 (100 mg BID) may be attempted if the investigator feels that a second rechallenge at that dose level is medically appropriate. If the subject cannot tolerate study drug at 100 mg BID after 2 rechallenges, then the subject should be discontinued from study drug therapy unless continued therapy is permitted by the Gilead Sciences medical monitor.

After a study drug dose reduction, the dose need not be re-escalated, even if there is minimal or no toxicity with the reduced dose. However, if the subject tolerates the lower dose level of study drug for ≥ 4 weeks then the dose may be increased to 150 mg BID, at the discretion of the investigator. Such re-escalation may be particularly warranted if further evaluation reveals that the adverse event that led to the dose reduction was not study-drug-related. The starting dose level should not intentionally be exceeded in this study.

Escalations or reductions in ofatumumab dosing are not planned. As noted in Table 5-4, ofatumumab administrations may be delayed to allow subjects to recover from ofatumumab-related adverse events or intercurrent illness.

Whenever possible, any dose adjustment of idelalisib 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 access the IWRS, select the subject number, and inform the IWRS of the need for dose titration. The IWRS will provide details regarding the kit numbers to be dispensed to the subject. The appropriate clinic staff should instruct the subject/caregiver about the change in dose.

Table 5-4. Recommendations and *Required* Actions for Idelalisib and Ofatumumab Dose Modification Based on Type and Severity of Treatment-Related Adverse Event or Laboratory Abnormality

NCI CTCAE Grade	Recommendations and *Required* Action (in italics)	
	Idelalisib	**Ofatumumab**
HEMATOLOGICAL ADVERSE EVENTS		
Neutropenia		
Grade ≤ 2 neutropenia	Maintain current dose level and schedule.	Maintain current dose level and schedule.
Grade ≤3 neutropenia	Maintain current dose level and schedule. ***Blood counts must be monitored at least weekly until ANC ≤ Grade 2***.	Maintain current dose level and schedule. Consider G-CSF support.
Grade 4 neutropenia (or occurrence of neutropenic fever or infection)	***Interrupt idelalisib. Blood counts must be monitored at least weekly until ANC ≤ Grade 2,*** at which point idelalisib dosing may be resumed at lower dose level.	Delay ofatumumab until Grade ≤ 3 (ANC ≥0.5 x 10^9/L) and/or neutropenic fever or infection is resolved; thereafter, resume at full dose. Consider G-CSF support to avoid delays. If delay is > 4 weeks, discontinue ofatumumab.
Thrombocytopenia		
Grade ≤ 3	Maintain current dose level and schedule.	Maintain current dose level and schedule.
Grade 4	During combination therapy period, maintain current idelalisib dose level. ***During continuing therapy period, withhold idelalisib for bruising or bleeding until Grade ≤ 3***. May resume idelalisib at same or reduced dose level at investigator discretion.	Delay ofatumumab until Grade ≤ 3 (platelets ≥25 x 10^9/L); thereafter, resume at full dose. If delay is > 4 weeks, discontinue ofatumumab.
NON-HEMATOLOGICAL ADVERSE EVENTS		
Cutaneous		
Grade ≤ 1	Maintain current dose level and schedule.	Maintain current dose level and schedule.
Grade 2	Maintain current dose level and schedule.	Delay ofatumumab until Grade ≤ 1; thereafter, resume at full dose.

NCI CTCAE Grade	Recommendations and *Required* Action (in italics)	
	Idelalisib	**Ofatumumab**
Grade 3 or 4	***Withhold idelalisib until Grade ≤ 1***. May resume at lower dose level or discontinue idelalisib at investigator discretion.	Delay ofatumumab until Grade ≤ 1; thereafter, may resume at full dose or discontinue ofatumumab at investigator discretion.
Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis		
Any Grade	***Discontinue idelalisib. Interrupt coadministered medications potentially associated with SJS or TEN. Institute treatment per institutional standards.***	
Gastrointestinal Inflammation/Diarrhea		
Grade ≤1	Provide anti-diarrheal agent (eg, loperamide) and maintain current idelalisib dose level and schedule. ***Obtain history and perform physical exam as outlined in Section 5.4.3.2***	Maintain current dose level and schedule.
Grade 2	Provide anti-diarrheal (eg, loperamide). Consider addition of anti-inflammatory agent (eg, sulfasalazine, budesonide). Maintain current study drug dose and schedule. ***Obtain stool culture, history, and perform physical exam as outlined in Section 5.4.3.2***	Maintain current dose level and schedule.
Grade 3	***Withhold idelalisib.*** Rule out infectious etiology including CMV. ***Consider anti-diarrheal agent (eg, loperamide) and/or addition of anti-inflammatory agent (eg, sulfasalazine, budesonide). Obtain stool culture, history, and perform physical exam as outlined in Section 5.4.3.2.*** Perform endoscopy with biopsy as outlined in Section 5.4.3.2. At Grade ≤1, may resume at lower dose level or discontinue study drug at investigator discretion.	Delay ofatumumab as necessary to ensure subject is sufficiently stable to receive further treatment; thereafter maintain full dose and schedule.
Grade 4	***Withhold idelalisib***. Rule out infectious etiology including CMV. ***Consider anti-diarrheal agent (eg, loperamide) and/or addition of anti-inflammatory agent (eg, sulfasalazine, budesonide). Obtain stool culture, history, and perform physical exam as outlined in Section 5.4.3.2.*** Peform endoscopy with biopsy as outlined in Section 5.4.3.2. At Grade ≤1, may resume at lower dose level or discontinue study drug at investigator discretion.	Delay ofatumumab as necessary to ensure subject is sufficiently stable to receive further treatment; thereafter maintain full dose and schedule.

NCI CTCAE Grade	Recommendations and *Required* Action (in italics)	
	Idelalisib	**Ofatumumab**
Hepatic Adverse Events (elevations in ALT, AST, or bilirubin)		
Grade ≤1 (ALT/AST≤3xULN) (Bilirubin≤1.5xULN)	Maintain current dose level and schedule.	Maintain current dose level and schedule.
Grade 2 (ALT/AST>3-5xULN) (Bilirubin>1.5-≤3xULN)	Maintain current dose level and schedule. Monitor ALT, AST, ALP, and bilirubin at least 1x per week until all abnormalities are Grade <1.	Maintain current dose level and schedule.
Grade 3 (ALT/AST>5-20xULN) (Bilirubin>3-10xULN)	Withhold idelalisib. Monitor ALT, AST, ALP, and bilirubin at least 1x per week until all abnormalities are Grade ≤ 1. If bilirubin abnormality was Grade < 3, resume idelalisib at same dose level. If bilirubin abnormality was Grade ≥ 3, resume idelalisib at lower dose level.	Delay ofatumumab as necessary to ensure subject is sufficiently stable to receive further treatment; thereafter maintain full dose and schedule.
Grade 4 (ALT/AST>20xULN) (Bilirubin>10xULN)	***Withhold idelalisib. Monitor ALT, AST, ALP, and bilirubin at least 1x per week until all abnormalities are Grade ≤ 1.*** If bilirubin abnormality was Grade < 4, resume idelalisib at lower dose level. ***If bilirubin abnormality was Grade 4, discontinue idelalisib.***	Delay ofatumumab as necessary to ensure subject is sufficiently stable to receive further treatment; thereafter maintain full dose and schedule.
Pneumonitis (with new onset or worsening of baseline, dyspnea, cough, or hypoxia without obvious infectious cause)		
Grade 1 (asymptomatic)	***Withhold idelalisib until resolution to baseline.*** May resume at lower dose level or discontinue study drug at investigator discretion.	Maintain current dose level and schedule.
Grade ≥ 2	***Discontinue idelalisib permanently in subjects with any severity of symptomatic pneumonitis and institute therapy as clinically appropriate.***	Delay ofatumumab as necessary to ensure subject is sufficiently stable to receive further treatment; thereafter maintain full dose and schedule.
Other Nonhematological Adverse Events		
Grade ≤ 2	Maintain current dose level and schedule	Maintain current dose level and schedule.
Grade ≥ 3	Withhold idelalisib until Grade ≤ 1. May resume idelalisib at initial or lower dose level or discontinue idelalisib at investigator discretion.	Delay ofatumumab as necessary to ensure subject is sufficiently stable to receive further treatment; thereafter maintain full dose and schedule or discontinue ofatumumab at investigator discretion.
Pneumocystis jirovecii pneumonia (PJP)		
Any Grade	***Discontinue idelalisib permanently***	

NCI CTCAE Grade	Recommendations and *Required* Action (in italics)	
	Idelalisib	**Ofatumumab**
Organizing Pneumonia		
Any Grade	***Discontinue idelalisib permanently***	
CMV infection/reactivation		
Any Grade	***Interrupt idelalisib upon unequivocal clinical or laboratory evidence of CMV infection. Provide 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.***	

Abbreviations: ALP=alkaline phosphatase, ALT=alanine aminotransferase, AST= aspartate aminotransferase, ANC=absolute neutrophil count, CTCAE=Common Terminology Criteria for Adverse Events, G-CSF=granulocyte colony-stimulating factor, NCI=National Cancer Institute, ULN=upper limit of normal, CMV=Cytomegalovirus

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

5.4.1. Carcinogenesis and Mutagenesis

Idelalisib was not genotoxic in a standard battery of assays. No carcinogenicity or mutagenicity studies of ofatumumab have been conducted. In a repeat-dose toxicity study, no tumorigenic or unexpected mitogenic responses were noted in cynomolgus monkeys treated for 7 months with up to 3.5 times the human dose of ofatumumab. Patients receiving therapies such as idelalisib or ofatumumab for CLL or iNHL have developed more aggressive lymphoid malignancies (eg, experienced Richter transformation) {Coutre 2011, Kahl 2011, Wierda 2010}. The specific association of the therapeutic agents with these types of events has not been determined.

Subjects who develop Richter transformation or acute myeloid leukemia should have study drug (idelalisib and ofatumumab) discontinued. For the new diagnosis of other types of disorders (eg, myelodysplastic syndrome, myeloproliferative disorders, a solid tumor), study drug (idelalisib and/or ofatumumab) may be continued at the investigator's discretion considering benefit:risk relating to therapy, CLL, and the new dysplastic or neoplastic condition.

5.4.2. Dermatological Events

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

For subjects who develop a severe rash for which an underlying etiology cannot be identified (e.g., infection, co-suspect drug), study drug ***must*** be interrupted. Once rash resolves to Grade <1 idelalisib can be resumed at a lower dose level or discontinued at the investigator's discretion.

Severe cutaneous reactions, including fatal events of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), have been reported in subjects receiving idelalisib. Assessment of potential causal association between idelalisib and the occurrence of SJS or TEN

has been confounded by the coadministration of antineoplastic agents (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 ***must*** be discontinued if such events occur.

Severe dermatological reactions can occur in patients receiving ofatumumab, most commonly as manifestations of an infusion reaction. Dermatological adverse events have included macular rash, vesicular rash, urticaria, and hyperhidrosis {Glaxo Group Limited 2011}.

In the case of the occurrence of mucocutaneous reactions during ofatumumab infusion, the recommendations for the management of infusion toxicity (see Section 5.3.3.3) should be followed. The safety of readministration of ofatumumab to patients with other types of severe mucocutaneous reactions has not been determined; thus, for subjects experiencing a Grade ≥ 3 non-infusion-related ofatumumab mucocutaneous reaction, consideration should be given to discontinuation of ofatumumab.

5.4.3. Gastrointestinal Events

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

For subjects who develop persistent diarrhea, causes related to concomitant medications or gastrointestinal infections such as Clostridium difficile (particularly for patients recently treated with broad spectrum antibiotics), Shigella, Campylobacter, Yersinia and CMV should be considered and treated if appropriate. Depending upon the clinical circumstances, endoscopy and biopsy, with bacterial and viral IHC staining should be considered. In the event that an infectious

cause is not identified, an antimotility agent (eg, loperamide) may lessen symptoms and intervention with enteric steroidal (eg, budesonide) or non-steroidal (eg, sulfasalazine) anti-inflammatory agents should be considered. In such subjects, rechallenge with idelalisib at a lower dose level has resulted in recurrence of symptoms in some but not all subjects and has not been associated with other severe adverse events.

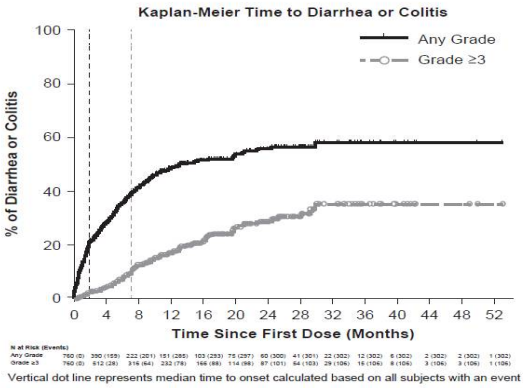
Upon recovery and depending upon the type and severity of the initial gastrointestinal event, idelalisib therapy may be continued or resumed and ofatumumab administration may be completed if continued drug administration offers the potential for clinical benefit.

5.4.3.1. 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

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



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

5.4.3.2. Evaluation for Gastrointestinal Events/Colitis

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

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

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

For Grade ≥ 3 or persistent Grade 2 colitis or diarrhea, without clear etiology (eg, clostridium difficile enterocolitis), endoscopy with biopsy is strongly recommended. All biopsy samples should include immunohistochemistry (IHC) and PCR for CMV, Adenovirus.

CCI [redacted]

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

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

- Small bowel diarrhea is characterized by large volume diarrhea (more than one per day), and is 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.

5.4.4. Hematological and Immunological Events

In the Phase 1 experience with idelalisib in CLL, patients 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. All subjects should have their blood counts monitored at least every 2 weeks for the first 6 months of idelalisib treatment. For subjects who develop ANC 0.5 to < 1.0 Gi/L, blood counts must be monitored weekly. For subjects who develop ANC < 0.5 Gi/L, 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.

Prolonged (≥ 1 week) severe neutropenia can occur with ofatumumab. Of 108 patients with normal neutrophil counts at baseline in the Phase 2 pivotal clinical trial experience {Wierda 2010}, 45 (42%) developed Grade ≥ 3 neutropenia and 19 (18%) developed Grade 4 neutropenia. Some patients experienced new onset Grade 4 neutropenia of > 2 weeks in duration {Glaxo Group Limited 2011}. Suppression of mean serum IgG and IgA levels has not been seen. Anemia and thrombocytopenia are not as prominent.

Because idelalisib is not associated with substantial myelotoxicity, alterations in idelalisib therapy for such events during combination idelalisib/ofatumumab therapy should be avoided, if possible. Dose modifications during combination idelalisib/ofatumumab therapy (Arm A) or during single-agent ofatumumab therapy (Arm B) should focus on alterations in ofatumumab scheduling; in subjects with persistent neutropenia despite G-CSF administration, ofatumumab doses may be delayed for as long as 4 weeks to allow recovery of neutrophil counts to Grade ≤ 3 (see Table 5-4). At the conclusion of combination therapy, subjects with protracted or symptomatic neutropenia or thrombocytopenia during continuing single-agent idelalisib therapy may warrant a study drug dose modification if myelosuppression is unresponsive to G-CSF supportive care or is symptomatic. No modification of either drug for changes in circulating CD4+ counts or Ig levels is planned.

5.4.5. 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 temporarily with holding 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 ofatumumab 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.

