CLINICAL STUDY PROTOCOL

Study Title:	Dose Optimization Study of Idelalisib in Follicular Lymphoma
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404
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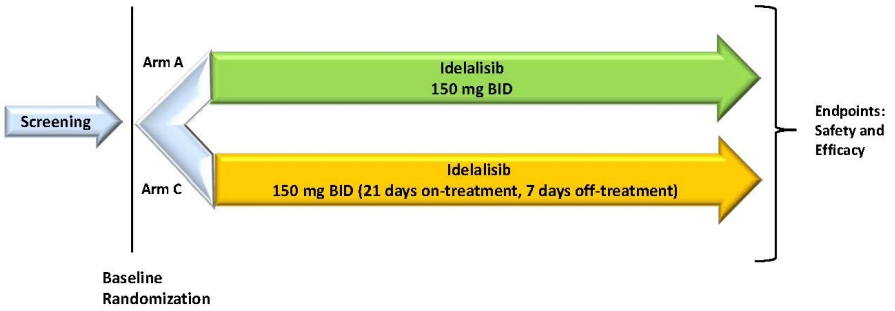
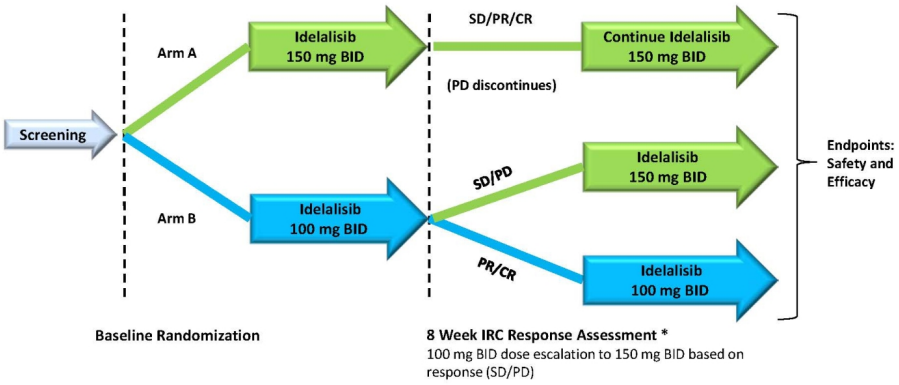
PROTOCOL SYNOPSIS
Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404

Study Title:	Dose Optimization Study of Idelalisib in Follicular Lymphoma
IND Number: **EudraCT Number:** **Clinical Trials.gov Identifier:**	101254 2015-000366-66 NCT02536300
Study Centers Planned:	Approximately 90 centers globally
Objectives:	The primary objective of this study is as follows: • Establish a safe and effective dosing regimen of idelalisib in subjects with relapsed or refractory follicular lymphoma (FL) who have no other therapeutic options The secondary objectives of this study are as follows: • Evaluate the overall response rate (ORR) • Evaluate the progression-free survival (PFS), duration of response (DOR), and overall survival (OS) • Evaluate the overall safety profile of idelalisib • Determine the pharmacokinetics (PK) of idelalisib and its major metabolite (GS-563117) The exploratory objective of this study is as follows: • CCI [redacted]
Study Design:	This randomized, open-label study will evaluate the safety and efficacy of idelalisib in subjects randomized to the following treatment arms: • Arm A: 150 mg idelalisib administered twice daily continuously. • Arm C: 150 mg idelalisib administered twice daily in 28-day cycles with 21 days on-treatment and 7 days off-treatment.

	The original protocol for this study included an Arm B, which was closed to enrollment as of Protocol Amendment 5. • Arm B (*closed to enrollment as of Protocol Amendment 5*): 100 mg idelalisib administered twice daily continuously.
	Study Design as of Protocol Amendment 5:  Study Design prior to Protocol Amendment 5:  * Unblinding and dose modifications may occur at any time during study participation if the IRC Assessment confirms progressive disease.

	In accordance with Protocol Amendment 6, subjects enrolled prior to implementation of Protocol Amendment 5 and still blinded will be unblinded at the time of Protocol Amendment 6 implementation; these subjects will continue at the randomized dose level if they are still on treatment. These subjects were previously randomized in a blinded manner to either 150 mg twice daily or 100 mg twice daily idelalisib. Based on the 8-week blinded independent review committee (IRC) response assessment, subjects with stable disease (SD) or progressive disease (PD) were unblinded in both arms. Subjects with a partial response (PR) or complete response (CR) maintained the blind and continued at the randomized dose level. Subjects randomized to 100 mg twice daily with SD or PD had the option to be dose escalated to 150 mg twice daily. Subjects randomized to 150 mg twice daily with SD will continue open-label idelalisib at 150 mg twice daily. Subjects randomized to 150 mg twice daily with PD will be discontinued from study treatment. These same unblinding and dose modification principles were applied at any time throughout study participation when disease progression was suspected and confirmed by IRC assessment.
Number of Subjects Planned:	Approximately 266 subjects: approximately 120 subjects in Arm A, approximately 26 subjects in Arm B, and approximately 120 subjects in Arm C. As of Protocol Amendment 5, Arm B enrollment was closed after enrollment of approximately 26 subjects into Arm B and approximately 26 subjects into Arm A. As of Protocol Amendment 5, subjects were randomized to 2 arms (Arm A and C) with a 1:1 ratio until the enrollment target of 120 subjects in each arm was met. The sample size was originally planned to include 240 subjects randomized to Arm A and Arm B with a 1:1 ratio (approximately 120 subjects receiving 150 mg twice daily in Arm A; approximately 120 subjects receiving 100 mg twice daily in Arm B).
Target Population:	The target population comprises adults with relapsed or refractory FL who have received at least 2 lines of prior therapy for FL with no other therapeutic options, have measurable lymphadenopathy, and require therapy according to standard response criteria.
Duration of Treatment:	Idelalisib will be administered continuously until the earliest of: disease progression, unacceptable toxicity, substantial noncompliance with study procedures or study drug, initiation of another systemic anti-cancer or experimental therapy, or withdrawal from the study.
Duration of Study:	The overall duration of the study is expected to be approximately 10 years.

Eligibility Criteria:

Inclusion Criteria

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

1) Male or female ≥ 18 years of age
2) Histologically confirmed diagnosis of B-cell FL, and grade limited to 1, 2, or 3a based on criteria established by the World Health Organization (WHO) 2008 classification of tumors of hematopoietic and lymphoid tissues
3) Relapsed or refractory FL and have received at least 2 lines of prior therapy for FL and have no other available therapeutic options. ***Note: Rituximab maintenance is not routinely considered a separate line of therapy when it is given as part of the prior rituximab-containing regimen given over a number of cycles followed by maintenance. Rituximab monotherapy may be considered a separate line of therapy when disease relapse occurs between the initiation of rituximab monotherapy and the preceding line of therapy. If there are any ambiguities about eligibility, the site should consult with the medical monitor.***
4) Ann Arbor Stage 2 (noncontiguous), 3, or 4 disease per Lugano Classification
5) Radiographically measurable lymphadenopathy or extranodal lymphoid malignancy as determined by IRC, defined as the presence of at least 1 lesion that measures ≥ 1.5 cm in the longest dimension [LD] and ≥ 1.0 cm in the longest perpendicular dimension as assessed by positron emission tomography-computed tomography [PET-CT], computed tomography [CT], or magnetic resonance imaging [MRI])
6) Have adequate performance status (such as Eastern Cooperative Oncology Group Performance Status of ≤ 2 or Karnofsky Performance Status of ≥ 60)
7) Required baseline laboratory data (within 4 weeks prior to start of study therapy) as shown in the table. ***Note: Confirmation should be considered for out-of-range values to determine if the abnormality is real or artifactual. Values should be obtained within the screening period and should generally be the most recent measurement obtained.***

Organ System	Parameter	Required Value
Hematopoietic[a]	ANC	≥ 1,000/μL
	Platelet	≥ 50,000/μL
	Hemoglobin	≥ 8 g/dL

	Hepatic	Serum total bilirubin	≤ 1.5 x ULN (unless elevated due to Gilbert syndrome)
		Serum ALT	≤ 2.5 x ULN
		Serum AST	
	Renal	Serum Creatinine	≤ 1.5 x ULN Calculated or Estimated CrCL > 30 mL/min
	Pregnancy	β-hCG[b]	Negative
	Infection	HIV	Negative HIV antibody[c]
		HBV	Negative HBsAg and negative HBc[d] antibody
		HCV	Negative viral RNA (if HCV antibody is positive)
		CMV	No CMV DNA detected or CMV DNA is below the lower limit of quantification by PCR AND No clinical signs or symptoms suggestive of active CMV infection
	ANC=absolute neutrophil count, β-hCG=beta human chorionic gonadotropin, ALT=alanine aminotransferase, AST=aspartate aminotransferase, CMV=cytomegalovirus, CrCL=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, PCR=polymerase chain reaction, RNA=ribonucleic acid, ULN=upper limit of normal a Grade ≥ 3 neutropenia, thrombocytopenia, or anemia is permitted if abnormality is related to bone marrow involvement with FL (as documented by bone marrow biopsy/aspirate obtained since the last prior therapy) b For women of childbearing potential only; serum β-hCG must be negative during screening and urine dipstick pregnancy test must be negative at baseline, prior to randomization c If screening test is positive, a negative confirmatory test will be required for eligibility. d Subjects who have positive HBc antibody may be enrolled if HBV DNA is undetectable by quantitative PCR		
	8) For female subjects of childbearing potential, willingness to use a protocol-recommended method of contraception during heterosexual intercourse from the signing of informed consent throughout the study treatment period and up to 30 days from the last dose of idelalisib (see Appendix 4) 9) For male subjects of reproductive potential having intercourse with females of childbearing potential, willingness to use a protocol-recommended method of contraception during heterosexual intercourse and to refrain from sperm donation throughout the study treatment period and for 90 days following discontinuation of idelalisib (see Appendix 4)		

	10) Lactating females must agree to discontinue nursing before study drug administration and until at least 30 days following the last dose of idelalisib 11) Indicate willingness to comply with scheduled visits, drug administration plan, imaging studies, laboratory tests, other study procedures, and study restrictions, including mandatory prophylaxis for *Pneumocystis jirovecii* pneumonia 12) Evidence of a signed informed consent indicating that the subject is aware of the neoplastic nature of their 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 <u>Exclusion Criteria</u> Subjects who meet *any* of the following exclusion criteria are not to be enrolled in this study: 1) History of lymphoid malignancy other than FL (eg, diffuse large B-cell lymphoma). Note: Biopsy documentation of the absence or presence of high grade lymphoma is not required 2) Known history of, or clinically apparent, central nervous system (CNS) lymphoma or leptomeningeal lymphoma. ***Note: Imaging documentation of the absence or presence of CNS disease is not required*** 3) Known presence of intermediate or high-grade myelodysplastic syndrome. Note: intermediate or high-grade myelodysplasia is defined as the presence of ≥ 5% bone marrow blasts; karotypic abnormalities other than normal, Y deletion, 5q deletion, or 20q deletion; or ≥ 2 lineages of cytopenias due to myelodysplasia 4) Known history of serious allergic reaction including anaphylaxis or Stevens-Johnson syndrome/toxic epidermal necrolysis 5) History of a non-lymphoid malignancy except for the following: adequately treated local basal cell or squamous cell carcinoma of the skin, cervical carcinoma *in situ*, superficial bladder cancer, asymptomatic prostate cancer without known metastatic disease and with no requirement for therapy or requiring only hormonal therapy and with normal prostate-specific antigen for ≥ 1 year prior to enrollment, or any other cancer or malignancy that has been in complete remission for ≥ 5 years 6) Evidence of ongoing systemic infection (eg, bacterial, fungal, viral) at the time of enrollment

	7) Known history of drug-induced liver injury, chronic active hepatitis B virus, chronic active hepatitis C virus, alcoholic liver disease, non-alcoholic steatohepatitis, cirrhosis of the liver, portal hypertension, primary biliary cirrhosis, or ongoing extrahepatic obstruction caused by cholelithiasis 8) History of or ongoing drug-induced pneumonitis 9) History of or ongoing inflammatory bowel disease 10) Known human immunodeficiency virus (HIV) infection 11) Cytomegalovirus (CMV): Ongoing infection, treatment, or specifically CMV antiviral prophylaxis within 28 days prior to the Screening Visit CMV test 12) Presence of any condition that could, in the opinion of the investigator, compromise the subject's ability to participate in the study, such as history of substance abuse, alcoholism, or a psychiatric condition 13) History of prior allogeneic bone marrow progenitor cell or solid organ transplantation 14) Ongoing immunosuppressive therapy, including systemic corticosteroids (> 10 mg prednisone or equivalent/day) with the exception of the use of topical, enteric, or inhaled corticosteroids as therapy for comorbid conditions or systemic corticosteroids for autoimmune anemia and/or thrombocytopenia 15) Concurrent participation in another therapeutic clinical study 16) Prior or ongoing clinically significant illness, medical condition, surgical history, physical finding, electrocardiogram (ECG) finding, or laboratory abnormality that, in the investigator's opinion, could adversely affect the safety of the subject or impair the assessment of study results 17) Prior treatment with PI3K inhibitors
Study Visits:	Clinic visits will occur at Screening, Day 1, every 2 weeks through Week 12, every 4 weeks through Week 24, at Weeks 32, 36, 40, 48, and every 12 weeks thereafter through the end of study. Subjects will be assessed for safety at each visit. Additional visits will be required between protocol-specified visits for laboratory testing only.

	Subjects enrolled as of Protocol Amendments 5 and 6: Subjects will be assessed for FL disease status by continuous use of a single radiographic imaging method including PET-CT, CT, or MRI at screening and at Weeks 12, 24, 36, 48, 60, and 84 until IRC documented disease progression, and at the End of Treatment (EOT) visit (unless radiographic assessments were performed within the 4 weeks prior to the EOT visit). After Week 84, radiographic assessments are performed at the discretion of the investigator. Screening CT/PET-CT/MRI may be performed within 6 weeks prior to the first dose. Subsequent scans may be done within 1 week prior to the clinic visit. Subjects enrolled prior to Protocol Amendment 5: Subjects will be assessed for FL disease status by continuous use of a single radiographic imaging method including PET-CT, CT, or MRI at screening and at Weeks 8, 16, 24, 36, 48, 60, and 84 until IRC documented disease progression, and at the EOT visit (unless radiographic assessments were performed within the 4 weeks prior to the EOT visit). After Week 84, radiographic assessments are performed at the discretion of the investigator. Screening CT/PET-CT/MRI may be performed within 6 weeks prior to the first dose. Subsequent scans may be done within 1 week prior to the clinic visit.
Study Drug, Dose, and Mode of Administration:	• Arm A: Idelalisib 150 mg will be taken twice daily orally starting on Day 1 and administered continuously. Dose reduction to 100 mg twice daily is available, if required. • Arm C: Idelalisib 150 mg will be taken twice daily orally starting on Day 1 and administered continuously for 21 days, followed by 7 days of no study drug, within each 28-day cycle. Dose reduction to 100 mg twice daily (21 days on-treatment, 7 days off-treatment) is available, if required. The original protocol for this study included an Arm B, which was closed to enrollment as of Protocol Amendment 5. • Arm B (*closed to enrollment as of Protocol Amendment 5*): Idelalisib 100 mg will be taken twice daily orally starting on Day 1 and administered continuously. Dose reductions are not available.

Criteria for Evaluation:	
Safety/Efficacy Primary Endpoints:	• ORR, defined as the proportion of subjects who achieve a PR or CR • Incidence of Grade ≥ 4 treatment-emergent adverse events (TEAEs)
Secondary Endpoints:	• DOR, defined as the interval from the first documentation of CR or PR to the earlier of the first documentation of disease progression by IRC or death from any cause • ORR by Week 24, defined as the proportion of subjects who achieve a PR or CR by Week 24 • Overall safety profile of idelalisib, including the incidence of adverse events (AEs) and clinically significant laboratory abnormalities, severity, timing, and relationship to idelalisib of any AEs; serious adverse events (SAEs); or AEs leading to interruption, reduction, or discontinuation of idelalisib • Time to onset of AEs of interest (AEI), defined as the interval from the start of idelalisib treatment to the first documentation of start of AEI • PFS, defined as the interval from randomization to the earlier of the first documentation of disease progression by IRC or death from any cause • OS, defined as the interval from randomization to death from any cause • Idelalisib trough (predose) and peak (1.5-hour samples) plasma concentrations assessed by a validated bioanalytical method
Exploratory Endpoint:	• CCI [redacted]
Statistical Methods:	The primary study analysis will be conducted when all enrolled subjects have discontinued the study or been on treatment for at least 48 weeks and completed response assessment of Week 48. <u>Analysis Data Set</u> The Intent-to-Treat (ITT) Analysis Set will include all subjects who are randomized regardless of whether subjects receive any study drug. Treatment assignment will be designated according to a subject's initial randomization. This analysis set will be used in the analysis of subject characteristics and efficacy.