5.4.6. Immunogenicity

It is unknown whether an idelalisib-specific antibody response can occur following exposure toidelalisib. There is a potential for immunogenicity with therapeutic proteins such as ofatumumab, and some patients show seroconversion during ofatumumab treatment. Although formal studies investigating the potential neutralizing effect of an antibody response against ofatumumab have not been conducted, fetuses from treated females exhibiting anti-ofatumumab antibody responses showed less perinatal B-cell depletion than antibody-negative littermates.

5.4.7. Infectious Events

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

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

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.

Among 138 CLL patients treated with ofatumumab {Wierda 2010}, 45 patients (29%) experienced Grade ≥3 infections, of which 19 (12%) were fatal. 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 5.4.5) 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.

5.4.8. Progressive Multifocal Leukoencephalopathy

PML due to polyomavirus JC has been observed in a patient with CLL who received ofatumumab therapy {Wierda 2010}. PML has been observed in patients who have received rituximab therapy for hematologic malignancies {Carson 2009}. The specific causal role of ofatumumab or rituximab is unknown because patients have often had other risk factors (eg, low CD4+ counts, concomitant chemotherapy or hematopoietic stem cell transplantation). For subjects receiving rituximab, most cases of PML were diagnosed within 12 months of the last infusion.

The diagnosis of PML should be considered in any subject presenting with new-onset or worsening neurologic manifestations {Glaxo Group Limited 2011}, 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. Subjects diagnosed with PML should receive no further ofatumumab. Idelalisib should also be permanently discontinued.

5.4.9. 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.

Ofatumumab-related pulmonary adverse events including pneumonia, interstitial lung disease, and other respiratory tract infections have been described {Coiffier 2008, Wierda 2010}.

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

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

For subjects with suspected Grade 1 pneumonitis, withhold idelalisib until resolution to baseline. Upon resolution to baseline, idelalisib may be resumed at lower dose level or discontinued at investigator discretion. For subjects with suspected Grade ≥ 2 pneumonitis (eg, new onset or worsening of baseline cough, dyspenea, 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.

5.4.10. Tumor Lysis Syndrome

Tumor lysis syndrome has not been observed with idelalisib monotherapy but may be seen with ofatumumab treatment. Patients with tumor lysis syndrome may experience hyperkalemia, hypocalcemia, hyperuricemia, hyperphosphatemia, cardiac dysrhythmias, and acute renal failure.

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 drug (idelalisib and/or ofatumumab) to maintain tumor control.

5.4.11. Pregnancy, Lactation, and Reproduction

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

Reproduction studies of ofatumumab in cynomolgus monkeys dosed with up to 3.5 times the human dose of ofatumumab weekly during the period of organogenesis (gestation days 20 to 50) had no maternal toxicity or teratogenicity {Glaxo Group Limited 2011}. However, fetuses from ofatumumab-treated females exhibited depletion of peripheral B cells and decreased spleen and placental weights as well as a decrease in the thymus weight. The kinetics of B-lymphocyte recovery and the potential long-term effects of perinatal B-cell depletion in offspring from ofatumumab-treated females have not been studied in animals. The biological significance of decreased placental and thymic weights is unknown.

Given the potential the risks to a fetus or infant as a result of exposure to idelalisib, women of reproductive potential entering this study must have a negative serum pregnancy test at baseline and must not be breastfeeding. Males and females of childbearing potential should abstain from

sexual intercourse or use an effective form of contraception (see Section 5.5.3). If a female study participant becomes pregnant or decides to breastfeed during the course of the study, all study therapy (idelalisib, ofatumumab) must be discontinued.

5.4.12. PJP Prophylaxis and Pregnancy

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

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

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

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

5.4.13. Ultraviolet Exposure

In vitro studies indicate enhanced cytotoxicity when embryonic murine fibroblasts treated with GS-563117 (the major metabolite ofidelalisib) 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.

5.5. 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.

5.5.1. Anticancer or Experimental Therapies Other than Investigational Treatments

Except for corticosteroids, no other systemic anticancer therapies (including 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.

5.5.2. Antiemetics and Antidiarrheals

Drug-related nausea and/or vomiting have not been commonly observed with idelalisib in prior studies. Mild to moderate nausea was seen in up to 12% of CLL patients receiving ofatumumab {Glaxo Group Limited 2011}. 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). The neurokinin receptor antagonist, aprepitant, may be considered but is a mild inhibitor of CYP3A4 and so may modestly increase idelalisib plasma exposures. 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.

5.5.3. Contraception

In the context of this protocol, a female subject is considered to be of child-bearing 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 ≥ 6 months).

Sexually active females of child-bearing potential must accept continuous heterosexual abstinence as a lifestyle choice or agree to use a protocol-recommended method of contraception during heterosexual intercourse throughout the study treatment period and for 30 days from the last dose of study drug or 12 months from the last dose of ofatumumab (whichever is later). The investigator should counsel subjects on the most effective methods for avoiding pregnancy during the trial. Protocol-recommended contraceptive methods are described in Table 5-5.

Table 5-5. Protocol-Recommended Contraceptive Methods

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

Abbreviation: IUD=intrauterine device

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

Sexually active male subjects who can father a child must 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 5-5); 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 idelalisib or > 12 months following the last dose of ofatumumab (whichever is later) (as noted in Table 5-5).

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

5.5.4. 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 (idelalisib or ofatumumab). However, systemic corticosteroids should be used to prevent ofatumumab infusion reactions (see Section 5.3.3). In addition, subjects who develop conditions that may be alleviated by systemic corticosteroid therapy are permitted to receive such drugs and are not required to discontinue study participation.

5.6. Diet

There are no specific dietary restrictions in the study. Idelalisib may be taken with or without food.

5.6.1. 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 (eg, 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 5-4).

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(s).

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

5.6.2. Drugs that Inhibit/Induce CYP3A-Dependent Metabolism

Idelalisib is metabolized primarily via aldehyde oxidase and in part by CYP3A. A clinical drug-drug interaction study indicated that administration of a potent CYP3A inhibitor together with idelalisib resulted in an ~80% increase in idelalisib plasma exposures (AUC) (see Section 1.3.5), 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 5-6:

Table 5-6. 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

5.6.3. 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, and 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.

5.6.4. Immunization

Because of its actions to inhibit PI3Kδ-dependent B-cell function, high doses of idelalisib can impair primary or secondary responses to immunization in animals. In randomized clinical trials, rituximab has been shown to reduce the antibody response to pneumococcal vaccination (a T-cell-independent antigen) or to anti-keyhole limpet hemocyanin antibodies (a novel protein antigen) {Genentech Inc 2011}. Response to tetanus toxoid vaccine (a T−cell-dependent antigen with existing immunity) or maintenance of a positive Candida skin test (as a measure of T-cell-mediated delayed-type hypersensitivity) was not altered. The ability to generate an immune response to any vaccine following administration of ofatumumab has not been studied {Glaxo Group Limited 2011}

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

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

5.6.5. Surgery

There are no known effects of idelalisib or ofatumumab on coagulation or wound healing. Pending receipt of additional information and considering the subject's current platelet counts, idelalisib may be continued in the peri-procedural period in subjects who require surgery or invasive procedures.

5.7. Duration of Study Drug

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

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

Note: Subjects in Arm A will continue receiving idelalisib or ofatumumab, even if the other drug must be discontinued due to toxicity.

5.8. Discontinuation of Study Drug

All study participants may receive idelalisib indefinitely and may receive ofatumumab through 12 infusions. However:

- Any subject has the right to discontinue study drug at any time.
- Any subject who has objective evidence of definitive CLL progression (confirmed by IRC) will discontinue study drug.
- Any subject unable to tolerate a second rechallenge with protocol-described, dose-modified idelalisib at Dose Level –1 (100 mg BID) (see Section 5.3.4) should discontinue idelalisib.
- 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.
- The investigator may discontinue study drug, if it is not in the subject's best interest to continue.
- 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.

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.

5.9. Discontinuation from Study

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

- Disease progression (confirmed by the IRC)
- Withdrawal of consent
- Initiation of other anticancer therapy
- 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

Subjects who permanently discontinue study drug(s) 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 study participation is ended.

5.10. Study Treatment Rationale

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

- Idelalisib was symptomatically well tolerated in patients with lymphoid malignancies receiving dose levels of 50 mg BID through 350 mg 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). Thus, while doses through 350 mg BID appear tolerable, the starting dose of 150 mg BID appears to appropriately balance safety with efficacy in idelalisib-naïve subjects.

- In an allergic rhinitis study, idelalisib induced statistically significant improvements in clinical and pharmacodynamic endpoints when administered at 100 mg BID over 7 days. These data support the pharmacological relevance of idelalisib-mediated PI3Kδ inhibition when administered at a dose-level approximating that to be used in this Phase 3 study.

- A positive correlation was noted between idelalisib dose and measures of tumor control and chemokine normalization in patients with B-cell malignancies. The majority of patients appear to have tumor responses and protracted PFS when receiving starting doses of ≥ 100 mg BID. Thus, treatment with a idelalisib at a starting dose of 150 mg BID appears to offer most patients the potential to benefit from therapy.

- Based on evaluations of idelalisib steady-state plasma C_{max}, AUC, and C_{trough} values over a range of doses, administration of starting doses of idelalisib of ≥ 150 mg BID appears appropriate to ensure adequate exposure in the majority of patients. Flattening of the exposure curves at starting dose levels of > 150 mg BID suggest that higher doses may achieve smaller incremental gains in exposure.

- 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 collective data support a study drug administration schedule of BID administration to maintain idelalisib plasma C_{trough} values without inducing excessively high plasma C_{max} values.

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

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

- Study 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 in Arm A is likely to extend treatment effect.

Use of ofatumumab in this study is based on product labeling, precedence established with ofatumumab and other monoclonal antibodies in patients with CLL, and clinical observations relating to coadministration of ofatumumab or other anti-CD20 antibodies with idelalisib:

- The ofatumumab dosing regimen (including the ofatumumab dose of 2000-mg/infusion) selected for the control arm (Arm B) of this study is the approved dose in product labeling {Glaxo Group Limited 2011}. Phase 1 pharmacodynamic data have suggested that this dose is appropriate to achieve CD20 target coverage when using ofatumumab as a single agent in patients with advanced, bulky lymphadenopathy {Coiffier 2010}.

- The ofatumumab dose of 1000 mg/infusion to be used in combination with idelalisib in the investigation arm (Arm A) of this study is supported by nonclinical and clinical data. Nonclinical data have indicated that exposure values consistent with a 1000-mg clinical dose are sufficient to provide saturation of the CD20 target {Bleeker 2008}. The findings of the Phase 1 pharmacodynamic study of ofatumumab suggest that this dose is appropriate in patients receiving concomitant therapy that could reduce tumor volume {Coiffier 2010}. Based on these collective results, current trials for patients with previously treated CLL use a 1000-mg dose of ofatumumab when giving the drug as a component of combination therapy. It is further conjectured that mobilization of CLL cells from sanctuary sites into the peripheral blood may enhance ofatumumab-mediated CLL cell killing. Additional benefits resulting from the lower ofatumumab dose may include reductions in the frequency and severity of ofatumumab-dependent infusion reactions and in the duration of ofatumumab administration.

- Administration of ofatumumab therapy for 24 weeks is consistent with recommendations in the ofatumumab package insert {Glaxo Group Limited 2011} and matches the total planned durations of drug administration typically employed with other antibodies (eg, alemtuzumab {Keating 2002a} or rituximab {Robak 2010} used in the therapy of previously treated CLL.

- In a Phase 1/2, single-arm, dose-ranging study, concomitant administration of idelalisib at a dose of 150 mg BID together with ofatumumab at a dose of 1,000 mg has been shown to be safe and active {Barrientos 2012, Furman 2012}.

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

- Recommendations for managing ofatumumab infusion reactions, and interrupting or discontinuing ofatumumab therapy for specific adverse events are consistent with experience described in product labeling {Glaxo Group Limited 2011}.

6. STUDY PROCEDURES

6.1. Enrollment and Study Management Procedures

6.1.1. Subject Recruitment

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

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

6.1.2. Subject Compensation for Participation

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

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

6.1.3. Screening

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

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

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

- CLL peripheral blood or bone marrow evaluations (ie, FISH, DNA mutational analysis, flow cytometry, and cytology) used for determining stratification and CLL prognosis if obtained within 12 weeks prior to randomization
- Baseline CT/MRI scan – if obtained within 6 weeks prior to randomization

6.2. Explanation of Study Visits

The specific study procedures to be conducted for each subject enrolled in the study are presented in tabular form in Appendix 7 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.

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

6.2.1. Visit 1 and Screening Period (Clinic and Radiology Visit)

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

In order to optimize scheduling convenience for the subject and for the investigational staff, screening procedures may be performed over as many days as necessary provided that screening is completed within 4 weeks prior to randomization. Of note, the screening period may be extended to 6 weeks for subjects with a delay in the analysis of stratification variables (TP53 mutation/17p deletion status or IgHV mutation status) or with a delay in the acquisition of adequate baseline radiographic imaging data.

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

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

Assessment or Procedure	Explanation
Informed consent	To be obtained before any screening procedures are initiated (unless procedures are performed as standard of care prior to informed consent)
IWRS access	Access IWRS to document that subject is in screening and obtain a screening number
Medical history	Including relevant information regarding CLL history, stage of disease (Rai and Binet staging system) reasons for treatment, prior therapies for CLL, documentation of relapsed or refractory CLL, and past history of other medically significant medical conditions
CIRS assessment	Recording of comorbid conditions using the CIRS scoring instrument (see Appendix 6)
Concomitant medications	Recording of ongoing concomitant medication use
Performance status	Using Karnofsky performance status criteria (Appendix 3)
Oxygen saturation	To be assessed by pulse oximetry while subject is breathing room air
Physical examination	Including assessment of height, weight, lymph nodes, spleen, and liver
Serum virology	Including HBsAg, HBc antibody, HCV antibody, HIV antibody, CMV serology; if HBc or HCV antibody is positive, subjects must be evaluated for the presence of HBV DNA or HCV RNA, respectively
Serum β-HCG	Women of child-bearing potential only
CLL peripheral blood evaluation	Including FISH for chromosome 11q deletion, 13q deletion, 17p deletion and 12 trisomy; DNA mutational analysis for TP53, 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; bone marrow aspirate may be used if peripheral blood lymphocyte count is too low
CLL serology	Serum β2 microglobulin
Coagulation	aPTT, PT, INR
Urinalysis	Including pH, protein, glucose, ketones, bilirubin, urobilinogen, blood, nitrite, leukocyte esterase
Hematology	Including hematocrit, hemoglobin, erythrocyte count; absolute counts of leukocytes, neutrophils, lymphocytes, monocytes, eosinophils, basophils, platelet count
Serum chemistry	Including sodium, potassium, chloride, glucose, urea, creatinine, calcium, phosphorus, total protein, albumin, ALT, AST, ALP, GGT, total bilirubin, LDH, uric acid, cholesterol, triglycerides

Assessment or Procedure	Explanation
12-lead ECG	To be obtained while subject is resting in the supine position
Radiology assessment	CT or MRI imaging of neck, chest, abdomen, and pelvis, to be scheduled within 6 weeks prior to randomization; the same method of assessment (CT, MRI) and the same technique should be used to characterize each identified and reported lesion at baseline and while on study
Bone marrow biopsy and aspirate	To be performed at investigator discretion in subjects for whom assessment of extent of CLL involvement and bone marrow cellularity is important in determining eligibility