	The Safety Analysis Set will include data from all subjects who receive at least 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. The PK Analysis Set will include data from subjects in the Safety Analysis Set who have received the study drug and have at least 1 sample with detectable drug concentration. An IRC will review radiographic data and pertinent clinical data in order to provide expert evaluation of tumor status, without receiving treatment assignment. The findings of the IRC will be considered primary for analyses of the primary efficacy endpoint and other tumor control endpoints. Tumor response status and progression will be assessed by the IRC using standard response criteria. <u>Efficacy Analysis</u> For the primary efficacy analysis, ORR will be evaluated by treatment arm using the IRC assessments in the ITT Analysis Set. Subjects who do not have sufficient baseline or on-study tumor assessment to characterize response will be counted as non-responders. Estimates and the corresponding 95% CIs based on the Clopper-Pearson exact method will be provided. The potential impact of subject baseline characteristics on treatment response may be explored with logistic regression modeling. The time-to-event efficacy endpoints including PFS, DOR, and OS will be analyzed using the Kaplan-Meier method in the ITT Analysis Set, and the analyses of DOR will include subjects who achieve a PR or CR. <u>Safety Analysis</u> Safety will be assessed via AEs, clinical laboratory tests, and concomitant medications. Information regarding study drug administration, study drug compliance, and other safety variables will be summarized by treatment arm. For the primary safety endpoint, the number and percentage of subjects who experienced at least 1 ≥ Grade 4 TEAE will be listed and summarized by treatment arm. The severity, timing, relationship to study drug, and drug interruptions for ≥ Grade 4 TEAEs will be summarized. The frequency, severity, timing, and drug interruptions for AEIs will be summarized by treatment arm using descriptive statistics. Time to onset and resolution of AEI will be analyzed using the Kaplan-Meier method.

	Pharmacokinetic Analysis Using data from the PK Analysis Set, idelalisib/metabolite plasma concentrations will be listed and summarized by treatment arm and visit using descriptive statistics. Relationship between drug exposure and efficacy or safety will be explored. Sample Size Calculation The planned sample size is approximately 266 subjects: approximately 120 subjects in Arm A, approximately 26 subjects in the previously closed Arm B, and approximately 120 subjects in Arm C. As of Protocol Amendment 5, Arm B enrollment was closed after enrollment of approximately 26 subjects into Arm B and approximately 26 subjects into Arm A. As of Protocol Amendments 5 and 6, subjects will be randomized to 2 arms (Arm A and C) with a 1:1 ratio until the enrollment target of 120 subjects in each arm is met. The ORR was approximately 56% for subjects with FL in Study 101-09. If the underlying true ORR is 56% for subjects in this study, the chance to observe 60 or more responders out of 120 subjects (observed ORR ≥ 50%) is 92%. With 120 subjects in each arm, the half-width of a two-sided 95% CI of ORR is ≤ 10% for an observed ORR in the range of 40%-60%, and the half-width of a two-sided 95% CI of ≥ Grade 4 TEAEs incidence rate is ≤ 10% for an observed AE rate in the range of 20%-40%. The sample size was originally planned to include 240 subjects randomized to Arm A and Arm B with a 1:1 ratio (approximately 120 subjects receiving 150 mg twice daily in Arm A; approximately 120 subjects receiving 100 mg twice daily in Arm B).

This study will be conducted in accordance with the guidelines of good clinical practices (GCPs) including archiving of essential documents.

GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

AE	adverse event
AEI	adverse event of interest
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AUC	area under the concentration versus time curve
β-hCG	beta-human chorionic gonadotropin
BID	twice daily
BUN	blood urea nitrogen
CFR	Code of Federal Regulations
CI	confidence interval
CLL	chronic lymphocytic leukemia
CMV	cytomegalovirus
COVID-19	coronavirus disease 2019
CNS	central nervous system
CR	complete response
CrCl	creatinine clearance
CRF	case report form
CRO	contract research organization
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DMC	data monitoring committee
DNA	deoxyribonucleic acid
DOR	duration of response
DRESS	drug reaction with eosinophilia and systemic symptoms
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eC_{cr}	estimated creatinine clearance
eCRF	electronic case report form
EOS	end of study
EOT	end of treatment
EU	European Union
FD&C	food, drug and cosmetics
FDA	Food and Drug Administration
FDG	fluorodeoxyglucose
FL	follicular lymphoma

FLIPI	Follicular Lymphoma International Prognostic Index
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GM-CSF	granulocyte-macrophage colony-stimulating factors
HBc antibody	anti-hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
IB	investigator's brochure
ICH	International Council for Harmonisation (of Technical Requirements for Pharmaceuticals for Human Use)
Ig	immunoglobulin
iNHL	indolent non-Hodgkin lymphoma
IRB/IEC	institutional review board or independent ethics committee
IRC	Independent Review Committee
ITT	intent-to-treat
IUD	intrauterine device
IV	intravenous
IWRS	Interactive Web Response System
LD	longest dimension
LDH	lactic dehydrogenase
LPD	longest perpendicular dimension
MRI	magnetic resonance imaging
ND	no disease
NE	not evaluable
NHL	non-Hodgkin lymphoma
ORR	overall response rate
OS	overall survival
PCR	polymerase chain reaction
PD	progressive disease
PE	physical examination
PET-CT	positron emission tomography–computed tomography
PFS	progression-free survival
PI3K	phosphatidylinositol 3-kinase
PJP	*Pneumocystis jirovecii* pneumonia
PK	pharmacokinetics
PML	progressive multifocal leukoencephalopathy
PPD	product of the perpendicular dimensions
PR	partial response

PT	preferred term
PVA	polyvinyl alcohol
PVE	Pharmacovigilance & Epidemiology
RNA	ribonucleic acid
SAE	serious adverse event
SD	stable disease
SJS	Stevens-Johnson syndrome
SLL	small lymphocytic lymphoma
SOC	system organ class
SOP	standard operating procedure
SPD	sum of the products of the diameters
StD	standard deviation
SUSAR	suspected unexpected serious adverse reactions
TEAE	treatment-emergent adverse event
TEN	toxic epidermal necrolysis
UGT1A4	uridine diphosphate glucuronosyltransferase 1A4
ULN	upper limit of normal
US	United States
WHO	World Health Organization

1. INTRODUCTION

1.1. Background

Follicular lymphoma (FL) is the most common subtype of indolent non-Hodgkin lymphoma (iNHL) in the United States (US); approximately 22% of all newly diagnosed non-Hodgkin lymphoma (NHL) and the second most frequent subtype of lymphoid malignancies in Western Europe; 5%-7% annual incidence {Dreyling 2014, National Comprehensive Cancer Network (NCCN) 2014}.

Computed tomography (CT) or magnetic resonance imaging (MRI) scans of the neck, chest, abdomen, and pelvis, as well as bone marrow aspirate and biopsy, are employed to stage iNHL {Zelenetz 2011}. The Lugano Classification for NHL modified the Ann Arbor classification for anatomic description of disease extent; single sites of involvement or a group of adjacent nodes (Stage 1), ≥ 2 sites of disease on the same side of the diaphragm (Stage 2), sites of disease on both sides of the diaphragm or nodes above the diaphragm with spleen involvement (Stage 3), or additional noncontiguous extralymphatic involvement (Stage 4) {Cheson 2014}.

For FL, the Follicular Lymphoma International Prognostic Index (FLIPI) has been developed to define outcomes {Solal-Celigny 2004}. The FLIPI characterizes patients in terms of 5 adverse prognostic factors: age > 60 years, Ann Arbor stage III-IV, hemoglobin < 12 g/dL, number of nodal areas > 4, and serum lactic dehydrogenase (LDH) above normal. Patients are scored as low risk (≤1 factor), intermediate risk (2 factors), or high risk (≥ 3 factors).

Radiation therapy to involved sites is the most common treatment for the infrequent patients with localized iNHL (Stage 1 or non-bulky Stage 2 disease) {Tsang 2005, Wilder 2001}. Systemic therapy is considered for the majority of patients with iNHL, in whom extensive lymphoma (Stage 2 bulky, Stage 3, or Stage 4 disease) is present {Zelenetz 2011}. Watchful waiting is possible but patients are generally treated if they have lymphoma-related symptoms or end-organ dysfunction, bulky disease, cytopenias, or persistent disease progression. Because iNHL requiring systemic therapy is essentially incurable and patients may be older and have comorbidities, the goal of therapy is primarily to alleviate lymphoma-related symptoms and prolong progression-free interval.

1.2. Idelalisib

Idelalisib was first approved under the tradename Zydelig® in the US on July 23, 2014 for the treatment of relapsed chronic lymphocytic leukemia (CLL), FL, and small lymphocytic lymphoma (SLL), followed by centrally-authorized approval in the European Union (EU) on September 18, 2014 for the treatment of relapsed CLL and refractory FL. Zydelig® is currently approved in over 35 countries, including the US, EU, Switzerland, Australia, and Canada. Refer to local labeling for the approved indication statements.