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

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

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

Table 6-2. Procedures and Assessments at Visit 2 (Treatment Start)

Assessment or Procedure	Explanation
Pre-Treatment Procedures and Assessments	
FACT-Leu	HRQL instrument (Appendix 2) to be administered before any other procedures are performed and before any study-related information is communicated to the subject
EQ-5D	Health utility instrument (Appendix 4) to be administered after FACT-Leu but before other procedures are performed and before study-related information is communicated to the subject
Adverse events	Recording of adverse events occurring since the initiation of the screening period
Assessment of Diarrhea / Colitis	Obtain history of onset and duration of diarrhea, including description of number of stools and stool composition (eg, watery, bloody, nocturnal), travel history, dietary changes and a medication review to identify possible diarrheogenic agents Perform physical examination including assessment for fever, dizziness, abdominal pain/cramping, and weakness (ie, evaluate for sepsis, bowel obstruction, dehydration)
Concomitant medications	Recording of concomitant medication use since the initiation of the screening period
Performance status	Using Karnofsky performance status criteria (Appendix 3)
Oxygen saturation	To be assessed by pulse oximetry while subject is breathing room air
Physical examination	Including assessment of weight, lymph nodes, spleen, and liver
Urine β-HCG dipstick	For women of child-bearing potential only
Hematology	Including hematocrit, hemoglobin, erythrocyte count; absolute counts of leukocytes, neutrophils, lymphocytes, monocytes, eosinophils, basophils, platelet count

Assessment or Procedure	Explanation
Serum chemistry	Including sodium, potassium, chloride, glucose, urea, creatinine, calcium, phosphorus, total protein, albumin, ALT, AST, ALP, GGT, total bilirubin, LDH, uric acid, cholesterol, triglycerides
Circulating cells	Including cells for analysis of PI3K/AKT/mTOR pathway activation and quantitation of CD4+, CD5+, CD8+, CD16/CD56+, CD19+, and CD+20 cells by flow cytometry
Biomarkers	Collection of plasma and serum for evaluation of circulating chemokines and cytokines
Serum Igs	Including quantitative levels of IgA, IgE, IgG, and IgM
CCI	
Idelalisib pharmacokinetics (Arm A)	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 stratify and randomize subject, and to obtain kit number(s)
Study Treatment Administration	
Study drug administration (Arm A)	First dose of idelalisib to be administered to the subject in clinic (with recording of the date and actual clock time of the study drug administration)
Pretreatment	Oral antipyretic, oral or IV antihistamine, and IV corticosteroid to be administered to the subject at the same time as idelalisib (Arm A) and ~30 to ~60 minutes prior to ofatumumab infusion
Ofatumumab infusion	Ofatumumab, 300 mg, to be administered by intravenous infusion ~30 to ~60 minutes after pretreatment
Ofatumumab infusion severity and duration assessment	Worst severity of ofatumumab infusion reaction to be graded and total duration of ofatumumab infusion to be recorded. Following the ofatumumab infusion, monitor the subject for infusion toxicity, including vital signs, ~every 15 minutes for ~1 hour
Post-Treatment Procedures and Assessments	
Idelalisib pharmacokinetics (Arm A)	Post-dose collection of plasma sample for idelalisib pharmacokinetics at 1.5 hours after study drug administration (with recording of the date and actual clock time of blood collection)
Study drug dispensing (Arm A)	Dispensing of 12-week supply of idelalisib to the subject with instructions for self-administration at home

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

6.2.3. Visit 3 (Clinic Visit)

The procedures outlined in Table 6-3 will be performed at Visit 3.

Table 6-3. Procedures and Assessments at Visit 3

Assessment or Procedure	Explanation
Pre-Treatment Procedures and Assessments	
FACT-Leu	HRQL instrument (Appendix 2) to be administered before any other procedures are performed and before any study-related information is communicated to the subject
EQ-5D	Health utility instrument (Appendix 4) to be administered after FACT-Leu but before other procedures are performed and before study-related information is communicated to the subject
Adverse events	Recording of adverse events occurring since the last clinic visit
Assessment of Diarrhea / Colitis	Obtain history of onset and duration of diarrhea, including description of number of stools and stool composition (eg, watery, bloody, nocturnal), travel history, dietary changes and a medication review to identify possible diarrheogenic agents Perform physical examination including assessment for fever, dizziness, abdominal pain/cramping, and weakness (ie, evaluate for sepsis, bowel obstruction, dehydration)
Concomitant medications	Recording of concomitant medication use since the last clinic visit
Performance status	Using Karnofsky performance status criteria (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 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 and to obtain kit number(s)
Study Treatment Administration	
Pretreatment	Oral antipyretic, oral or IV antihistamine, and IV corticosteroid to be administered to the subject at the same time as idelalisib (Arm A) and ~30 to ~60 minutes prior to ofatumumab infusion
Ofatumumab infusion	Ofatumumab, 1000 mg (Arm A) or 2000 mg (Arm B) to be administered by intravenous infusion ~30 to ~60 minutes after pretreatment
Ofatumumab infusion severity and duration assessment	Worst severity of ofatumumab infusion reaction to be graded and total duration of ofatumumab infusion to be recorded. Following the ofatumumab infusion, monitor the subject for infusion toxicity, including vital signs, ~every 15 minutes for ~1 hour

Assessment or Procedure	Explanation
Post-Treatment Procedures and Assessments	
Instruction regarding in-clinic study drug dosing (Arm A)	Instruction to the subject that the morning dose of idelalisib should not be taken on the day of the next treatment clinic visit.

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

6.2.4. Visit 4 (Clinic Visit)

The procedures outlined in Table 6-4 will be performed at Visit 4.

Table 6-4. Procedures and Assessments at Visit 4

Assessment or Procedure	Explanation
Pre-Treatment Procedures and Assessments	
FACT-Leu	HRQL instrument (Appendix 2) to be administered before any other procedures are performed and before any study-related information is communicated to the subject
EQ-5D	Health utility instrument (Appendix 4) to be administered after FACT-Leu but before other procedures are performed and before study-related information is communicated to the subject
Adverse events	Recording of adverse events occurring since the last clinic visit
Assessment of Diarrhea / Colitis	Obtain history of onset and duration of diarrhea, including description of number of stools and stool composition (eg, watery, bloody, nocturnal), travel history, dietary changes and a medication review to identify possible diarrheogenic agents Perform physical examination including assessment for fever, dizziness, abdominal pain/cramping, and weakness (ie, evaluate for sepsis, bowel obstruction, dehydration)
Concomitant medications	Recording of concomitant medication use since the last clinic visit
Performance status	Using Karnofsky performance status criteria (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 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

Assessment or Procedure	Explanation
Idelalisib pharmacokinetics (Arm A)	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 and to obtain kit number(s)
Study Treatment Administration	
Study drug administration (Arm A)	Morning dose of idelalisib to be administered to the subject in clinic (with recording of the date and actual clock time of the study drug administration)
Pretreatment	Oral antipyretic, oral or IV antihistamine, and IV corticosteroid to be administered to the subject at the same time as idelalisib (Arm A) and ~30 to ~60 minutes prior to ofatumumab infusion
Ofatumumab infusion	Ofatumumab, 1000 mg (Arm A) or 2000 mg (Arm B) to be administered by intravenous infusion ~30 to ~60 minutes after pretreatment
Ofatumumab infusion severity and duration assessment	Worst severity of ofatumumab infusion reaction to be graded and total duration of ofatumumab infusion to be recorded. Perform final check of vital signs ~15 to 30 minutes following the end of the infusion
Post-Treatment Procedures and Assessments	
Idelalisib pharmacokinetics (Arm A)	Post-dose collection of plasma sample for idelalisib pharmacokinetics at 1.5 hours after study drug administration (with recording of the date and actual clock time of blood collection)

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

6.2.5. Visits 5, 7, and 8 (Clinic Visit)

The procedures outlined in Table 6-5 will be performed at Visits 5, 7, and 8.

Table 6-5. Procedures and Assessments at Visits 5, 7, and 8

Assessment or Procedure	Explanation
Pre-Treatment Procedures and Assessments	
FACT-Leu	HRQL instrument (Appendix 2) to be administered before any other procedures are performed and before any study-related information is communicated to the subject
EQ-5D	Health utility instrument (Appendix 4) to be administered after FACT-Leu but before other procedures are performed and before study-related information is communicated to the subject
Adverse events	Recording of adverse events occurring since the last clinic visit
Assessment of Diarrhea / Colitis	Obtain history of onset and duration of diarrhea, including description of number of stools and stool composition (eg, watery, bloody, nocturnal), travel history, dietary changes and a medication review to identify possible diarrheogenic agents Perform physical examination including assessment for fever, dizziness, abdominal pain/cramping, and weakness (ie, evaluate for sepsis, bowel obstruction, dehydration)
Concomitant medications	Recording of concomitant medication use since the last clinic visit
Performance status	Using Karnofsky performance status criteria (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 and to obtain kit number(s)
Study Treatment Administration	
Pretreatment	Oral antipyretic, oral or IV antihistamine, and IV corticosteroid to be administered to the subject at the same time as idelalisib (Arm A) and ~30 to ~60 minutes prior to ofatumumab infusion
Ofatumumab infusion	Ofatumumab, 1000 mg (Arm A) or 2000 mg (Arm B) to be administered by intravenous infusion ~30 to ~60 minutes after pretreatment
Ofatumumab infusion severity and duration assessment	Worst severity of ofatumumab infusion reaction to be graded and total duration of ofatumumab infusion to be recorded. Perform final check of vital signs ~15 to 30 minutes following the end of the infusion
Post-Treatment Procedures and Assessments	
Instruction regarding in-clinic study drug dosing (Arm A)	Instruction to the subject that the morning dose of idelalisib should not be taken on the day of the next treatment clinic visit; instruction to .be given at Visits 5 and 8 (in anticipation of pharmacokinetic blood sample collection at Visits 6 and 9, respectively)

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 (Clinic Visit)

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

Table 6-6. Procedures and Assessments at Visit 6

Assessment or Procedure	Explanation
Pre-Treatment Procedures and Assessments	
FACT-Leu	HRQL instrument (Appendix 2) to be administered before any other procedures are performed and before any study-related information is communicated to the subject
EQ-5D	Health utility instrument (Appendix 4) to be administered after FACT-Leu but before other procedures are performed and before study-related information is communicated to the subject
Adverse events	Recording of adverse events occurring since the last clinic visit
Assessment of Diarrhea / Colitis	Obtain history of onset and duration of diarrhea, including description of number of stools and stool composition (eg, watery, bloody, nocturnal), travel history, dietary changes and a medication review to identify possible diarrheogenic agents Perform physical examination including assessment for fever, dizziness, abdominal pain/cramping, and weakness (ie, evaluate for sepsis, bowel obstruction, dehydration)
Concomitant medications	Recording of concomitant medication use since the last clinic visit
Performance status	Using Karnofsky performance status criteria (Appendix 3)
Oxygen saturation	To be assessed by pulse oximetry while subject is breathing room air
Physical examination	Including assessment of weight, lymph nodes, spleen, and liver
Urine β-HCG dipstick	For women of child-bearing potential only
Hematology	Including hematocrit, hemoglobin, erythrocyte count; absolute counts of leukocytes, neutrophils, lymphocytes, monocytes, eosinophils, basophils, platelet count
Serum chemistry	Including sodium, potassium, chloride, glucose, urea, creatinine, calcium, phosphorus, total protein, albumin, ALT, AST, ALP, GGT, total bilirubin, LDH, uric acid, cholesterol, triglycerides
HBV DNA by PCR	Only subjects who are HBc antibody positive and HBV DNA negative at screening, per Section 5.4.5.
Circulating cells	Including cells for analysis of PI3K/AKT/mTOR pathway activation and quantitation of CD4+, CD5+, CD8+, CD16/CD56+, CD19+, and CD+20 cells by flow cytometry
Biomarkers	Collection of plasma and serum for evaluation of circulating chemokines and cytokines
Serum Igs	Including quantitative levels of IgA, IgE, IgG, and IgM
CMV Surveillance	Arm A only: Surveillance for active disease must be conducted approximately every 4 weeks.
Idelalisib pharmacokinetics (Arm A)	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 and obtain kit number(s)

Assessment or Procedure	Explanation
Study Treatment Administration	
Study drug administration (Arm A)	Morning dose of idelalisib to be administered to the subject in clinic (with recording of the date and actual clock time of the study drug administration)
Pretreatment	Oral antipyretic, oral or IV antihistamine, and IV corticosteroid to be administered to the subject at the same time as idelalisib (Arm A) and ~30 to ~60 minutes prior to ofatumumab infusion
Ofatumumab infusion	Ofatumumab, 1000 mg (Arm A) or 2000 mg (Arm B) to be administered by intravenous infusion ~30 to ~60 minutes after pretreatment
Ofatumumab infusion severity and duration assessment	Worst severity of ofatumumab infusion reaction to be graded and total duration of ofatumumab infusion to be recorded. Perform final check of vital signs ~15 to 30 minutes following the end of the infusion
Post-Treatment Procedures and Assessments	
Idelalisib pharmacokinetics (Arm A)	Post-dose collection of plasma sample for idelalisib pharmacokinetics at 1.5 hours after study drug administration (with recording of the date and actual clock time of blood collection)

Abbreviations: β-HCG= beta human chorionic gonadotropin, AKT=AKT (a serine/threonine protein kinase), ALP=alkaline phosphatase, ALT=alanine aminotransferase, AST=aspartate aminotransferase, EQ-5D=EuroQoL Five-Dimension, FACT-Leu=Functional Assessment of Cancer Therapy-Leukemia, HRQL=health-related quality of life, GGT=gamma-glutamyltransferase, Ig=immunoglobulin, IWRS=interactive web response system, LDH=lactate dehydrogenase, mTOR=mammalian target of rapamycin, PI3K=phosphatidylinositol 3-kinase, CMV Surveillance=Arm A only: Surveillance for active disease must be conducted approximately every 4 weeks.

6.2.7. Visit 9 (Clinic and Radiology Visit)

The procedures outlined in Table 6-7 will be performed at Visit 9.

Table 6-7. Procedures and Assessments at Visit 9

Assessment or Procedure	Explanation
Pre-Visit Tumor Assessment	
Radiology assessment	CT or MRI imaging of neck, chest, abdomen, and pelvis within 1 week of the visit; the same method of assessment (CT or MRI) should be used as was used at baseline.
Pre-Treatment Procedures and Assessments	
FACT-Leu	HRQL instrument (Appendix 2) to be administered before any other procedures are performed and before any study-related information is communicated to the subject
EQ-5D	Health utility instrument (Appendix 4) to be administered after FACT-Leu but before other procedures are performed and before study-related information is communicated to the subject
Adverse events	Recording of adverse events occurring since the last clinic visit
Assessment of Diarrhea / Colitis	Obtain history of onset and duration of diarrhea, including description of number of stools and stool composition (eg, watery, bloody, nocturnal), travel history, dietary changes and a medication review to identify possible diarrheogenic agents Perform physical examination including assessment for fever, dizziness, abdominal pain/cramping, and weakness (ie, evaluate for sepsis, bowel obstruction, dehydration)
Concomitant medications	Recording of concomitant medication use since the last clinic visit
Performance status	Using Karnofsky performance status criteria (Appendix 3)
Oxygen saturation	To be assessed by pulse oximetry while subject is breathing room air
Physical examination	Including assessment of weight, lymph nodes, spleen, and liver
Urine β-HCG dipstick	For women of child-bearing potential only
Hematology	Including hematocrit, hemoglobin, erythrocyte count; absolute counts of leukocytes, neutrophils, lymphocytes, monocytes, eosinophils, basophils, platelet count
Serum chemistry	Including sodium, potassium, chloride, glucose, urea, creatinine, calcium, phosphorus, total protein, albumin, ALT, AST, ALP, GGT, total bilirubin, LDH, uric acid, cholesterol, triglycerides
HBV DNA by PCR	Only subjects who are HBc antibody positive and HBV DNA negative at screening, per Section 5.4.5.
Circulating cells	Including cells for analysis of PI3K/AKT/mTOR pathway activation and quantitation of CD4+, CD5+, CD8+, CD16/CD56+, CD19+, and CD+20 cells by flow cytometry
Biomarkers	Collection of plasma and serum for evaluation of circulating chemokines and cytokines
Serum Igs	Including quantitative levels of IgA, IgE, IgG, and IgM
CMV Surveillance	Arm A only: Surveillance for active disease must be conducted approximately every 4 weeks.