Idelalisib is a potent competitive inhibitor of the adenosine triphosphate binding site of the phosphatidylinositol 3-kinase (PI3K) p110δ catalytic domain, which has been shown to be prominently expressed in cells of hematopoietic origin {Okkenhaug 2003, Vanhaesebroeck 2005}. The effects of p110δ on lymphocyte activation/function, cellular proliferation, and protection from apoptosis provide the rationale for targeting this isoform as a therapy for hematologic malignancies. Further details on the preclinical pharmacology, toxicology, metabolism and pharmacokinetics (PK) of idelalisib can be found in the idelalisib investigator's brochure (IB).

1.3. Rationale for This Study

Zydelig® (idelalisib) received accelerated approval in the US for the treatment of patients with relapsed FL who have received at least 2 prior systemic therapies based on results from a single-arm study (101-09) in 125 subjects with iNHL, including 72 subjects with FL, who had relapsed within 6 months following rituximab and an alkylating agent and had received at least 2 prior treatments. In Study 101-09, all subjects received idelalisib 150 mg twice daily, with dose reductions to 100 mg twice daily allowed during the study to manage toxicity, consistent with the subsequently approved Zydelig® dosing regimen. The present study, GS-US-313-1580, is being conducted as a US postmarketing requirement (PMR 2180-10) under the accelerated approval regulations to verify the clinical benefit of Zydelig® monotherapy in patients with relapsed or refractory FL.

The subject population to be enrolled under the original version of this protocol comprised patients with previous systemic treatment for FL or SLL. In 2016, following identification of a safety signal and termination of several ongoing studies evaluating idelalisib in unapproved combinations (see Section 1.4, Anticipated Risks), the subject population in this study was restricted to align with the Zydelig® EU Summary of Product Characteristics while the European Medicines Agency Pharmacovigilance Risk Assessment Committee conducted a review under Article 20 of Regulation (EC) No 726/2004. The outcome of the Article 20 procedure confirmed a positive risk-benefit profile in the approved Zydelig® indications. Following discussions with the Food and Drug Administration (FDA) regarding this postmarketing study requirement, and a careful benefit-risk evaluation, the eligible subject population in Protocol Amendment 5 is being modified to include patients with relapsed or refractory FL who have received at least 2 lines of prior therapy for FL, have no other therapeutic options, and require therapy according to standard response criteria.

Prior to Protocol Amendment 5, this study was originally designed to evaluate the safety and efficacy of administration of idelalisib in subjects with FL at either 150 mg twice daily (Arm A) or 100 mg twice daily (Arm B). Based on the 8-week response assessment, subjects randomized to 100 mg twice daily idelalisib with stable disease (SD) or progressive disease (PD) would dose escalate to 150 mg twice daily. Subjects randomized to 150 mg twice daily with SD would continue 150 mg twice daily idelalisib. Subjects randomized to 150 mg twice daily with PD were discontinued. The rationale for selecting an 8-week independent review committee (IRC) confirmed response assessment was based on data from Study 101-09 in which: 56% (40/71) of responses occurred at the first assessment by 2 months, 83% (59/71) occurred by 4 months, and 96% (67/71) occurred by 6 months.

The idelalisib safety profile in relapsed iNHL has observed Grade ≥ 3 transaminase elevations with a median time to onset of 1.6 months and minimal occurrence beyond 4 months. Pneumonitis may develop at any time during treatment (median time to onset of 4.8 months, range from 3.7 to 14.1 months). Grade ≥ 3 diarrhea/colitis has a median time to onset of 5 months and continues to occur throughout treatment at a rate of 0.041 per person years. Grade ≥ 3 rash has occurred at a median time to onset of 2 months, range from 0.4-7.9 months. These events are managed by dose interruptions, reductions, and re-escalation or discontinuation as medically appropriate.

As of Protocol Amendment 5, enrollment to Arm B was closed. This decision was based on preliminary data suggesting that Arm B appeared unlikely to meet Gilead's FDA PMR 2180-10 objective of achieving an overall response rate (ORR) ≥ 50% and there would have been insufficient exposure to the 100 mg twice daily dosing regimen to evaluate intermediate and long-term safety.

As of Protocol Amendments 5 and 6, this open-label study will evaluate the approved dosing regimen of 150 mg twice daily (Arm A) and an alternative dosing regimen (Arm C), with the goal of assessing whether the efficacy of the approved dosing regimen could be confirmed and alternative dosing regimen can achieve similar efficacy as the approved dosing regimen with reduced toxicity. Arm A will utilize the standard dosing schedule of continuous idelalisib administered twice daily. Subjects in Arm C will receive idelalisib at the approved dose of 150 mg twice daily for the first 21 days of each 28-day cycle, followed by 7 days off treatment.

As of Protocol Amendment 6, there will be a planned global unblinding of all blinded subjects.

In addition to the aforementioned efficacy assessments, this study will assess the incidence of Grade ≥ 4 treatment-emergent adverse events (TEAEs) in each treatment arm. Of the 72 subjects with FL in Study 101-09, 23 subjects (32%) reported at least 1 Grade ≥ 4 TEAE, most frequently neutropenia (5 subjects [7%]), hypokalaemia (3 subjects [4%]), infections (2 subjects [3%]), increased aspartate aminotransferase (AST) (2 subjects [3%]), and thrombocytopenia (2 subjects [3%]).

1.4. Risk/Benefit Assessment for the Study

Anticipated Benefits

This study randomizes patients with FL to one of 2 idelalisib regimens, the approved regimen or the alternative regimen. The alternative regimen with an intermittent dosing schedule (Arm C), results in lower idelalisib exposure, and thus has the potential for decreased frequency and severity of TEAEs. Subjects on the alternate regimen may thus benefit from reduced toxicity and fewer dose interruptions. Since the study requires response assessments on a 12-week schedule during the first 15 months of study treatment, a lack of response or progression of disease will be identified in a subject's treatment course. Consequently, while there is the possibility of decreased efficacy in Arm C, the risk to the individual subject is minimized by the response assessment schedule, with the option for subjects on Arm C to discontinue treatment.

Anticipated Risks

In 2016, an increased risk of death and a higher incidence of serious adverse events (SAEs), predominantly infectious events, were observed among subjects receiving idelalisib in combination with standard therapies compared to the control groups in a pooled analysis conducted by the independent data monitoring committee (DMC) of 3 Phase 3 clinical studies in patients with first-line CLL and early-line iNHL. Global regulatory agencies were notified of these findings and independently reviewed the data. These reviews confirmed a positive benefit-risk profile of Zydelig® (idelalisib) in the approved indications. Zydelig® country product labels were subsequently updated to include measures to minimize the risk of serious infections, including *Pneumocystis jirovecii* pneumonia (PJP) prophylaxis and cytomegalovirus (CMV) monitoring, in line with the risk minimization measures employed in clinical studies.

While CMV and PJP are important risks, these pathogens accounted for a relatively small proportion of the serious infections observed; therefore, more general measures are also used to minimize the risk of serious infections. In particular, treatment should not be initiated in subjects with evidence of ongoing systemic infection and subjects should be monitored for respiratory signs and symptoms throughout treatment and advised to report new respiratory symptoms promptly. Subjects should be administered PJP prophylaxis as described in Section 7.5.6.

Regular clinical and laboratory screening for CMV infection is mandated in all subjects. Blood counts should also be monitored in all subjects as described in Section 7.5.5.

Conclusion

The overall benefit-risk assessment for patients enrolled in this study is favorable. The risk of serious toxicity, shared by all patients receiving idelalisib, is mitigated by the protocol-specified safety assessments and PJP prophylaxis, as described above. There is a hypothetical risk of decreased efficacy in subjects receiving the alternate dosing regimen (Arm C), which is mitigated by the frequent scheduled response assessments as well as the possibility that subjects in Arm C may experience less drug-related toxicity than those in Arm A.

During a pandemic, additional potential risks to subjects may include adequate study drug availability, interruptions to the study visit schedule, and adherence to protocol-specified safety monitoring or laboratory assessments. Refer to Appendix 8 for further details on the risks and risk mitigation strategy.