Assessment or Procedure	Explanation
Bone marrow biopsy and/or aspirate	To be performed post-baseline to confirm CR or PD. If the subject does not otherwise meet criteria for CR or if the nature of PD does not require bone marrow confirmation, it is not necessary to obtain a follow-up bone marrow biopsy/aspirate
Idelalisib pharmacokinetics (Arm A)	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 and to obtain kit number(s)
Study Treatment Administration	
Study drug administration (Arm A)	Morning dose of idelalisib to be administered to the subject in clinic (with recording of the date and actual clock time of the study drug administration)
Pretreatment	Oral antipyretic, oral or IV antihistamine, and IV corticosteroid to be administered to the subject at the same time as idelalisib (Arm A) and ~30 to ~60 minutes prior to ofatumumab infusion
Ofatumumab infusion	Ofatumumab, 1000 mg (Arm A) or 2000 mg (Arm B) to be administered by intravenous infusion ~30 to ~60 minutes after pretreatment
Ofatumumab infusion severity and duration assessment	Worst severity of ofatumumab infusion reaction to be graded and total duration of ofatumumab infusion to be recorded. Perform final check of vital signs ~15 to 30 minutes following the end of the infusion
Post-Treatment Procedures and Assessments	
Idelalisib pharmacokinetics (Arm A)	Post-dose collection of plasma sample for idelalisib pharmacokinetics at 1.5 hours after study drug administration (with recording of the date and actual clock time of blood collection)
Instruction regarding in-clinic study drug dosing (Arm A)	Instruction to the subject that the morning dose of idelalisib should not be taken on the day of the next treatment clinic visit.

Abbreviations: β-HCG= beta human chorionic gonadotropin, AKT=AKT (a serine/threonine protein kinase), ALP=alkaline phosphatase, ALT=alanine aminotransferase, AST=aspartate aminotransferase, CT=computed tomography, EQ-5D=EuroQoL Five-Dimension, FACT-Leu=Functional Assessment of Cancer Therapy-Leukemia, HRQL=health-related quality of life, GGT=gamma-glutamyltransferase, Ig=immunoglobulin, IWRS=interactive web response system, LDH=lactate dehydrogenase, MRI=magnetic resonance imaging, mTOR=mammalian target of rapamycin, PI3K=phosphatidylinositol 3-kinase, CMV Surveillance=Arm A only: Surveillance for active disease must be conducted approximately every 4 weeks.

6.2.8. Visit 10 (Clinic Visit)

The procedures outlined in Table 6-8 will be performed at Visit 10.

Table 6-8. Procedures and Assessments at Visit 10

Assessment or Procedure	Explanation
Pre-Treatment Procedures and Assessments	
FACT-Leu	HRQL instrument (Appendix 2) to be administered before any other procedures are performed and before any study-related information is communicated to the subject
EQ-5D	Health utility instrument (Appendix 4) to be administered after FACT-Leu but before other procedures are performed and before study-related information is communicated to the subject
Adverse events	Recording of adverse events occurring since the last clinic visit
Assessment of Diarrhea / Colitis	Obtain history of onset and duration of diarrhea, including description of number of stools and stool composition (eg, watery, bloody, nocturnal), travel history, dietary changes and a medication review to identify possible diarrheogenic agents Perform physical examination including assessment for fever, dizziness, abdominal pain/cramping, and weakness (ie, evaluate for sepsis, bowel obstruction, dehydration)
Concomitant medications	Recording of concomitant medication use since the last clinic visit
Study drug return/accounting	Counting returned idelalisib
Performance status	Using Karnofsky performance status criteria (Appendix 3)
Oxygen saturation	To be assessed by pulse oximetry while subject is breathing room air
Physical examination	Including assessment of weight, lymph nodes, spleen, and liver
Urine β-HCG dipstick	For women of child-bearing potential only
Hematology	Including hematocrit, hemoglobin, erythrocyte count; absolute counts of leukocytes, neutrophils, lymphocytes, monocytes, eosinophils, basophils, platelet count
Serum chemistry	Including sodium, potassium, chloride, glucose, urea, creatinine, calcium, phosphorus, total protein, albumin, ALT, AST, ALP, GGT, total bilirubin, LDH, uric acid, cholesterol, triglycerides
HBV DNA by PCR	Only subjects who are HBc antibody positive and HBV DNA negative at screening, per Section 5.4.5.
Circulating cells	Including cells for analysis of PI3K/AKT/mTOR pathway activation and quantitation of CD4+, CD5+, CD8+, CD16/CD56+, CD19+, and CD+20 cells by flow cytometry
Biomarkers	Collection of plasma and serum for evaluation of circulating chemokines and cytokines
Serum Igs	Including quantitative levels of IgA, IgE, IgG, and IgM
CMV Surveillance	Arm A only: Surveillance for active disease must be conducted approximately every 4 weeks.

Assessment or Procedure	Explanation
Idelalisib pharmacokinetics (Arm A)	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 and to obtain kit number(s)
Study Treatment Administration	
Study drug administration (Arm A)	Morning dose of idelalisib to be administered to the subject in clinic (with recording of the date and actual clock time of the study drug administration)
Pretreatment	Oral antipyretic, oral or IV antihistamine, and IV corticosteroid to be administered to the subject at the same time as idelalisib (Arm A) and ~30 to ~60 minutes prior to ofatumumab infusion
Ofatumumab infusion	Ofatumumab, 1000 mg (Arm A) or 2000 mg (Arm B) to be administered by intravenous infusion ~30 to ~60 minutes after pretreatment
Ofatumumab infusion severity and duration assessment	Worst severity of ofatumumab infusion reaction to be graded and total duration of ofatumumab infusion to be recorded. Perform final check of vital signs ~15 to 30 mins following the end of the infusion
Post-Treatment Procedures and Assessments	
Idelalisib pharmacokinetics (Arm A)	Post-dose collection of plasma sample for idelalisib pharmacokinetics at 1.5 hours after study drug administration (with recording of the date and actual clock time of blood collection)
Study drug dispensing (Arm A)	Dispensing of 12-week supply of idelalisib to the subject with instructions for self-administration at home

Abbreviations: β-HCG= beta human chorionic gonadotropin, AKT=AKT (a serine/threonine protein kinase), ALP=alkaline phosphatase, ALT=alanine aminotransferase, AST=aspartate aminotransferase, EQ-5D=EuroQoL Five-Dimension, FACT-Leu=Functional Assessment of Cancer Therapy-Leukemia, HRQL=health-related quality of life, GGT=gamma-glutamyltransferase, Ig=immunoglobulin, IWRS=interactive web response system, LDH=lactate dehydrogenase, mTOR=mammalian target of rapamycin, PI3K=phosphatidylinositol 3-kinase, CMV Surveillance=Arm A only: Surveillance for active disease must be conducted approximately every 4 weeks.

6.2.9. Visit 11 (Clinic and Radiology Visit)

The procedures outlined in Table 6-9 will be performed at Visit 11.

Table 6-9. Procedures and Assessments at Visit 11

Assessment or Procedure	Explanation
Pre-Visit Tumor Assessment	
Radiology assessment	CT or MRI imaging of neck, chest, abdomen, and pelvis within 1 week of the visit; the same method of assessment (CT or MRI) should be used as was used at baseline.
Pre-Treatment Procedures and Assessments	
FACT-Leu	HRQL instrument (Appendix 2) to be administered before any other procedures are performed and before any study-related information is communicated to the subject
EQ-5D	Health utility instrument (Appendix 4) to be administered after FACT-Leu but before other procedures are performed and before study-related information is communicated to the subject
Adverse events	Recording of adverse events occurring since the last clinic visit
Assessment of Diarrhea / Colitis	Obtain history of onset and duration of diarrhea, including description of number of stools and stool composition (eg, watery, bloody, nocturnal), travel history, dietary changes and a medication review to identify possible diarrheogenic agents Perform physical examination including assessment for fever, dizziness, abdominal pain/cramping, and weakness (ie, evaluate for sepsis, bowel obstruction, dehydration)
Concomitant medications	Recording of concomitant medication use since the last clinic visit
Performance status	Using Karnofsky performance status criteria (Appendix 3)
Oxygen saturation	To be assessed by pulse oximetry while subject is breathing room air
Physical examination	Including assessment of weight, lymph nodes, spleen, and liver
Urine β-HCG dipstick	For women of child-bearing potential only
Hematology	Including hematocrit, hemoglobin, erythrocyte count; absolute counts of leukocytes, neutrophils, lymphocytes, monocytes, eosinophils, basophils, platelet count
Serum chemistry	Including sodium, potassium, chloride, glucose, urea, creatinine, calcium, phosphorus, total protein, albumin, ALT, AST, ALP, GGT, total bilirubin, LDH, uric acid, cholesterol, triglycerides
HBV DNA by PCR	Only subjects who are HBc antibody positive and HBV DNA negative at screening, per Section 5.4.5.
Circulating cells	Including cells for analysis of PI3K/AKT/mTOR pathway activation and quantitation of CD4+, CD5+, CD8+, CD16/CD56+, CD19+, and CD+20 cells by flow cytometry
Biomarkers	Collection of plasma and serum for evaluation of circulating chemokines and cytokines
Serum Igs	Including quantitative levels of IgA, IgE, IgG, and IgM
CMV Surveillance	Arm A only: Surveillance for active disease must be conducted approximately every 4 weeks.

Assessment or Procedure	Explanation
Bone marrow biopsy and/or aspirate	To be performed post-baseline to confirm CR or PD. If the subject does not otherwise meet criteria for CR or if the nature of PD does not require bone marrow confirmation, it is not necessary to obtain a follow-up bone marrow biopsy/aspirate
IWRS access	Access of IWRS to document subject visit and to obtain kit number(s)
Study Treatment Administration	
Pretreatment	Oral antipyretic, oral or IV antihistamine, and IV corticosteroid to be administered to the subject at the same time as idelalisib (Arm A) and ~30 to ~60 minutes prior to ofatumumab infusion
Ofatumumab infusion	Ofatumumab, 1000 mg (Arm A) or 2000 mg (Arm B) to be administered by intravenous infusion ~30 to ~60 minutes after pretreatment
Ofatumumab infusion severity and duration assessment	Worst severity of ofatumumab infusion reaction to be graded and total duration of ofatumumab infusion to be recorded. Perform final check of vital signs ~15 to 30 minutes following the end of the infusion

Abbreviations: β-HCG= beta human chorionic gonadotropin, AKT=AKT (a serine/threonine protein kinase), ALP=alkaline phosphatase, ALT=alanine aminotransferase, AST=aspartate aminotransferase, CT=computed tomography, EQ-5D=EuroQoL Five-Dimension, FACT-Leu=Functional Assessment of Cancer Therapy-Leukemia, HRQL=health-related quality of life, GGT=gamma-glutamyltransferase, Ig=immunoglobulin, IWRS=interactive web response system, LDH=lactate dehydrogenase, MRI=magnetic resonance imaging, mTOR=mammalian target of rapamycin, PI3K=phosphatidylinositol 3-kinase, CMV Surveillance= Arm A only: Surveillance for active disease must be conducted approximately every 4 weeks.

6.2.10. Visit 12 (Clinic Visit)

The procedures outlined in Table 6-10 will be performed at Visit 12.

Table 6-10. Procedures and Assessments at Visit 12

Assessment or Procedure	Explanation
Pre-Treatment Procedures and Assessments	
FACT-Leu	HRQL instrument (Appendix 2) to be administered before any other procedures are performed and before any study-related information is communicated to the subject
EQ-5D	Health utility instrument (Appendix 4) to be administered after FACT-Leu but before other procedures are performed and before study-related information is communicated to the subject
Adverse events	Recording of adverse events occurring since the last clinic visit
Assessment of Diarrhea / Colitis	Obtain history of onset and duration of diarrhea, including description of number of stools and stool composition (eg, watery, bloody, nocturnal), travel history, dietary changes and a medication review to identify possible diarrheogenic agents Perform physical examination including assessment for fever, dizziness, abdominal pain/cramping, and weakness (ie, evaluate for sepsis, bowel obstruction, dehydration)
Concomitant medications	Recording of concomitant medication use since the last clinic visit
Performance status	Using Karnofsky performance status criteria (Appendix 3)
Oxygen saturation	To be assessed by pulse oximetry while subject is breathing room air

Assessment or Procedure	Explanation
Physical examination	Including assessment of weight, lymph nodes, spleen, and liver
Urine β-HCG dipstick	For women of child-bearing potential only
Hematology	Including hematocrit, hemoglobin, erythrocyte count; absolute counts of leukocytes, neutrophils, lymphocytes, monocytes, eosinophils, basophils, platelet count
Serum chemistry	Including sodium, potassium, chloride, glucose, urea, creatinine, calcium, phosphorus, total protein, albumin, ALT, AST, ALP, GGT, total bilirubin, LDH, uric acid, cholesterol, triglycerides
HBV DNA by PCR	Only subjects who are HBc antibody positive and HBV DNA negative at screening, per Section 5.4.5.
Circulating cells	Including cells for analysis of PI3K/AKT/mTOR pathway activation and quantitation of CD4+, CD5+, CD8+, CD16/CD56+, CD19+, and CD+20 cells by flow cytometry
Biomarkers	Collection of plasma and serum for evaluation of circulating chemokines and cytokines
Serum Igs	Including quantitative levels of IgA, IgE, IgG, and IgM
CMV Surveillance	Arm A only: Surveillance for active disease must be conducted approximately every 4 weeks.
IWRS access	Access of IWRS to document subject visit and to obtain kit number(s)
Study Treatment Administration	
Pretreatment	Oral antipyretic, oral or IV antihistamine, and IV corticosteroid to be administered to the subject at the same time as idelalisib (Arm A) and ~30 to ~60 minutes prior to ofatumumab infusion
Ofatumumab infusion	Ofatumumab, 1000 mg (Arm A) or 2000 mg (Arm B) to be administered by intravenous infusion ~30 to ~60 minutes after pretreatment
Ofatumumab infusion severity and duration assessment	Worst severity of ofatumumab infusion reaction to be graded and total duration of ofatumumab infusion to be recorded. Perform final check of vital signs ~15 to 30 minutes following the end of the infusion
Post-Treatment Procedures and Assessments	
Instruction regarding in-clinic study drug dosing (Arm A)	Instruction to the subject that the morning dose of idelalisib should not be taken on the day of the next treatment clinic visit.