1.5. Compliance

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

2. OBJECTIVES

The primary objective of this study is as follows:

- Establish a safe and effective dosing regimen of idelalisib in subjects with relapsed or refractory FL who have no other therapeutic options

The secondary objectives of this study are as follows:

- Evaluate the ORR
- Evaluate the progression-free survival (PFS), duration of response (DOR), and overall survival (OS)
- Evaluate the overall safety profile of idelalisib
- Determine the PK of idelalisib and its major metabolite (GS-563117)

The exploratory objective of this study is as follows:

- CCI [redacted]

3. STUDY DESIGN

3.1. Endpoints

The primary endpoints of this study are as follows:

- ORR, defined as the proportion of subjects who achieve a partial response (PR) or complete response (CR)
- Incidence of Grade ≥ 4 treatment-emergent adverse events (TEAEs)

The secondary endpoints of this study are as follows:

- DOR, defined as the interval from the first documentation of CR or PR to the earlier of the first documentation of disease progression by IRC or death from any cause
- ORR by Week 24, defined as the proportion of subjects who achieve a PR or CR by Week 24
- Overall safety profile of idelalisib, including the incidence of adverse events (AEs) and clinically significant laboratory abnormalities, severity, timing, and relationship to idelalisib of any AEs; SAEs; or AEs leading to interruption, reduction, or discontinuation of idelalisib
- Time to onset of AEs of interest (AEIs) defined as the interval from the start of idelalisib treatment to the first documentation of start of AEI
- PFS, defined as the interval from randomization to the earlier of the first documentation of disease progression by IRC or death from any cause
- OS, defined as the interval from randomization to death from any cause
- Idelalisib trough (predose) and peak (1.5-hour samples) plasma concentrations assessed by validated bioanalytical method

The exploratory endpoint is as follows:

- CCI [redacted]

3.2. Study Design

This is a randomized, open-label, multi-center study that will be conducted globally.

Subjects will be randomized in a 1:1 ratio, until the enrollment target per arm is met, to the following treatment arms:

- Arm A: 150 mg twice daily idelalisib administered continuously

- Arm C: 150 mg twice daily idelalisib administered in 28-day cycles (21 days on-treatment, 7 days off-treatment)

The original protocol for this study included an Arm B, which was closed to enrollment as of Protocol Amendment 5.

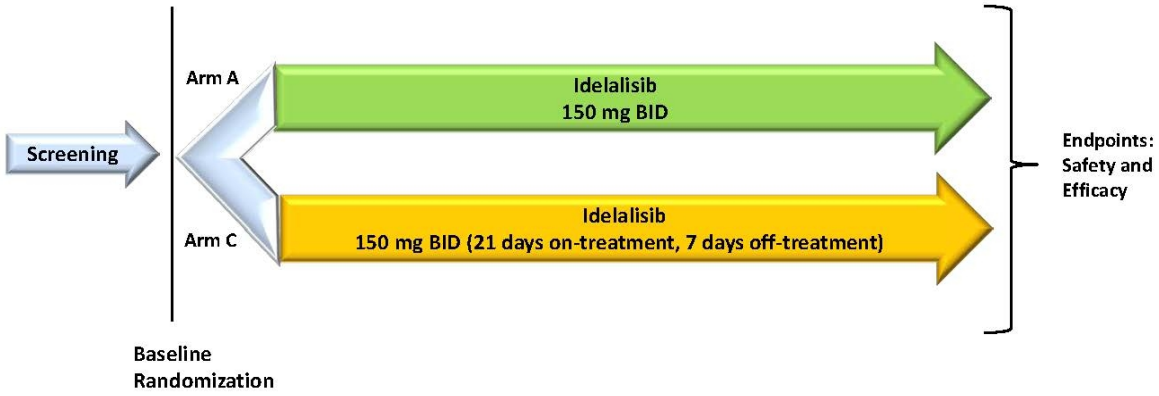
- Arm B (*closed to enrollment as of Protocol Amendment 5*): 100 mg twice daily idelalisib administered continuously

Clinic visits will occur at Screening, Day 1, every 2 weeks through Week 12, every 4 weeks through Week 24, at Weeks 32, 36, 40, 48, and every 12 weeks thereafter through end of study (EOS). Subjects will be assessed for safety at each visit. Additional visits will be required between clinic visits for laboratory testing only.

Subjects will be assessed for FL disease status by continuous utilization of a single modality including positron emission tomography–computed tomography (PET-CT), CT, or MRI. If permanent discontinuation of idelalisib occurs prior to IRC documented progression of FL, subjects shall remain on study until progression of FL or withdrawal from the study for reasons specified in Section 3.5.2.

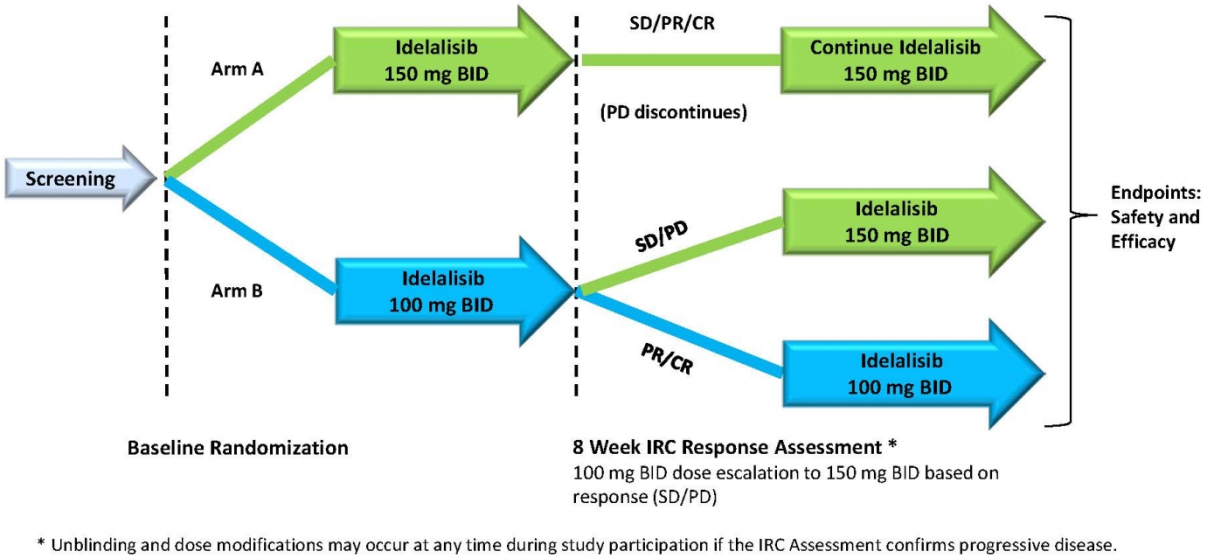
3.2.1. Study Schema

Figure 3-1. Study Schema



3.2.2. Subjects Enrolled Prior to Protocol Amendment 5

Subjects enrolled prior to implementation of Protocol Amendment 5 followed the previous study design as shown here.



* Unblinding and dose modifications may occur at any time during study participation if the IRC Assessment confirms progressive disease.

In accordance with Protocol Amendment 6, subjects enrolled prior to implementation of Protocol Amendment 5 and still blinded will be unblinded at the time of Protocol Amendment 6 implementation; these subjects will continue at the randomized dose level if they are still on treatment. These subjects were previously randomized in a blinded manner to either 150 mg twice daily or 100 mg twice daily idelalisib. Based on the 8-week blinded IRC response assessment, subjects with SD or PD were unblinded in both arms. Subjects with a PR or CR maintained the blind and continued at the randomized dose level. Subjects randomized to 100 mg twice daily with SD or PD had the option to be dose escalated to 150 mg twice daily. Subjects randomized to 150 mg twice daily with SD will continue open-label idelalisib at 150 mg twice daily. Subjects randomized to 150 mg twice daily with PD will be discontinued from study treatment. These same unblinding and dose modification principles were applied at any time throughout study participation when disease progression was suspected and confirmed by IRC assessment.

Subjects should follow study procedures as outlined in Section 6 and Appendix 2 Study Procedures Table. Idelalisib will be administered until meeting criteria for discontinuation of study drug as described in Section 3.5.1.

3.3. Study Treatments

Subjects will be randomized to the following treatment arms:

- Arm A: Idelalisib 150 mg will be taken twice daily orally starting on Day 1 and administered continuously

- Arm C: Idelalisib 150 mg will be taken twice daily orally starting on Day 1 and administered continuously for 21 days, followed by 7 days of no study drug, within each 28-day cycle. Study drug should not be taken on scheduled "off-treatment" days, regardless of prior missed doses, study drug interruptions for toxicity, or PK samples.

The original protocol for this study included an Arm B, which was closed to enrollment as of Protocol Amendment 5.

- Arm B (closed to enrollment as of Protocol Amendment 5): 100 mg idelalisib will be taken twice daily orally starting on Day 1 and administered continuously. Subjects randomized to 100 mg twice daily with SD or PD may be dose escalated to 150 mg twice daily.

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. If needed for toxicity management, a dose reduction is available as described in Section 5. The study drug, idelalisib, will be supplied by Gilead. The formulation, packaging, and dosing regimen are further described in Section 5.

3.4. Duration of Treatment

Idelalisib will be administered until a subject meets the criteria for discontinuation of study drug as described in Section 3.5.1.

3.5. Discontinuation Criteria

3.5.1. Discontinuation of Study Drug

Study drug should be discontinued under the following conditions, in consultation with the Gilead Medical Monitor:

- Disease progression based on IRC response assessment

  — For Arm B subjects only: Subjects randomized to 100 mg twice daily with IRC confirmed SD or PD may be dose escalated to 150 mg twice daily. Thereafter, Arm B subjects who are assigned to open-label 150 mg twice daily and have IRC documented PD after escalation must discontinue study drug.