Abbreviations: β-HCG= beta human chorionic gonadotropin, AKT=AKT (a serine/threonine protein kinase), ALP=alkaline phosphatase, ALT=alanine aminotransferase, AST=aspartate aminotransferase, EQ-5D=EuroQoL Five-Dimension, FACT-Leu=Functional Assessment of Cancer Therapy-Leukemia, HRQL=health-related quality of life, GGT=gamma-glutamyltransferase, Ig=immunoglobulin, IWRS=interactive web response system, LDH=lactate dehydrogenase, ,mTOR=mammalian target of rapamycin, PI3K=phosphatidylinositol 3-kinase, CMV Surveillance= Arm A only: Surveillance for active disease must be conducted approximately every 4 weeks.

6.2.11. Visit 13 (Clinic and Radiology Visit)

The procedures outlined in Table 6-11 will be performed at Visit 13.

Table 6-11. Procedures and Assessments at Visit 13

Assessment or Procedure	Explanation
Pre-Visit Tumor Assessment	
Radiology assessment	CT or MRI imaging of neck, chest, abdomen, and pelvis within 1 week of the visit; the same method of assessment (CT or MRI) should be used as was used at baseline.
Pre-Treatment Procedures and Assessments	
FACT-Leu	HRQL instrument (Appendix 2) to be administered before any other procedures are performed and before any study-related information is communicated to the subject
EQ-5D	Health utility instrument (Appendix 4) to be administered after FACT-Leu but before other procedures are performed and before study-related information is communicated to the subject
Adverse events	Recording of adverse events occurring since the last clinic visit
Assessment of Diarrhea / Colitis	Obtain history of onset and duration of diarrhea, including description of number of stools and stool composition (eg, watery, bloody, nocturnal), travel history, dietary changes and a medication review to identify possible diarrheogenic agents Perform physical examination including assessment for fever, dizziness, abdominal pain/cramping, and weakness (ie, evaluate for sepsis, bowel obstruction, dehydration)
Concomitant medications	Recording of concomitant medication use since the last clinic visit
Study drug return/accounting	Counting returned idelalisib
Performance status	Using Karnofsky performance status criteria (Appendix 3)
Oxygen saturation	To be assessed by pulse oximetry while subject is breathing room air
Physical examination	Including assessment of weight, lymph nodes, spleen, and liver
Urine β-HCG dipstick	For women of child-bearing potential only
Hematology	Including hematocrit, hemoglobin, erythrocyte count; absolute counts of leukocytes, neutrophils, lymphocytes, monocytes, eosinophils, basophils, platelet count
Serum chemistry	Including sodium, potassium, chloride, glucose, urea, creatinine, calcium, phosphorus, total protein, albumin, ALT, AST, ALP, GGT, total bilirubin, LDH, uric acid, cholesterol, triglycerides
HBV DNA by PCR	Only subjects who are HBc antibody positive and HBV DNA negative at screening, per Section 5.4.5.
Circulating cells	Including cells for analysis of PI3K/AKT/mTOR pathway activation and quantitation of CD4+, CD5+, CD8+, CD16/CD56+, CD19+, and CD+20 cells by flow cytometry
Biomarkers	Collection of plasma and serum for evaluation of circulating chemokines and cytokines
Serum Igs	Including quantitative levels of IgA, IgE, IgG, and IgM

Assessment or Procedure	Explanation
CMV Surveillance	Arm A only: Surveillance for active disease must be conducted approximately every 4 weeks.
Bone marrow biopsy and/or aspirate	To be performed post-baseline to confirm CR or PD. If the subject does not otherwise meet criteria for CR or if the nature of PD does not require bone marrow confirmation, it is not necessary to obtain a follow-up bone marrow biopsy/aspirate
Idelalisib pharmacokinetics (Arm A)	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 and to obtain kit number(s)
Study Treatment Administration	
Study drug administration (Arm A)	Morning dose of idelalisib to be administered to the subject in clinic (with recording of the date and actual clock time of the study drug administration)
Pretreatment	Oral antipyretic, oral or IV antihistamine, and IV corticosteroid to be administered to the subject at the same time as idelalisib (Arm A) and ~30 to ~60 minutes prior to ofatumumab infusion
Ofatumumab infusion	Ofatumumab, 1000 mg (Arm A) or 2000 mg (Arm B) to be administered by intravenous infusion ~30 to ~60 minutes after pretreatment
Ofatumumab infusion severity and duration assessment	Worst severity of ofatumumab infusion reaction to be graded and total duration of ofatumumab infusion to be recorded. Perform final check of vital signs ~15 to 30 minutes following the end of the infusion
Post-Treatment Procedures and Assessments	
Idelalisib pharmacokinetics (Arm A)	Post-dose collection of plasma sample for idelalisib pharmacokinetics at 1.5 hours after study drug administration (with recording of the date and actual clock time of blood collection)
Study drug dispensing (Arm A)	Dispensing of 12-week supply of idelalisib to the subject with instructions for self-administration at home

Abbreviations: β-HCG= beta human chorionic gonadotropin, AKT=AKT (a serine/threonine protein kinase), ALP=alkaline phosphatase, ALT=alanine aminotransferase, AST=aspartate aminotransferase, CT=computed tomography, EQ-5D=EuroQoL Five-Dimension, FACT-Leu=Functional Assessment of Cancer Therapy-Leukemia, HRQL=health-related quality of life, GGT=gamma-glutamyltransferase, Ig=immunoglobulin, IWRS=interactive web response system, LDH=lactate dehydrogenase, MRI=magnetic resonance imaging, mTOR=mammalian target of rapamycin, PI3K=phosphatidylinositol 3-kinase, CMV Surveillance= Arm A only: Surveillance for active disease must be conducted approximately every 4 weeks.

6.2.12. Visits 14 and 16 (Clinic Visits)

The procedures outlined in Table 6-12 will be performed at Visits 14 and 16.

Table 6-12. Procedures and Assessments at Visits 14 and 16

Assessment or Procedure	Explanation
FACT-Leu	HRQL instrument (Appendix 2) to be administered before any other procedures are performed and before any study-related information is communicated to the subject
EQ-5D	Health utility instrument (Appendix 4) to be administered after FACT-Leu but before other procedures are performed and before study-related information is communicated to the subject
Adverse events	Recording of adverse events occurring since the last clinic visit
Assessment of Diarrhea / Colitis	Obtain history of onset and duration of diarrhea, including description of number of stools and stool composition (eg, watery, bloody, nocturnal), travel history, dietary changes and a medication review to identify possible diarrheogenic agents Perform physical examination including assessment for fever, dizziness, abdominal pain/cramping, and weakness (ie, evaluate for sepsis, bowel obstruction, dehydration)
Concomitant medications	Recording of concomitant medication use since the last clinic visit
Performance status	Using Karnofsky performance status criteria (Appendix 3)
Oxygen saturation	To be assessed by pulse oximetry while subject is breathing room air
Physical examination	Including assessment of weight, lymph nodes, spleen, and liver
Urine β-HCG dipstick	For women of child-bearing potential only
Hematology	Including hematocrit, hemoglobin, erythrocyte count; absolute counts of leukocytes, neutrophils, lymphocytes, monocytes, eosinophils, basophils, platelet count
Serum chemistry	Including sodium, potassium, chloride, glucose, urea, creatinine, calcium, phosphorus, total protein, albumin, ALT, AST, ALP, GGT, total bilirubin, LDH, uric acid, cholesterol, triglycerides
Circulating cells	Including cells for analysis of PI3K/AKT/mTOR pathway activation and quantitation of CD4+, CD5+, CD8+, CD16/CD56+, CD19+, and CD+20 cells by flow cytometry
Biomarkers	Collection of plasma and serum for evaluation of circulating chemokines and cytokines
CMV Surveillance	Arm A only: Surveillance for active disease must be conducted approximately every 4 weeks.
Serum Igs	Including quantitative levels of IgA, IgE, IgG, and IgM
IWRS access	Access of IWRS to document subject visit and to obtain kit numbers (if applicable)

Abbreviations: β-HCG= beta human chorionic gonadotropin, AKT=AKT (a serine/threonine protein kinase), ALP=alkaline phosphatase, ALT=alanine aminotransferase, AST=aspartate aminotransferase, EQ-5D=EuroQoL Five-Dimension, FACT-Leu=Functional Assessment of Cancer Therapy-Leukemia, HRQL=health-related quality of life, GGT=gamma-glutamyltransferase, Ig=immunoglobulin, IWRS=interactive web response system, LDH=lactate dehydrogenase, ,mTOR=mammalian target of rapamycin, PI3K=phosphatidylinositol 3-kinase, CMV Surveillance= Arm A only: Surveillance for active disease must be conducted approximately every 4 weeks.

6.2.13. Visits 15 and 17 (Clinic and Radiology Visits)

The procedures outlined in Table 6-13 will be performed at Visits 15 and 17.

Table 6-13. Procedures and Assessments at Visits 15 and 17

Assessment or Procedure	Explanation
Pre-Visit Tumor Assessment	
Radiology assessment	CT or MRI imaging of neck, chest, abdomen, and pelvis within 1 week of the visit; the same method of assessment (CT or MRI) should be used as was used at baseline.
Visit Procedures and Assessments	
FACT-Leu	HRQL instrument (Appendix 2) to be administered before any other procedures are performed and before any study-related information is communicated to the subject
EQ-5D	Health utility instrument (Appendix 4) to be administered after FACT-Leu but before other procedures are performed and before study-related information is communicated to the subject
Adverse events	Recording of adverse events occurring since the last clinic visit
Assessment of Diarrhea / Colitis	Obtain history of onset and duration of diarrhea, including description of number of stools and stool composition (eg, watery, bloody, nocturnal), travel history, dietary changes and a medication review to identify possible diarrheogenic agents Perform physical examination including assessment for fever, dizziness, abdominal pain/cramping, and weakness (ie, evaluate for sepsis, bowel obstruction, dehydration)
Concomitant medications	Recording of concomitant medication use since the last clinic visit
Study drug return/accounting	Counting returned idelalisib
Performance status	Using Karnofsky performance status criteria (Appendix 3)
Oxygen saturation	To be assessed by pulse oximetry while subject is breathing room air
Physical examination	Including assessment of weight, lymph nodes, spleen, and liver
Urine β-HCG dipstick	For women of child-bearing potential only; also performed 6 weeks (± 5 days) following Visit 17
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
HBV DNA by PCR	Only subjects who are HBc antibody positive and HBV DNA negative at screening, per Section 5.4.5.
Circulating cells	Including cells for analysis of PI3K/AKT/mTOR pathway activation and quantitation of CD4+, CD5+, CD8+, CD16/CD56+, CD19+, and CD+20 cells by flow cytometry
Biomarkers	Collection of plasma and serum for evaluation of circulating chemokines and cytokines
Serum Igs	Including quantitative levels of IgA, IgE, IgG, and IgM

Assessment or Procedure	Explanation
CMV Surveillance	Arm A only: Surveillance for active disease must be conducted approximately every 4 weeks.
Bone marrow biopsy and/or aspirate	To be performed post-baseline to confirm CR or PD. If the subject does not otherwise meet criteria for CR or if the nature of PD does not require bone marrow confirmation, it is not necessary to obtain a follow-up bone marrow biopsy/aspirate
IWRS access	Access of IWRS to document subject visit and to obtain kit numbers (if applicable)
Study drug dispensing (Arm A)	Dispensing of 12-week supply of idelalisib to the subject with instructions for self-administration at home

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

6.2.14. Visit 18 and Subsequent Visits (Every 12 Weeks) (Clinic and Radiology Visits)

The procedures outlined in Table 6-14 will be performed at Visit 18 and subsequent visits (every 12 weeks).

Table 6-14. Procedures and Assessments at Visit 18 and Subsequent Visits (Every 12 Weeks)

Assessment or Procedure	Explanation
Pre-Visit Tumor Assessment	
Radiology assessment	CT or MRI imaging of neck, chest, abdomen, and pelvis within 1 week of the visit; the same method of assessment (CT or MRI) should be used as was used at baseline.
Visit Procedures and Assessments	
FACT-Leu	HRQL instrument (Appendix 2) to be administered before any other procedures are performed and before any study-related information is communicated to the subject
EQ-5D	Health utility instrument (Appendix 4) to be administered after FACT-Leu but before other procedures are performed and before study-related information is communicated to the subject
Adverse events	Recording of adverse events occurring since the last clinic visit
Assessment of Diarrhea / Colitis	Obtain history of onset and duration of diarrhea, including description of number of stools and stool composition (eg, watery, bloody, nocturnal), travel history, dietary changes and a medication review to identify possible diarrheogenic agents Perform physical examination including assessment for fever, dizziness, abdominal pain/cramping, and weakness (ie, evaluate for sepsis, bowel obstruction, dehydration)
Concomitant medications	Recording of concomitant medication use since the last clinic visit
Study drug return/accounting	Counting returned idelalisib

Assessment or Procedure	Explanation
Performance status	Using Karnofsky performance status criteria (Appendix 3)
Oxygen saturation	To be assessed by pulse oximetry while subject is breathing room air
Physical examination	Including assessment of weight, lymph nodes, spleen, and liver
Urine β-HCG dipstick	For women of child-bearing potential only; also performed 6 weeks (± 5 days) following Visit 18 and subsequent visits
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
HBV DNA by PCR	Only subjects who are HBc antibody positive and HBV DNA negative at screening, per Section 5.4.5.
Circulating cells	Including cells for analysis of PI3K/AKT/mTOR pathway activation and quantitation of CD4+, CD5+, CD8+, CD16/CD56+, CD19+, and CD+20 cells by flow cytometry
Biomarkers	Collection of plasma and serum for evaluation of circulating chemokines and cytokines
Serum Igs	Including quantitative levels of IgA, IgE, IgG, and IgM
CMV Surveillance	Arm A only: Surveillance for active disease must be conducted approximately every 4 weeks.
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 and until the CD4+ T-cell count is documented to be >200 cells/mcL.
Serum complement	CH50
Bone marrow biopsy and/or aspirate	To be performed post-baseline to confirm CR or PD. If the subject does not otherwise meet criteria for CR or if the nature of PD does not require bone marrow confirmation, it is not necessary to obtain a follow-up bone marrow biopsy/aspirate
IWRS access	Access of IWRS to document subject visit and to obtain kit numbers (if applicable)
Study drug dispensing (Arm A)	Dispensing of 12-week supply of idelalisib to the subject with instructions for self-administration at home

Abbreviations: β-HCG= beta human chorionic gonadotropin, AKT=AKT (a serine/threonine protein kinase), ALP=alkaline phosphatase, ALT=alanine aminotransferase, AST=aspartate aminotransferase, CT=computed tomography, EQ-5D=EuroQoL Five-Dimension, FACT-Leu=Functional Assessment of Cancer Therapy-Leukemia, HRQL=health-related quality of life, GGT=gamma-glutamyltransferase, Ig=immunoglobulin, IWRS=interactive web response system, LDH=lactate dehydrogenase, MRI=magnetic resonance imaging, mTOR=mammalian target of rapamycin, PI3K=phosphatidylinositol 3-kinase, CMV Surveillance= Arm A only: Surveillance for active disease must be conducted approximately every 4 weeks.