- Initiation of non-study specific systemic anticancer therapy or concurrent participation in any other therapeutic clinical study

- Any subject for whom the blind is intentionally broken by the subject or the study site outside of the planned protocol unblinding
- If, in the investigator's opinion, it is not in the subject's best interest to continue
- Pregnancy or breastfeeding begins during the study
- Subject noncompliance
- Subject request to discontinue study drug, for any reason
- Unacceptable toxicity, either as assessed by the investigator or as specified in Section 5.3.2 and Table 5-2, including inability of the subject to tolerate a rechallenge of study drug

Subjects who permanently discontinue study drug for a reason other than disease progression (as confirmed by the IRC) should continue with disease assessments per the study procedures table (Appendix 2) until disease progression, study participation has ended, or another anti-cancer or experimental therapy is initiated (see Section 5.4.2).

3.5.2. Discontinuation from Study

Discontinuation from the study may occur in the following instances:

- Disease progression based on IRC response assessment
  - For Arm B subjects only: Subjects randomized to 100 mg twice daily with IRC confirmed SD or PD may be dose escalated to 150 mg twice daily. Thereafter, Arm B subjects who are assigned to open-label 150 mg twice daily and have IRC documented PD after escalation must discontinue the study treatment.
- Initiation of non-study specific systemic anti-cancer therapy (see Section 5.4.2) or concurrent participation in any other therapeutic clinical study
- In subjects for whom the blind is intentionally broken by the study site or the subject outside of the planned protocol unblinding
- If, in the investigator's opinion and in consultation with Gilead, it is determined not to be in the subject's best interest to continue
- Pregnancy or breastfeeding begins during the study
- Death
- Discontinuation of the study at the request of Gilead, a regulatory agency, or an institutional review board or independent ethics committee (IRB/IEC) occurs

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

3.6. Biomarker Assessments

3.6.1. CCI

CCI

CCI

3.6.2. CCI

CCI

CCI

CCI

4. SUBJECT POPULATION

4.1. Number of Subjects and Subject Selection

The planned sample size is approximately 266 subjects: approximately 120 subjects in Arm A, approximately 26 subjects in Arm B, and approximately 120 subjects in Arm C. As of Protocol Amendment 5, Arm B enrollment was closed after enrollment of approximately 26 subjects into Arm B and approximately 26 subjects into Arm A.

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 GCP or a regulatory authority audit. Any questions regarding a subject's eligibility should be discussed with the Medical Monitor prior to enrollment. Entry into screening does not guarantee enrollment into the study. In order to manage the total study enrollment, Gilead, at its sole discretion, may suspend screening and/or enrollment at any site or study-wide at any time.

4.2. Inclusion Criteria

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

1) Male or female ≥ 18 years of age

2) Histologically confirmed diagnosis of B-cell FL, and grade limited to 1, 2, or 3a based on criteria established by the World Health Organization (WHO) 2008 classification of tumors of hematopoietic and lymphoid tissues

3) Relapsed or refractory FL and have received at least 2 lines of prior therapy for FL and have no other available therapeutic options. ***Note: Rituximab maintenance is not routinely considered a separate line of therapy when it is given as part of the prior rituximab-containing regimen given over a number of cycles followed by maintenance. Rituximab monotherapy may be considered a separate line of therapy when disease relapse occurs between the initiation of rituximab monotherapy and the preceding line of therapy. If there are any ambiguities about eligibility, the site should consult with the medical monitor.***

4) Ann Arbor Stage 2 (noncontiguous), 3, or 4 disease per Lugano Classification

5) Radiographically measurable lymphadenopathy or extranodal lymphoid malignancy as determined by the IRC (defined as the presence of ≥ 1 lesion that measures ≥ 1.5 cm in the LD and ≥ 1.0 cm in the longest perpendicular dimension [LPD] as assessed by PET-CT, CT, or MRI)

6) Have adequate performance status (such as Eastern Cooperative Oncology Group [ECOG] Performance Status of ≤ 2 or Karnofsky Performance Status of ≥ 60)

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

Organ System	Parameter	Required Value
Hematopoietic[a]	ANC	≥ 1,000/μL
	Platelet	≥ 50,000/μL
	Hemoglobin	≥ 8g/dL
Hepatic	Serum total bilirubin	≤ 1.5 x ULN (unless elevated due to Gilbert syndrome)
	Serum ALT	≤ 2.5 x ULN
	Serum AST	
Renal	Serum Creatinine	≤ 1.5 x ULN Calculated or Estimated CrCL > 30 mL/min
Pregnancy	β-hCG[b]	Negative
Infection	HIV	Negative HIV antibody[c]
	HBV	Negative HBsAg and negative HBc[d] antibody
	HCV	Negative viral RNA (if HCV antibody is positive)
	CMV	No CMV DNA detected or CMV DNA is below the lower limit of quantification by PCR AND No clinical signs or symptoms suggestive of active CMV infection

ANC=absolute neutrophil count, β-hCG=beta human chorionic gonadotropin, ALT=alanine aminotransferase, AST=aspartate aminotransferase, CMV=cytomegalovirus, CrCL=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, PCR=polymerase chain reaction, RNA=ribonucleic acid, ULN=upper limit of normal

a Grade ≥ 3 neutropenia, thrombocytopenia, or anemia is permitted if abnormality is related to bone marrow involvement with FL (as documented by bone marrow biopsy/aspirate obtained since the last prior therapy)

b For women of childbearing potential only; serum β-hCG must be negative during screening and urine dipstick pregnancy test must be negative at baseline prior to randomization

c If screening test is positive, a negative confirmatory test will be required for eligibility

d Subjects who have positive HBc antibody may be enrolled if HBV DNA is undetectable by quantitative PCR

8) For female subjects of childbearing potential, willingness to use a protocol-recommended method of contraception during heterosexual intercourse from the signing of informed consent throughout the study treatment period and up to 30 days from the last dose of idelalisib (see Appendix 4)

9) For male subjects of reproductive potential having intercourse with females of childbearing potential, willingness to use a protocol-recommended method of contraception during heterosexual intercourse and to refrain from sperm donation throughout the study treatment period and for 90 days following discontinuation of idelalisib (see Appendix 4)

10) Lactating females must agree to discontinue nursing before study drug administration and until at least 30 days following last dose of idelalisib

11) Indicate willingness to comply with scheduled visits, drug administration plan, imaging studies, laboratory tests, other study procedures, and study restrictions, including mandatory prophylaxis for PJP

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

4.3. Exclusion Criteria

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

1) History of lymphoid malignancy other than FL (eg, diffuse large B-cell lymphoma). ***Note: Biopsy documentation of the absence or presence of high grade lymphoma is not required***

2) Known history of, or clinically apparent, central nervous system (CNS) lymphoma or leptomeningeal lymphoma. ***Note: Imaging documentation of the absence or presence of CNS disease is not required***

3) Known presence of intermediate- or high-grade myelodysplastic syndrome. ***Note: intermediate- or high-grade myelodysplasia is defined as the presence of ≥ 5% bone marrow blasts; karotypic abnormalities other than normal, Y deletion, 5q deletion, or 20q deletion; or ≥ 2 lineages of cytopenias due to myelodysplasia***

4) Known history of serious allergic reaction including anaphylaxis or Stevens-Johnson syndrome/toxic epidermal necrolysis

5) History of a non-lymphoid malignancy except for the following: adequately treated local basal cell or squamous cell carcinoma of the skin, cervical carcinoma *in situ*, superficial bladder cancer, asymptomatic prostate cancer without known metastatic disease and with no requirement for therapy or requiring only hormonal therapy and with normal prostate-specific antigen for ≥ 1 year prior to enrollment, or any other cancer or malignancy that has been in complete remission for ≥ 5 years

6) Evidence of ongoing systemic infection (eg, bacterial, fungal, viral) at the time of enrollment

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

8) History of or ongoing drug-induced pneumonitis

9) History of or ongoing inflammatory bowel disease

10) Known human immunodeficiency virus (HIV) infection

11) CMV: Ongoing infection, treatment, or specifically CMV antiviral prophylaxis within 28 days prior to the Screening Visit CMV test

12) Presence of any condition that could, in the opinion of the investigator, compromise the subject's ability to participate in the study, such as history of substance abuse, alcoholism, or a psychiatric condition

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

14) Ongoing immunosuppressive therapy, including systemic corticosteroids (> 10 mg prednisone or equivalent/day) with the exception of the use of topical, enteric, or inhaled corticosteroids as therapy for comorbid conditions or systemic corticosteroids for autoimmune anemia and/or thrombocytopenia

15) Concurrent participation in another therapeutic clinical study

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

17) Prior treatment with PI3K inhibitors

5. INVESTIGATIONAL MEDICINAL PRODUCTS

5.1. Randomization, Blinding and Treatment Codes

As of Protocol Amendments 5 and 6, this is an open-label, randomized study. Randomization to the treatment assignment (Arm A or C) will occur via the Interactive Web Response System (IWRS).