6.2.15. 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 6-15. 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 6-15. 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; the same method of assessment (CT or MRI) should be used as was used at baseline
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
Assessment of Diarrhea / Colitis	Obtain history of onset and duration of diarrhea, including description of number of stools and stool composition (eg, watery, bloody, nocturnal), travel history, dietary changes and a medication review to identify possible diarrheogenic agents Perform physical examination including assessment for fever, dizziness, abdominal pain/cramping, and weakness (ie, evaluate for sepsis, bowel obstruction, dehydration)
Concomitant medications	Recording of concomitant medication used since prior visit
Study drug return/accounting	Counting returned idelalisib
Performance status	Using Karnofsky performance status criteria (Appendix 3)
Oxygen saturation	To be assessed by pulse oximetry while subject is breathing room air
Physical examination	Including assessment of weight, lymph nodes, spleen, and liver
Serum β-HCG	Women of child-bearing potential only
CLL peripheral blood evaluation	Including FISH for chromosome 11q deletion, 13q deletion, 17p deletion and 12 trisomy; DNA mutational analysis for TP53, 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; bone marrow aspirate may be used if peripheral blood lymphocyte count is too low
CLL serology	Serum β2 microglobulin
CCI	
Urine β-HCG dipstick	For women of child-bearing potential only

Assessment or Procedure	Explanation
Hematology	Including hematocrit, hemoglobin, erythrocyte count; absolute counts of leukocytes, neutrophils, lymphocytes, monocytes, eosinophils, basophils, platelet count
Serum chemistry	Including sodium, potassium, chloride, glucose, urea, creatinine, calcium, phosphorus, total protein, albumin, ALT, AST, ALP, GGT, total bilirubin, LDH, uric acid, cholesterol, triglycerides
Circulating cells	Including cells for analysis of PI3K/AKT/mTOR pathway activation and quantitation of CD4+, CD5+, CD8+, CD16/CD56+, CD19+, and CD+20 cells by flow cytometry
Biomarkers	Collection of plasma and serum for evaluation of circulating chemokines and cytokines
Serum Igs	Including quantitative levels of IgA, IgE, IgG, and IgM
Serum complement	CH50
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 and until the CD4+ T-cell count is documented to be >200 cells/mcL.
IWRS	Access IWRS to document that subject has permanently discontinued study therapy

a An end-of-study CT/MRI tumor assessment should be performed unless the subject already has radiographic confirmation of definitive disease progression or a CT/MRI has been performed within 4 weeks prior to end-of-study.

Abbreviations: β-HCG=beta human chorionic gonadotropin, AKT=AKT (a serine/threonine protein kinase), ALP=alkaline phosphatase, ALT=alanine aminotransferase, AST=aspartate aminotransferase, CLL=chronic lymphocytic leukemia, CT=computed tomography, EQ-5D=EuroQoL Five-Dimension, FACT-Leu=Functional Assessment of Cancer Therapy-Leukemia, FISH= fluorescence in-situ hybridization, GGT=gamma-glutamyltransferase, Ig=immunoglobulin, IgH_V=immunoglobulin heavy-chain variable-region, IWRS=interactive web response system, LDH=lactate dehydrogenase, MRI=magnetic resonance imaging, mTOR=mammalian target of rapamycin, PI3K=phosphatidylinositol 3-kinase, RNA=ribonucleic acid, ZAP-70=zeta-associated protein 70, CMV Surveillance= Arm A only: Surveillance for active disease must be conducted approximately every 4 weeks.

6.2.16. 30 Day and Long-Term Follow-up

A 30 Day follow-up visit will be performed 30 days (± 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 conducted at annual intervals (± 4 weeks) for 5 years, starting at the EOS 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 status.

6.3. Sample Storage

CCI [redacted]

CCI [redacted]

6.4. Blood Collection

The maximum amount of blood to be drawn at a visit is ~114 mL and the total amount of blood to be drawn over the initial 52-week study period (including the 4-week screening period, through Week 48 of the study, and with a possible end-of-study visit) is ~587 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 ~2.9 mL/kg and a total blood volume per body weight per average 6-week period of ~1.7 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 laboratory manual.

CCI [redacted]

6.5. Study Procedure Rationale

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

7. EFFICACY ASSESSMENTS

7.1. Tumor Status Assessments

The determination of CLL response and progression will be based on standardized IWCLL criteria {Hallek 2008}, as specifically modified for this study to reflect current recommendations which consider the mechanism of action of idelalisib and similar drugs {Cheson 2012}. During the course of the study, investigators will assess the status of each subject's CLL according to schedule. If CLL progression is suspected, the IRC will be notified and will review radiographic and pertinent clinical data in order to provide expert interpretation (see Section 10.4.2). The findings of the IRC will be considered primary for analyses of PFS and other tumor control endpoints.

7.2. Method of Assessment

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

During screening, clinical and imaging-based tumor assessments should be performed within the specified screening period. Clinical tumor assessments should be performed at each designated clinical visit (see Appendix 7). On-study CT/MRI tumor assessments should be performed as indicated in Appendix 7, until ~129 events have been observed in the study population. An end-of-study CT/MRI tumor assessment should be performed unless the subject already has radiographic confirmation of disease progression ≤4 weeks prior. If a subject permanently discontinues study drug prior to objective documentation of CLL progression, investigators should continue further follow-up according to the protocol specified schedule until CLL progression is documented by the central IRC.

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

Index lesions measuring > 1.5 cm in the LD and > 1.0 cm in the LPD, will be prioritized during baseline index lesion selection.

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 should be assessed by physical examination and 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 {Bezerra 2005}, {Asghar 2011}, with the LVD being obtained by multiplying the number of sections on which the spleen is visualized by the thickness of the sections (eg, if the spleen is seen in 14 contiguous cross-sectional images with 0.5-cm thickness, the LVD is recorded as 7 cm).

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 s LVD is required for declaration of a splenomegaly response. Conversely, an increase in splenic enlargement by ≥ 50% (minimum increase of 2 cm) from nadir 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 to ≤ 18 cm in the LVD is required for declaration of a hepatomegaly response. Conversely, an increase in liver enlargement by ≥ 50% (minimum increase of 2 cm) from nadir 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 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 progressive disease/recurrence (taking as reference for PD the smallest measurements recorded since treatment started). BOR of CR or PR needs to be maintained at least 8 weeks to confirm a response. Subjects who initially responded but did not have an evaluable follow-up visit or did not maintain a response (i.e. progressed) for at least 8 weeks will not be counted as a confirmed responder. Subjects with a best overall response of NE or ND will be counted in the denominators in calculations of tumor response rates. Where imaging data are available, these data will supersede physical examination data in determining tumor status.

7.5.1. Complete Response

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

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

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

7.5.2. Partial Response

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

- No evidence of new disease
- 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 as defined in Section 7.4.2
  - In a subject with enlargement of the liver at baseline, a hepatomegaly response as defined in Section 7.4.2
  - A decrease by ≥ 50% from baseline in the CLL marrow infiltrate or in B-lymphoid nodules
  - No index, splenic, liver, or non-index disease with worsening that meets the criteria for definitive PD
- Peripheral blood counts meeting ≥ 1 of the following criteria:
  - ANC ≥ 1.5 x 10^9/L or ≥ 50% increase over baseline without need for exogenous growth factors (eg, G-CSF)
  - Platelet count ≥ 100 x 10^9/L or ≥ 50% increase over baseline without need for exogenous growth factors
  - Hemoglobin ≥ 110 g/L (11.0 g/dL) or ≥ 50% increase over baseline without red blood cell transfusions or need for exogenous growth factors (eg, erythropoietin)

7.5.3. Stable Disease

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

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

7.5.4. Definitive Progressive Disease

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

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

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

- Evidence of worsening of index lesions, spleen or liver, or non-index disease:
  - Increase from the nadir by ≥ 50% in the SPD of index lesions
  - Increase from the nadir by ≥ 50% in the LD 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 splenic 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 x 10^9/L and there has been a decrease by > 50% from the highest on-study platelet count

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

Note: 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/or spleen are missing at that time point (with the exception that absence of splenic images will not result in an NE designation in a subject known to have undergone splenectomy).

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

- Index disease absent at both baseline and on-treatment
- Non-index disease absent at both baseline and on-treatment

- Enlargement of the liver and spleen absent at both baseline and on-treatment

- Abnormalities of peripheral blood counts (elevated ALC and abnormally low ANC, platelet count, and hemoglobin) and evidence of CLL in bone marrow (if available) absent at both baseline and on treatment

7.6. Lymphocytosis During Therapy

Idelalisib can mobilize CLL cells from tissues into the peripheral blood. This characteristic pharmacological action can be prominent early in therapy but can persist over time and should not be confused with disease progression in subjects who have persistent control of other CLL-related signs and symptoms. ***In the absence of other objective evidence of disease progression and on both arms of the study, the occurrence of lymphocytosis will not preclude subjects from meeting the criteria for a PR if other criteria for PR are met and will not be considered evidence of CLL progression if occurring in isolation.*** Subjects with lymphocytosis should be continued on study drug until the occurrence of definitive disease progression (ie, disease progression that is manifest by worsening CLL-related signs other than lymphocytosis alone), or the occurrence of another reason to discontinue study drug as described in Section 5.8.

7.7. Documentation of Definitive CLL Progression

Of importance, CLL response and progression data will be subjected to IRC review (see Section 10.4.2). The subject should continue study drug pending confirmation of progression status. CT/MRI should be attempted in order to document definitive disease progression, and thus allow objective confirmation by the IRC.

8. ADVERSE EVENTS AND TOXICITY MANAGEMENT

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

8.1.1. Adverse Event

An adverse event (AE) is any untoward medical occurrence in a clinical study subject which does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and/or unintended sign, symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. AEs may also include pre- or post-treatment complications that occur as a result of protocol specified procedures. 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
- Laboratory abnormalities not requiring clinical intervention or further investigation. Such abnormalities will be captured as part of overall laboratory monitoring
- Medical or surgical procedures such as surgery, endoscopy, tooth extraction, and transfusion. The condition that led to the procedure may be an adverse event and must be reported
- Pre-existing diseases, conditions, or laboratory abnormalities present or detected before the screening visit that do not worsen
- Situations where an untoward medical occurrence has not occurred (eg, hospitalization for elective surgery, social and/or convenience admissions)
- Overdose without clinical sequelae
- 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 at AE. It is considered to be pre-existing and should be documented on the medical history eCRF

8.1.2. Serious Adverse Events

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

- Death
- Life-threatening (Note: The term “life-threatening” in the definition of “serious” refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.)

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

8.1.2.1. Protocol-Specific Serious Adverse Event Instructions

Hospital admissions for administration of the study drug, procedures required by the study protocol, or tumor-related diagnostic procedures are not considered SAEs.

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 Sections 8.1.1 and 8.1.2. If the laboratory abnormality is part of a syndrome, record the syndrome or diagnosis (eg, anemia), not the laboratory result (ie, decreased hemoglobin).

8.2. Assessment of Adverse Events and Serious Adverse Events

The investigator or qualified sub-investigator 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 sub-investigator 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)

8.2.2. Assessment of Severity

The severity of adverse events will be graded using the CTCAE, Version 4.03. 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.

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

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 eCRF database and Gilead Drug Safety and Public Health (DSPH) or designee as instructed. This also includes any SAEs resulting from protocol-associated procedures performed from screening onwards.

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

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

SAEs will be reported using a paper SAE reporting form. During the course of the study, there may be a 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.

All SAEs will be recorded on the SAE 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/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.

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

Given the endpoints of the study and 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 study drugs caused or contributed to the disease progression (ie, by a means other than lack of effect). Unrelated disease progression should be captured on the eCRF.

These 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.

8.5. Toxicity Management

Please refer to the current Idelalisib IB and local ofatumumab prescribing information for information related to toxicity management. See Section 5.3.4 for more information related to recommended dose modifications associated with toxicities.

8.5.1. Warnings & Precautions

Refer to the current Idelalisib IB for updated information. At the time of protocol approval, the following Warnings and Precautions were relevant.

8.5.1.1. 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 repeated throughout the program and transaminase elevations are now well characterized as follows: they occur within the first 3 months of treatment; are generally asymptomatic and transient in nature; Grade 1 or 2 elevations commonly resolve despite continued idelalisib treatment; and Grade 3 or 4 elevations can be managed by temporarily withholding idelalisib. Successful rechallenge after resolution at lower dose levels 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 early during therapy is therefore important to permit appropriate study drug (idelalisib) interruption and reinstitution so that subjects who appear to be benefiting can continue with study drug treatment.

8.5.1.2. Severe Diarrhea

Cases of ≥ Grade 3 diarrhea have been reported in subjects with hematologic malignancies treated with idelalisib for which the more common etiologies anticipated for the study population could not be readily identified. In the majority of such cases, subjects presented after several months of idelalisib administration with several weeks of watery diarrhea unresponsive to antidiarrheals or to empiric treatment with antimicrobials. Resolution has been documented in almost all cases, and treatment regimens have included budesonide, mesalamine, systemic steroids, and supportive care, with some subjects receiving more than 1 treatment approach concomitantly. Resolution of the diarrhea occurred within approximately 1 month from the discontinuation of idelalisib (regardless of treatment approach.) In subjects with ≥ Grade 3 diarrhea who were rechallenged with idelalisib, recurrence of diarrhea has occurred in some but not all subjects.

For subjects who develop severe persistent diarrhea for which an underlying etiology cannot be identified (eg, infection), study drug (idelalisib) should be interrupted. Resumption of study drug should be considered once diarrhea resolves if the subject is experiencing evidence of clinical benefit from therapy. Refer to Gastrointestinal Inflammation/Diarrhea section in Table 5-4 for specific instruction related to Grade.

8.5.1.3. Maculopapular Rash

Rash in association with idelalisib was first reported in Study 101-01, a Phase 1, placebo-controlled, sequential dose escalation study in healthy male volunteers. Three of 6 subjects at the 200 mg dose experienced mild (2 subjects) and moderate (1 subject) rashes on Day 7 of idelalisib exposure. One subject was rechallenged with 100 mg BID idelalisib for 7 days with no recurrence. A second subject was rechallenged with 200 mg BID idelalisib

and on Day 5 had a recurrence of rash on the thorax. Skin biopsies of the rash following rechallenge showed a histological pattern consistent with a maculopapular exanthema due to delayed type hypersensitivity reaction. In the Phase 1 study 101-02, rash was among the most frequently reported AEs, although the frequency of ≥ Grade 3 and serious dermatological AEs have remained low. Subjects 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 steroids.
The occurrence of ≥ Grade 3 rash has been more frequent when idelalisib was administered in combination with immunochemotherapy agents. Rechallenge with idelalisib has resulted in recurrence of rash in some but not all subjects.

For subjects who develop a severe maculopapular rash for which an underlying etiology cannot be identified (eg, infection, co-suspect drug), study drug (idelalisib) should be interrupted. Resumption of study drug should be considered once rash resolves if the subject is experiencing evidence of clinical benefit from therapy.

8.5.1.4. Pneumonitis and Organizing Pneumonia

Some subjects receiving idelalisib alone or in combination have developed evidence of pneumonitis or organizing pneumonia with infection having been ruled out on bronchoscopy. Some of these events have required mechanical ventilation or have been fatal. Nonclinical evaluations of pulmonary function and pathology do not indicate a direct toxic effect of idelalisib on the lungs, and disease-related factors or toxicity from prior or concomitant therapies may have contributed to these clinical events.

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, dyspenea, 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.

Idelalisib has induced embryo lethality and teratogenicity when administered to pregnant female rats at maternally toxic doses. The specific effects of idelalisib on human embryogenesis, fetal development, or post-natal development are unknown.

All female subjects of reproductive potential are required to have a negative pregnancy test prior to initial study drug (idelalisib) administration. Idelalisib must not be administered to female study participants of childbearing potential unwilling to use protocol-specified highly effective contraception with heterosexual intercourse. Administration to female study participants who are breastfeeding is prohibited. Female study subjects who become pregnant must be removed from study drug (idelalisib) therapy as soon as pregnancy is diagnosed. If an in utero study drug exposure in a female subject occurs or a male subject receiving study drug conceives a child, Gilead must be notified immediately and follow up reporting actions must be taken as specified in study protocols.

8.5.1.5. Drug-Drug Interactions

Consistent with nonclinical data indicating that GS-563117, the dominant idelalisib metabolite, is a reversible and time-dependent inhibitor of CYP3A, coadministration with idelalisib resulted in higher midazolam systemic exposures (AUC: approximately 5-fold increase; C_{max}: approximately 2.3-fold increase), indicating that idelalisib is a strong inhibitor of CYP3A. Accordingly, coadministration of CYP3A substrates with idelalisib may result in an increase in their systemic exposures (eg, antiarrhythmics, calcium channel blockers, benzodiazepines, certain HMG-CoA reductase inhibitors, phosphodiesterase-5 [PDE5] inhibitors, and warfarin). Avoid coadministration of idelalisib with drugs that are highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events, including narrow therapeutic index CYP3A substrates (eg, alfentanil, cyclosporine, sirolimus, tacrolimus, cisapride, pimozide, fentanyl, quinidine, ergotamine, dihydroergotamine, astemizole, and terfenadine).

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

8.6. Special Situations Reports

8.6.1. 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. They also include reports of adverse reactions in infants following exposure from breastfeeding, and reports of adverse reactions associated with product complaints and reports arising from occupational exposure.

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

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

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

8.6.2. Instructions for Reporting Special Situations

8.6.2.1. 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 Gilead DSPH or designee using the pregnancy report form within 24 hours of becoming aware of the pregnancy. Refer to the eCRF completion guidelines for full instructions on the mechanism of pregnancy reporting.

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

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

A spontaneous abortion is always considered to be an SAE, and therefore should be reported as such. Furthermore, any SAE occurring as an adverse pregnancy outcome post study must be reported to Gilead DSPH or designee.

The subject should receive appropriate monitoring and care until the conclusion of the pregnancy. The outcome should be reported to Gilead DSPH or designee 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.

Pregnancies of female partners of male study subjects exposed to Gilead or other drugs required on study (ofatumumab) must also be reported and relevant information should be submitted to Gilead DSPH or designee using the pregnancy and pregnancy outcome forms within 24 hours. Monitoring of the subject should continue until the conclusion of the pregnancy. If the end of the pregnancy occurs after the study has been completed, the outcome should be reported directly to Gilead DSPH.

Gilead DSPH contact information is as follows: Email: PPD and
Fax: PPD

Refer to Section 5.5.3 for Pregnancy Precautions, Definitions for Female of Childbearing Potential, and Contraceptive Recommendations.

8.6.2.2. Reporting Other Special Situations

All other special situations (excluding pregnancy) must be reported on the special situations report form and forwarded to Gilead DSPH or designee 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. 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 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 noted in Section 3.1, the primary objective of this clinical trial will be to evaluate the effect of the addition of idelalisib to ofatumumab on PFS.

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

9.2. Analysis Endpoints

9.2.1. Primary Endpoint

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

9.2.2. Secondary and Exploratory Endpoints

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

Of these endpoints, 5 endpoints are designated as secondary endpoints for which sequential testing will be performed to control Type I error rate (see Section 9.4.1.6). These secondary endpoints will be ORR, lymphadenopathy node response rate, OS, PFS in the subgroup of subjects with 17p deletion and/or TP53 mutatation, and CR rate. Other endpoints will be considered exploratory.

9.3. Analysis Conventions

9.3.1. Analysis Sets

9.3.1.1. Intent-to-Treat Analysis Set

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

This analysis set will be used in the analyses of subject characteristics, PFS, ORR, OS, CR rate and health outcome variables. The analysis of PFS based on the ITT analysis set will be considered the primary analysis of the study. Subjects in the ITT analysis set who do not have sufficient baseline or on-study tumor status information to be adequately assessed for response status (ie, those with best overall responses of NE or ND) will be included in the denominators in calculations 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. Study drug 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 statistical analysis plan which will be finalized prior to database lock.

The PP analysis set will be used in sensitivity analyses of the primary and the following secondary efficacy variables: PFS, ORR, lymphadenopathy node response rate, and PFS in the subgroup of subjects with 17p deletion and/or TP53 mutation.

9.3.1.3. Safety Analysis Set

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

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

9.3.1.4. Pharmacodynamic/Pharmacokinetic Analysis Sets

The pharmacodynamic/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 analysis set), n (number with data), mean, and standard deviation,
95% confidence intervals (CIs) on the mean, median, minimum, and maximum. Summary tables for categorical variables will include: N, n, percentage, and 95% CIs on the percentage. Unless otherwise indicated, 95% CIs for binary variables will be calculated using the binomial distribution (exact method) and will be 2-sided. Data will be described and summarized by relevant treatment arm, analysis set, and timepoint. As appropriate, changes from baseline to each subsequent timepoint will be described and summarized by treatment arm. Similarly, as appropriate, the best change from baseline during the study will also be described and summarized by treatment arm. Graphical techniques (eg, waterfall plots, Kaplan-Meier curves, line plots) may be used when such methods are appropriate and informative.

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

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

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

Tumor control assessments will be based on standardized IWCLL criteria {Hallek 2008}, as specifically modified for this study considering the pharmacology of idelalisib and ofatumumab. 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, date that response is confirmed, 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. Where imaging data are available, these data will supersede physical examination data in determining tumor status. For purposes of analysis, subjects who have only physical examination evidence of definitive disease progression that is not confirmed by CT/MRI will be considered to have progressed at the time of the physical examination finding. Because of the characteristic redistribution lymphocytosis that expected with PI3Kδ inhibition, lymphocyte count will be ignored in the evaluations of progression.

Changes in tumor status as provided by the investigator and changes in tumor status as adjudicated by the IRC (see Section 10.4.2) will be described. The findings of the IRC will be considered primary for analyses of PFS and other tumor control endpoints.

The following censoring conventions will be applied:

- PFS: Data from surviving, non-progressing subjects will be censored at the earliest of the time of initiation of antitumor treatment other than the study treatment or the last time that lack of definitive CLL progression was objectively documented. Data from subjects who have CLL progression or die after ≥2 consecutive missing tumor assessments will be censored at the last time prior to the missing assessments that lack of definitive CLL progression was objectively documented.

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

Subject baseline characteristics will be listed and summarized by treatment arm and stratification factor for the ITT and responding analysis sets. Baseline data (eg, from the CIRS or FACT-Leu) will not be reconciled with other medical information (eg, adverse event data or past medical history data). Efficacy Analyses

9.4.1.1. Primary and Supportive Analyses of the Primary Endpoint

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

The following exploratory sensitivity analyses will be performed:

- PFS will be compared between the treatment arms in the ITT analysis set using Kaplan-Meier methods and an unstratified log-rank test.
- PFS will also be compared between treatment arms in the PP analysis set using Kaplan-Meier methods and a stratified log-rank test.
- PFS will be further analyzed by censoring data from surviving, non-progressing subjects only at the last time that lack of definitive CLL progression was objectively documented. An additional worst-case sensitivity analysis will be performed in which surviving, nonprogressing subjects who are lost to follow-up are categorized as having an event at the time of the last known CLL tumor status assessment if they were in Arm A and are categorized as censored at the time of the last known CLL tumor status assessment if they were in Arm B. These analyses will be performed in the ITT analysis set using Kaplan-Meier methods and the stratified log-rank test.

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

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

Differences between the treatment arms in TTR, DOR, and OS will be assessed in the appropriate analysis set using Kaplan-Meier methods and stratified log-rank tests. Medians, ranges, hazard ratios and corresponding 95% CIs will be presented.

A supportive Cox regression analysis of OS in the ITT analysis set will be performed using the same methods as in the analysis of PFS if a sufficient number of events occur.

Sensitivity analysis for ORR, CR rate, DOR, and TTR will be performed based on responses without the need for confirmation.

9.4.1.3. Categorical Endpoints

Differences between Arms A and B for ORR, CR and PR rates, nodal response rate, splenomegaly response rate, hepatomegaly response rate, ALC response rate, platelet response rate, hemoglobin response rate, and neutrophil response rate will be compared using Cochran-Mantel-Haenszel Chi-square tests for association between treatment and response, after adjusting for stratification factors. In the analyses of ORR, subjects who do not have sufficient baseline or on-study tumor assessment to characterize response will be counted as failures. For all analyses, odds ratios and the corresponding 95% CIs will be presented.

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

9.4.1.4. Continuous Endpoints

Differences between treatment arms for percentage changes in lymph node area and for changes in performance status, PI3K/AKT/mTOR pathway activation, and plasma chemokines/cytokines will be assessed using analysis of covariance (ANCOVA) with baseline values and stratification factors as covariates; in these analyses, both changes from baseline to each subsequent timepoint and best overall on-study changes will be compared. Least-squares means and 95% CI will be presented.

9.4.1.5. Health-Related Quality of Life and Performance Status

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

The mean and change from baseline in mean scores to each subsequent assessment will be summarized for the FACT-Leu 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. Mixed-effects models will be used to assess the treatment effect on change from baseline over time.

The EQ-5D questionnaire data will be scored, processed, and standardized according to the user manual. U.S. preference-weighted index score computed using EQ-5D data {Shaw 2005} will be calculated. Change from baseline in EQ-5D visual analogue scale and EQ-5D index will be summarized and analyzed using mixed-effects models.

9.4.1.6. Control of Type I Error Rate in Efficacy Analyses

In the efficacy analyses, the following procedures will be implemented to preserve the overall type I error rate across the primary and secondary endpoints of the study at a 2-sided significance level of 0.05.

The primary endpoint analysis will serve as the gatekeeper for the secondary endpoint analyses, ie, the primary efficacy hypothesis must be made before the efficacy hypotheses for the secondary efficacy endpoints can be tested. The secondary endpoints will be the following:

- ORR
- Lymphadenopathy node response rate
- CR rate
- OS
- PFS in the subgroup of subjects with 17p deletion and/or TP53 mutation

If the primary hypothesis is rejected, the 5 secondary endpoints will be sequentially tested at the 2-sided 0.03 significance level in the order listed above. If a null hypothesis is not rejected, formal sequential testing will be stopped and only nominal significance will be cited for the remaining secondary endpoints. Analyses and p-values will be reported for all the efficacy endpoints, including the primary endpoint, the secondary endpoints, and all of the exploratory endpoints.

9.4.2. Exposure and Safety Analyses

9.4.2.1. Study Drug Administration and Study Drug Compliance

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

Idelalisib 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).

9.4.2.2. Idelalisib Plasma Concentrations

The idelalisib plasma concentrations immediately pre-dose and at 1.5 hours after administration of the dose of study drug at each relevant clinic visit among subjects treated on Arm A of the study will be summarized and visit using descriptive statistics.

9.4.2.3. Prior and Concomitant Medication Use

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

Descriptions of prior medication use will be focused on drugs and regimens used as treatments for CLL. To the extent available, information on the sequencing, type, dose, schedule, timing, duration of use, and efficacy of prior regimens will be provided.

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, and corticosteroids) during study treatment, and within 30 days post-study treatment, will be described.

9.4.2.4. Adverse Events

All adverse events will be listed. The focus of adverse event summarization will be on treatment-emergent adverse events. A treatment-emergent adverse event is defined as an adverse event that occurs or worsens in the period from the first dose of study treatment (idelalisib or ofatumumab) to 30 days after the last dose of study drug.

Adverse events will be classified using MedDRA (http://www.meddra.org) 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.

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

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

The severity of ofatumumab-related infusion reactions and of the total durations of ofatumumab infusions will be compared between treatment arms to determine whether idelalisib pretreatment modifies the magnitude of such events or alters the length of the ofatumumab infusion due to such events; the focus of this analysis will be on the first 2 ofatumumab infusions (ie, those on Study Day 1 and on Day 8). However, assessment of infusion reaction severity and duration will be performed for all 12 planned infusions of ofatumumab. Comparisons will be done using the Chi-square test for severity grade and the Wilcoxon rank-sum test for infusion duration.

Separate listings and summaries will be prepared for long-term follow-up safety data.

9.4.2.5. Laboratory Evaluations

All laboratory data will be listed. Summaries of laboratory data will be based on observed data.The focus of laboratory data summarization will be on treatment-emergent laboratory abnormalities. A treatment-emergent laboratory abnormality is defined as an abnormality that, compared to baseline, worsens by ≥1 grade in the period from the first dose of study drug (idelalisib or ofatumumab) 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, by visit, and by combination therapy vs monotherapy periods (during ofatumumab treatment vs following ofatumumab treatment). 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.

9.4.2.6. 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, by visit, and by combination therapy vs monotherapy periods (during ofatumumab treatment vs following ofatumumab treatment). 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).

9.4.3. Other Analyses

9.4.3.1. Health Care Resource Utilization

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

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

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

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

9.4.3.2. Data Explorations

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

9.5. Sample Size

Based on data from the Phase 2 pivotal study ofatumumab {Wierda 2010} and considering the population of subjects to be enrolled to this study, it is reasonable to assume that administration of ofatumumab to subjects with previously treated CLL in Arm B of this trial will result in a median PFS of ~8 months. An improvement in median PFS from 8 months to 14 months due to the addition of idelalisib to ofatumumab in Arm A of the study would correspond to a benefit ratio of 1.75 (hazard ratio 0.57).

It is assumed that PFS times are exponentially distributed in each of the 2 arms. With a hazard ratio equal to 1 under the null hypothesis of no difference between the 2 treatment arms and a hazard ratio of 0.57 under the alternative hypothesis of superiority of the idelalisib-containing combination, 129 events (definitive CLL progressions or deaths) are required to achieve a power of >0.85 based on a log-rank test with a 2-sided significance level of 0.05. Further assuming a planned accrual period of 12 months (with approximately half of the subjects enrolled during the initial 60% of the accrual period, and the remaining half of the subjects enrolled during the last 40% of the accrual period), a minimum follow-up period of 12 months, and an expectation that 10% of subjects will be lost to follow-up (5% during the accrual period and 5% during the follow-up period), and to ensure the primary analysis on PFS will be performed before or at the planned minimum 12-month follow-up period, 170 subjects will be enrolled into Arm A and 85 subjects will be enrolled into Arm B in order to achieve the expected number of events by the end of the planned minimum 12-month follow-up period. If the planned subject enrollment does not appear adequate to accrue the expected number of events within the proposed follow-up period, the sample size may be adjusted upward.

It is expected that there will be approximately 65 deaths at the time of final analysis. This would provide ~85% power to detect a HR of 0.45 for overall survival based on a log-rank test at 2-sided alpha level of 0.03.

The resulting safety data set provided by the idelalisib-treated subjects (N=170) compares favorably with the safety data set derived from the initial pivotal registration trials for ofatumumab (N=138) {Wierda 2010}, oral fludarabine (N=78) {Boogaerts 2001}, or alemtuzumab (N=93) {Keating 2002a}.