Subjects enrolled prior to Protocol Amendment 5:

The identity of the treatments was concealed by central blinding of study drug assignments. Blinding was accomplished through use of a placebo that was well-matched to the active drug in appearance. Subjects, caregivers, investigational site personnel, Gilead study team members, and all other study personnel remained blinded to the identity of the treatment assignments; these assignments were available only to the IWRS, the independent DMC for the study, an independent bioanalytical group that supported the DMC, and drug safety personnel who were not part of the study team.

Once Protocol Amendment 6 has been implemented, subjects who are blinded to study treatment will be unblinded and will continue on the assigned randomized dose.

5.1.1. Procedures for Breaking Treatment Codes

This section applies only to subjects enrolled prior to Protocol Amendment 5. Subjects with IRC confirmed SD or PD will be unblinded. Subjects who died or discontinued from study may be unblinded.

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

Study treatment will be discontinued if a subject's treatment assignment is disclosed outside of the allowed protocol unblinding. All subjects will be followed until study completion unless consent to do so is specifically withdrawn by the subject.

Gilead Pharmacovigilance & Epidemiology (PVE) may independently unblind cases for expedited reporting of suspected unexpected serious adverse reactions (SUSARs).

5.2. Description and Handling of Idelalisib

5.2.1. Formulation

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

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

Prior to Protocol Amendment 5, a well-matched placebo was provided as the study was still blinded. Until global unblinding takes place, placebo will continue to be supplied to the blinded subjects. The placebo tablets match the active idelalisib tablets in appearance. The placebo tablets include the following inactive ingredients: silicified microcrystalline cellulose, sodium starch glycolate, magnesium stearate, red iron oxide (150 mg placebo tablets only), FD&C Yellow #6/Sunset Yellow FCF Aluminum Lake (100 mg placebo tablets only), polyethylene glycol, talc, PVA, and titanium dioxide.

5.2.2. Packaging and Labeling

Study drug(s) to be distributed to centers in participating countries shall be labeled to meet applicable requirements of the United States Food and Drug Administration (FDA), EU Guideline to Good Manufacturing Practice - Annex 13 (Investigational Medicinal Products), and/or other local regulations.

<u>Subjects enrolled as of Protocol Amendments 5 and 6:</u>

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

<u>Subjects enrolled prior to Protocol Amendment 5:</u>

Study drug (idelalisib/placebo) will be provided in blister cards. The blister cards are made of polyvinyl chloride/polychlorotrifluoroethylene film and have aluminum foil lidding materials.

Once Protocol Amendment 6 is implemented, study drug (idelalisib/placebo) will not be provided to subjects who are currently blinded once they have been unblinded. These subjects will continue on the assigned open-label treatment dose.

Each blister card contains 120 tablets (4-week supply plus a modest overage) of one of the relevant dose strengths.

The 100 mg or 150 mg tablets will be combined with matching placebo tablets in one blister card while ensuring the blind is maintained.

Each blister card will have a unique number. Labeling for blister cards dispensed to subjects in the 2 treatment arms will appear identical.

Subjects will be unblinded once Protocol Amendment 6 has been approved by the Ministry of Health, Central Ethics Committee, and Local Ethics Committee (if applicable). At that time, idelalisib will be provided in bottles. Idelalisib tablets are packaged in white, high density polyethylene bottles. Each bottle contains 60 tablets and polyester coil packing material. Each bottle is enclosed with a white, continuous-thread, child-resistant polypropylene screw cap with an induction-sealed and aluminum-faced liner.

5.2.3. Storage and Handling

Until dispensed to subjects, the study drug product should be stored in a securely locked area, accessible only to authorized personnel.

Idelalisib should be stored at controlled room temperature of 25°C (77°F); excursions are permitted between 15°C and 30°C (59°F and 86°F). Storage conditions are specified on the label. To ensure the stability and proper identification, study drug(s) should not be stored in a container other than the container in which they were supplied.

Measures that minimize drug contact with the body should always be considered during handling, preparation, and disposal procedures. Any unused study drug should be disposed of in accordance with local requirements.

5.3. Dosage and Administration

The prescribed dose of study drug (idelalisib/placebo) should be taken orally. At each dose administration, the study drug is to be swallowed whole with 120 to 240 mL (approximately 4 to 8 ounces) of water. In the case of tablets breaking in the oral cavity, additional water should be taken as a rinse.

Study drug may be taken with or without food. There are no known dietary restrictions related to study drug use.

Study drug will be taken twice daily. Study drug should be taken at approximately the same times each day. Ideally, doses should be taken at approximately 12 hour intervals as instructed (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 PK. Clinic staff should record study drug administration information, including the date and exact clock time of each dose for doses of study drug administered in the clinic or hospital. Prior to these visits, subjects should be reminded not to take their morning dose of study drug before coming into the clinic. Subjects should also be reminded to bring their study drug with them to clinic for dosing.

Thereafter, subjects will be given an adequate supply of tablets to take at home.

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

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

5.3.1. Idelalisib Dose Levels

Idelalisib dose levels are shown in Table 5-1. Subjects will be randomized to Arm A or C. Dose modifications may be made in response to toxicity; see Table 5-2 for dose adjustment rules.

Table 5-1. Idelalisib Dose Levels

Subjects enrolled prior to Protocol Amendment 5:

Dose Level	Dosing Regimen	
Dose Level 0	150 mg BID	100 mg BID
Dose Level -1	100 mg BID	100 mg BID

Subjects enrolled as of Protocol Amendment 5:

Treatment Arm	Starting Dose	Reduced Dose
Arm A	150 mg BID	100 mg BID
Arm C*	150 mg BID	100 mg BID

BID=twice daily
*Arm C: administered in 28-day cycles (21 days on-treatment, 7 days off-treatment)

Consistent with the dose adjustment rules presented in Table 5-2, if a subject experiences an AE that is suspected to be related to idelalisib during the course of study, idelalisib administration should be held, as defined in Table 5-2, until the AE resolves or stabilizes to an acceptable degree. Thereafter, idelalisib may be reinitiated, consistent with the instructions in Section 5.3.2. For any AE that is not included in Table 5-2, reinitiation of idelalisib should be per investigator's discretion.

After an idelalisib dose reduction, the dose need not be re-escalated. However, if the subject tolerates the reduced dose of idelalisib for ≥ 4 weeks, then the dose may be increased back to starting dose at the discretion of the investigator. Such a re-escalation may be particularly warranted if further evaluation reveals that the AE that led to the dose reduction was not related to idelalisib.

5.3.2. Idelalisib Dose Adjustments

The dose adjustment recommendations and requirements in Table 5-2 are based on the Common Terminology Criteria for Adverse Events (CTCAE) grade of specific toxicities. However, exceptions are expected for subjects who initiate study treatment with low blood counts. Clinical judgment should apply, and in cases of uncertainty, the medical monitor should be contacted.

The dose modification instructions focus on the types of events most commonly attributed to idelalisib. The modifications in Table 5-2 include both recommended as well as required actions. When a modification is indicated as a recommendation it only serves as a guideline; variations from the recommendation may be warranted based on an investigator's individual judgment in considering potential risks, benefits, and therapeutic alternatives available to each subject. Refer to Section 7.5 for specific AE or condition recommendations.

NOTE: For subjects randomized to Arm C, study drug should not be taken on scheduled "off-treatment" days, regardless of prior missed doses, study drug interruptions for toxicity, or PK samples.

Table 5-2. Modification of Study Treatment in Response to Adverse Events

Pneumonitis *(with new onset or worsening of baseline dyspnea, cough, or hypoxia without obvious infectious cause)*	
Grade 1 (asymptomatic)	Required Action: Withhold idelalisib until resolution to baseline. May resume at reduced dose level (100 mg BID) or discontinue at investigator discretion.
Grade ≥ 2	Required Action: Discontinue idelalisib permanently in subjects with any severity of symptomatic pneumonitis and institute therapy as clinically appropriate.
***Pneumocystis jirovecii* pneumonia (PJP)**	
Any Grade	Required Action: Discontinue idelalisib permanently.
Organizing Pneumonia	
Any Grade	Required Action: Discontinue idelalisib permanently.
Cytomegalovirus (CMV)	
Required Actions: 1. Interrupt idelalisib upon unequivocal clinical or laboratory evidence of CMV infection. 2. Institute 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.	