9.6. Timing of Analyses

9.6.1. Interim Analysis

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

Two formal interim efficacy analyses for PFS are planned. The first interim analysis will be performed when ~50% of the expected 129 events occur. The second interim will be performed when ~75% of the expected events occur. Type I error rate for testing PFS will be controlled by using the O'Brien-Fleming boundaries. Based on the planned number of PFS events for the 2 interim analyses, the 2-sided alpha for the interim and the final analyses are (0.003, 0.018, 0.044). The significant levels will be recalculated based on the actual observed number of events at the time of the interim and final analyses.

9.6.2. Final Efficacy Analysis

The efficacy analysis will be conducted after approximately 129 events (definitive CLL progression or death) are accrued. It is expected that this number of events will occur after a minimum of approximately 12 months of follow-up. Once outstanding data queries have been resolved, the database will be locked and the efficacy analysis of the study will be performed.

9.6.3. Follow-up Analyses

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

10. RESPONSIBILITIES

10.1. Investigator Responsibilities

10.1.1. Good Clinical Practice

The investigator will ensure that this study is conducted in accordance with the principles of the "Declaration of Helsinki" (as amended in Edinburgh, Tokyo, Venice, Hong Kong, and South Africa), International Conference on Harmonsation (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 Practive Directive 2005/28/EC.

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

The investigator an all applicable subinvestigators will comply with US Federal Regulation 21 CFR, Part 54, 1998 providing documentation of their financial interest or arrangements with Gilead Sciences, or proprietary interests in the drug being studied. This documentation must be provided prior to the investigator's (and any subinvestigator's) participation in the study. 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 (IRB)/Independent Ethics Committee (IEC) Review and Approval

This investigator (or sponsor as appropriate according to local regulations) will submit this protocol, informed consent form, and any accompanying material to be provided to the subject (such as advertisements, subject information sheets, or descriptions of the study used to obtain informed consent) to an IRB/IEC. The investigator will not begin any study subject activities until approval from the IRB/IEC has been documented and provided as a letter to the investigator. Before implementation, the investigator will submit to and receive documented approval from the IRB/IEC for any modifications made to the protocol or any accompanying material to be provided to the subject after initial approval, with the exception of those necessary to reduce immediate risk to study subjects Informed Consent.

The investigator is responsible for obtaining written informed consent from each individual participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study and before undertaking any study-related procedures. The investigator must use the most current IRB/ or IEC-approved consent form for documenting written informed consent. Each informed consent (or assent as applicable) will be appropriately signed and dated by the subject or the subject's legally authorized representative and the person

conducting the consent discussion, and also by an impartial witness if required by IRB or IEC or local requirements. The consent form will inform subjects about pharmacogenomics analysis results.

10.1.3. 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.

10.1.4. 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)
- Documentation of the reason(s) a consented subject is not enrolled
- 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 retained by the investigator will be stored and maintained by the investigator until notification is received from Gilead Sciences that the retained samples and records no longer need to be retained. 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.

10.1.5. Case Report Forms

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

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

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

10.1.6. Drug Accountability

As described in the relevant sections for (see Section 5.2.1.7 for idelalisib and Section 5.2.2.6 for ofatumumab), the investigator is responsible for ensuring adequate accountability of all used and unused investigational medicinal product 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.

10.1.7. 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.

10.1.8. 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 8.4.

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 advance written consent of Gilead or > 2 years after the completion of the study at all participating institutions.

No such communication, presentation, or publication will include Gilead Sciences' confidential information (see Section 10.1.3).

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 for 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, and the clinical investigators, 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 operate under a charter developed as a collaborative document between Gilead Sciences and the DMC.

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

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

Based on the results of its deliberations during the course of the study, the DMC can recommend appropriate actions (eg, 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. The specifics of the IRC's processes and reading methods will be described in an independent review charter developed by the contracted imaging facility in conjunction with Gilead Sciences. The findings of the IRC will be considered primary for analyses of PFS and other tumor control endpoints.

11. REFERENCES

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12. APPENDICES

Appendix 1. Investigator Signature Page

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STUDY ACKNOWLEDGEMENT

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

GS-US-312-0119, Version 11.0, 30 August 2017

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

PPD

Gilead Sciences Medical Monitor

PPD

01 Sep 2017

Date

INVESTIGATOR STATEMENT

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

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

Principal Investigator
Printed Name

Signature

Date

Site Number

Appendix 2. Functional Assessment of Cancer Therapy: Leukemia

FACT-Leu (Version 4)

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

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

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

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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 ☐

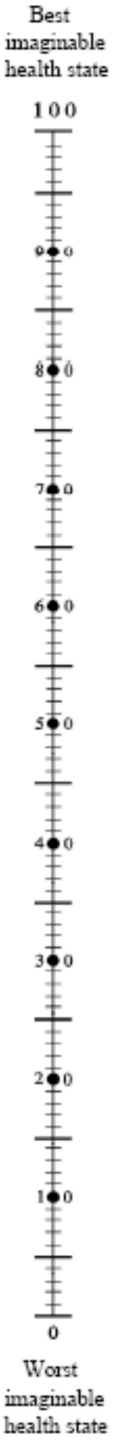
Anxiety/Depression

- 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 {Cockcroft 1976}. The formula appropriate to the units in which serum creatinine was measured and the subject's gender should be used.

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

Abbreviation: eC_{cr}=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 lists of organ-specific diagnoses, please select any conditions present in the study subject. If the subject has recurrent or ongoing chronic conditions that are not described in the list for a given organ system, please indicate the name of the conditions under "other chronic condition" for that organ system. Please take into account that CLL-induced discomfort, symptoms, or disability should not be considered. If additional explanation would be helpful, text comments may be inserted.

Organ System	Diagnosis	Comment
Cardiac	Chronic heart failure	
	Angina pectoris	
	Medically relevant arrhythmia	
	Valve dysfunction	
	Congenital heart disease	
	Cardiomyopathy	
	Myocarditis	
	Chronic pericarditis	
	Endocarditis	
	Other chronic cardiac condition:	
	Other chronic cardiac condition:	
Vascular	Hypertension	
	Thrombosis	
	Peripheral diabetic microvascular disease	
	Peripheral artery disease	
	Aortic aneurysm	
	Aortitis	
	Raynaud disease	
	Vasculitis	
	Other chronic vascular condition:	
	Other chronic vascular condition:	
Hematological/ Immunological	Sickle cell anemia	
	Hemoglobinopathy	
	Polycythemia	
	Thrombocythemia	
	Hemophilia	
	Paroxysmal nocturnal hemoglobinuria	

Organ System	Diagnosis	Comment
	Thrombotic thrombocytopenic purpura	
	Dysfibrinogenemia	
	HIV	
	Other chronic hematological or immunological condition:	
	Other chronic hematological or immunological condition:	
Respiratory	Asthma	
	Chronic obstructive pulmonary disease	
	Cystic fibrosis	
	Emphysema	
	Chronic bronchitis	
	Chronic pleural effusions	
	Pulmonary fibrosis	
	Sarcoidosis	
	Pulmonary embolism	
	Pulmonary arterial hypertension	
	Lung cancer	
	Other chronic respiratory condition:	
	Other chronic respiratory condition	
Ophthalmological/ otolaryngological	Loss of vision	
	Glaucoma	
	Cataract	
	Macular degeneration	
	Diabetic retinopathy	
	Loss of hearing	
	Otitis/chronic otitis	
	Vestibular impairment	
	Vertigo	
	Temporomandibular disorder	
	Sialolithiasis	
	Chronic sinusitis	
	Laryngeal/pharyngeal disorders	
	Other chronic ophthalmological or otolaryngological condition:	

Organ System	Diagnosis	Comment
Upper Gastrointestinal	Chronic esophagitis	
	Dysphagia	
	Achalasia	
	Gastroduodenal ulceration	
	Celiac disease	
	Irritable bowel syndrome	
	Short bowel syndrome	
	Malnutrition	
	Malabsorption	
	Small bowel obstruction	
	Hernia	
	Pseudomyxoma peritonei	
	Upper gastrointestinal cancer	
	Other chronic upper gastrointestinal condition:	
	Other chronic upper gastrointestinal condition:	
Lower Gastrointestinal	Diverticulitis	
	Inflammatory bowel disease	
	Volvulus	
	Colon cancer	
	Other chronic lower gastrointestinal condition:	
	Other chronic lower gastrointestinal condition:	
Hepatic/ Pancreatic	Chronic hepatitis or hepatic cirrhosis	
	Biliary obstructive disorders	
	Pancreatitis	
	Hepatic, biliary, or pancreatic cancer	
	Other chronic hepatic or pancreatic condition:	
	Other chronic hepatic or pancreatic condition:	
Renal	Chronic kidney disease	
	Diabetic nephropathy	
	Pyelonephritis	
	Renal cancer	
	Other chronic renal condition:	
	Other chronic renal condition	

Organ System	Diagnosis	Comment
Gynecological/ Urological	Recurrent/chronic urinary tract infection	
	Nephrolithiasis	
	Bladder dysfunction	
	Vaginal/vulvar disease	
	Uterine/ovarian disease	
	Prostatitis	
	Bladder, uterine, ovarian, prostate, or other cancer	
	Prostate hypertrophy	
	Other chronic gynecological or urological condition:	
	Other chronic gynecological or urological condition:	
Dermatologic/ musculoskeletal	Dermatitis	
	Dermatomyositis	
	Myopathy	
	Gout	
	Psoriasis	
	Keratosis	
	Urticaria	
	Scleroderma	
	Basal cell carcinoma	
	Squamous cell carcinoma	
	Melanoma	
	Osteomyelitis	
	Osteoarthritis	
	Rheumatoid arthritis	
	Spondyloarthritis	
	Temporal arteritis/polymyalgia rheumatica	
	Polychondritis	
	Fibromyalgia	
	Osteoporosis	
	Systemic lupus erythematosus	
	Dermatomyositis	
	Sjögren syndrome	
	Other chronic dermatological or musculoskeletal condition:	
	Other chronic dermatological or musculoskeletal condition:	

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

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

Abbreviation: CIRS=Cumulative Illness Rating Scale

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

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

Abbreviation: CIRS=Cumulative Illness Rating Scale

Appendix 7. Schedule of Study Procedures

Period	Screen	Treatment																		Follow-up	
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18+**		**30 day**	**Long-term**
Week	**-4**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**12**	**16**	**20**	**24**	**30**	**36**	**42**	**48**				
Study Day	**Within -28 Days**	**1**	**8**	**15**	**22**	**29**	**36**	**43**	**50**	**78**	**106**	**134**	**162**	**204**	**246**	**288**	**330**	**Q12 Weeks**	**End of Study**	**Within +30 days**	**To +5 years**
Visit Window			**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±7**			
Informed consent	X																				
Medical history	X																				
CIRS assessment	X																				
Serum virology	X																				
CMV Surveillance[e]						X			X	X	X	X	X	X	X	X	X	X			
PJP prophylaxis																		X[g]	X[g]		
β-HCG (women of child-bearing potential)	X	X				X			X	X	X	X	X	X	X	X	X[a]	X[a]	X		
CLL peripheral blood evaluation	X																		X		
CLL serology	X																		X		
Coagulation	X																				
Urinalysis	X																				
12-lead ECG	X																				
CCI [redacted]																					

Period	Screen	Treatment																		Follow-up	
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18+**		**30 day**	**Long-term**
Week	**-4**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**12**	**16**	**20**	**24**	**30**	**36**	**42**	**48**				
Study Day	**Within -28 Days**	**1**	**8**	**15**	**22**	**29**	**36**	**43**	**50**	**78**	**106**	**134**	**162**	**204**	**246**	**288**	**330**	**Q12 Weeks**	**End of Study**	**Within +30 days**	**To +5 years**
Visit Window			**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±7**			
IWRS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
HRQL/ healthy utility – FACT-Leu/ EQ-5D		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Adverse events[f]		X	X	X	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	X	X	X	
Performance status	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Oxygen saturation (by pulse oximetry)	X	X	X	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		
Hematology/ serum chemistry	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Circulating cells/biomarkers/ serum Igs		X	X	X		X			X	X	X	X	X	X	X	X	X	X	X		
Serum CH50																		X	X		

Period	Screen	Treatment																	Follow-up	
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18+		30 day	Long-term
Week	-4	1	2	3	4	5	6	7	8	12	16	20	24	30	36	42	48				
Study Day	Within -28 Days	1	8	15	22	29	36	43	50	78	106	134	162	204	246	288	330	Q12 Weeks	End of Study	Within +30 days	To +5 years
Visit Window			±2	±2	±2	±2	±2	±2	±2	±3	±3	±3	±3	±3	±3	±3	±3	±7			
Idelalisib administration in clinic (Arm A only)		X		X		X			X	X			X								
Premedication and ofatumumab administration		X	X	X	X	X	X	X	X	X	X	X	X								
Infusion reaction severity/duration assessment		X	X	X	X	X	X	X	X	X	X	X	X								
Idelalisib pharmacokinetics (Arm A only)		X		X		X			X	X			X								
Idelalisib dispensing/ accounting (Arm A only)		X								X			X		X		X	X	X		
Radiology assessment (CT/MRI)[b]	X								X		X		X		X		X	X	X		
Bone marrow biopsy/aspirate[c]	X								X		X		X		X		X	X			
HBV DNA by PCR[d]						X			X	X	X	X	X		X		X	X			

Period	Screen	Treatment																		Follow-up	
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18+**			
Week	**-4**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**12**	**16**	**20**	**24**	**30**	**36**	**42**	**48**			**30 day**	**Long-term**
Study Day	**Within -28 Days**	**1**	**8**	**15**	**22**	**29**	**36**	**43**	**50**	**78**	**106**	**134**	**162**	**204**	**246**	**288**	**330**	**Q12 Weeks**	**End of Study**	**Within +30 days**	**To +5 years**
Visit Window			**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±7**			
Post-study CLL therapy																					X
Long-term follow-up																					X

a After Visit 17 and 18, urine β-HCG to be performed every 6 weeks ±5 d (women of child-bearing potential only)
b At screening, CT/ MRI may be performed within 6 weeks prior to start of randomization; CT or MRI imaging of neck, chest, abdomen, and pelvis can be performed within 1 week of the visit. CT/MRI assessments will continue until ~129 events have been observed in the study population
c At baseline, to be performed at investigator discretion to determine extent of CLL involvement and bone marrow cellularity. Post-baseline, to confirm CR or PD; if the subject does not otherwise meet criteria for CR or if the nature of PD does not require bone marrow confirmation, it is not necessary to obtain a follow-up bone marrow biopsy/aspirate.
d Only subjects who are HBc antibody positive and HBV DNA negative at screening. Subjects will be tested monthly for the duration of ofatumumab therapy and every 3 months thereafter for 1 year from the last dose of ofatumumab per Section 5.4.5.
e After screening, CMV surveillance for active disease must be conducted approximately every 4 weeks for subjects in Arm A.
f If reported, obtain history of onset and duration of diarrhea, including description of number of stools and stool composition (eg, watery, bloody, nocturnal), travel history, dietary changes and a medication review to identify possible diarrheogenic agents.Perform physical examination including assessment for fever, dizziness, abdominal pain/cramping, and weakness (ie, evaluate for sepsis, bowel obstruction, dehydration).
g 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 and until the CD4+ T-cell count is documented to be >200 cells/mcL.

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