Rash Grade ≥ 3			
Required Actions: Withhold idelalisib until Grade ≤ 1. May resume at reduced dose level (100 mg BID) or discontinue at investigator discretion.			
SJS/TEN			
Required Actions: 1. Discontinue idelalisib 2. Interrupt coadministered medications potentially associated with SJS or TEN 3. Institute treatment per institutional standards			
Bowel perforation			
Required Action: Discontinue idelalisib permanently.			
Progressive Multifocal Leukoencephalopathy (PML)			
Any Grade	Required Action: Withhold idelalisib until PML is excluded. Refer to Section 7.5.2		
ALT/AST, Bilirubin			
ALT/AST	**> 3-5 x ULN (Grade 2)**	**> 5-20 x ULN (Grade 3)**	**> 20 x ULN (Grade 4)**
	Required Action: Monitor at least weekly until Grade ≤ 1. Recommended Action: Maintain idelalisib dose.	Required Actions: Withhold idelalisib. Monitor at least weekly until ALT/AST are Grade ≤ 1. Recommended Action: May resume idelalisib at reduced dose level (100 mg BID) when ALT/AST are Grade ≤ 1.	Required Action: Discontinue idelalisib permanently.
Bilirubin	**> 1.5-3 x ULN (Grade 2)**	**> 3-10 x ULN (Grade 3)**	**> 10 x ULN (Grade 4)**
	Required Action: Monitor at least weekly until Grade ≤ 1. Recommended Action: Maintain idelalisib dose.	Required Actions: Withhold idelalisib. Monitor at least weekly until bilirubin is Grade ≤ 1. Recommended Actions: May resume idelalisib at reduced dose level (100 mg BID) when bilirubin is Grade ≤ 1.	Required Action: Discontinue idelalisib permanently.
Diarrhea or colitis, any Grade			
Required Actions: 1. 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 2. Perform physical examination including assessment for fever, dizziness, abdominal pain/cramping, and weakness (ie, evaluate for sepsis, bowel obstruction, dehydration) Recommended Actions: 1. Provide anti-diarrheal and maintain current idelalisib dose level and schedule 2. Differentiate between small-bowel and large-bowel diarrhea 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), possible associated dehydration, weight loss and paraumbilical pain. Consider an endoscopic small-bowel biopsy and evaluate other etiologies such as celiac disease.
- Large-bowel diarrhea may present with lower pelvic pain, tenesmus, and generally smaller stool volumes with gross blood frequently found in the stool. Consider a colonoscopic evaluation and biopsy.

3. Ensure good hydration status

Grade ≥ 2 diarrhea or colitis (unless clinical diagnosis is established from medical history and physical examination)

Required Actions:

1. Monitor diarrhea at least weekly until resolved.
2. Stool culture for routine pathogens (Salmonella, Shigella, Campylobacter species), testing for Clostridium difficile toxin, Rotavirus, Cytomegalovirus (CMV), and Adenovirus
3. Stool for Ova and Parasites (Cryptosporidium parvum, Isospora belli, Enterocytozoon bieneusi, Septata intestinalis, Strongyloides, Microsporidia, Entamoeba histolytica, Cyclospora), Giardia antigen

Grade ≥ 3 diarrhea or colitis or persistent Grade 2 diarrhea or colitis without clear etiology

Required Actions:

1. Withhold idelalisib.
2. Consider anti-diarrheal (eg, loperamide) and/or addition of anti-inflammatory agent (eg, sulfasalazine, budesonide).

Recommended Actions:

1. Endoscopy with biopsy is strongly recommended. All biopsy samples should include immunohistochemistry and PCR for CMV, Adenovirus.
2. CCI [redacted]
3. At Grade ≤1, may resume idelalisib at reduced dose level (100 mg BID) or discontinue at investigator discretion.

Grade 4 diarrhea or colitis

Required Actions: Discontinue idelalisib permanently.

Neutropenia	
Grade 2 (ANC 1.0 to < 1.5 Gi/L)	Recommended Action: Maintain idelalisib dose level and schedule.
Grade 3 (ANC 0.5 to < 1.0 Gi/L)	Required Action: ANC must be monitored at least weekly until ANC Grade ≤ 2. Recommended Action: Maintain idelalisib dose level and schedule.
Grade 4 (ANC < 0.5 Gi/L) ***(or occurrence of neutropenic fever or infection)***	Dosing: • Required Action: Withhold idelalisib. • Recommended Action: May resume idelalisib at reduced dose level (100 mg BID) when ANC Grade ≤ 3. Required Action: ANC must be monitored at least weekly until ANC Grade ≤ 2. Recommended Action: Neutropenia should be managed according to established clinical guidelines.
Thrombocytopenia	
Grade 2 (Platelets 50 to < 75 Gi/L)	Recommended Action: Maintain idelalisib dose.

Grade 3 (Platelets 25 to < 50 Gi/L)	Required Action: Monitor platelet counts at least weekly. Recommended Action: Maintain idelalisib dose.
Grade 4 (Platelets < 25 Gi/L)	Required Actions: Interrupt idelalisib. Monitor platelet counts at least weekly. Recommended Action: May resume idelalisib at reduced dose level (100 mg BID) after platelets ≥ 25 Gi/L (Grade ≤ 3)

ALT=alanine aminotransferase; ANC=absolute neutrophil count; AST=aspartate aminotransferase; BID=twice daily; ULN=upper limit of normal

a Refer to Section 6.1.5.6 for recommendations if the differentiation between small-bowel and large-bowel diarrhea is unclear.

5.4. Prior and Concomitant Medications

5.4.1. Idelalisib

No specific premedications are required in conjunction with idelalisib. Subjects must begin PJP prophylaxis when they begin taking study drug and will remain on prophylaxis until after study drug is discontinued. See Section 7.5.6 for additional information.

5.4.2. Anti-Cancer or Experimental Therapies Other than Idelalisib

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

5.4.3. Granulocyte Colony-Stimulating Factors and Erythropoietin

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

5.4.4. Corticosteroids

Subjects may receive topical or inhaled, enteric, or systemic corticosteroids while on study. The use of systemic corticosteroids is discouraged because their potential antineoplastic activity in subjects with iNHL may confound interpretation of idelalisib-mediated antitumor effects. However, subjects who develop severe or life-threatening conditions that may be alleviated by systemic corticosteroid therapy are permitted to receive such drugs and are not required to discontinue study participation.

5.4.5. Drugs that Alter CYP3A-Dependent Metabolism

Idelalisib is metabolized to its major metabolite GS-563117 via aldehyde oxidase and cytochrome P450 3A (CYP3A). Idelalisib also undergoes minor metabolism by uridine diphosphate glucuronosyltransferase 1A4 (UGT1A4). The AUC of idelalisib was increased 1.8-fold when idelalisib was coadministered with a strong CYP3A inhibitor. Therefore, if subjects are taking concomitant strong CYP3A inhibitors, the subject should be monitored closely for signs of idelalisib toxicity and the dose modifications for adverse reactions should be followed in the event of toxicity (see Table 5-2).

Additionally, idelalisib exposures are approximately 75% lower when coadministered with rifampin, a highly potent inducer of CYP3A. Therefore, avoid coadministration of strong inducers of CYP3A (rifampin, carbamazepine, phenytoin, and St. John's wort) with idelalisib.

5.4.6. 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 an approximately 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 3-hydroxy-3-methyl-glutaryl-Coenzyme A reductase inhibitors, phosphodiesterase-5 inhibitors, warfarin). Avoid coadministration of drugs that are narrow therapeutic index CYP3A substrates (eg, alfentanil, cyclosporine, sirolimus, tacrolimus, cisapride, pimozide, fentanyl, quinidine, ergotamine, dihydroergotamine, astemizole, terfenadine) with idelalisib.

5.4.7. COVID-19 Vaccination Guidelines

Administration of a coronavirus disease 2019 (COVID-19) vaccine is not considered contraindicated with idelalisib. Investigators should use their clinical judgment in determining if and when to enroll study participants who have received a COVID-19 vaccine, or whether to continue, interrupt, or discontinue study treatment in subjects who are administered a COVID-19 vaccine during study conduct.

5.5. Accountability for Idelalisib

The investigator is responsible for ensuring adequate accountability of all used and unused study drug. This includes acknowledgement of receipt of each shipment of study drug (quantity and condition). All used and unused study drug dispensed to subjects must be returned to the site.

Study drug accountability records will be provided to each study site to:

- Record the date received and quantity of study drug
- Record the date, subject number, subject initials, the study drug blister card number/bottle number dispensed
- Record the date, quantity of used and unused study drug returned, along with the initials of the person recording the information

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

5.5.1. Investigational Medicinal Product Return or Disposal

Gilead recommends that used and unused study drug supplies be destroyed at the site. If the site has an appropriate standard operating procedure (SOP) for drug destruction as determined by Gilead, the site may destroy used (empty or partially empty) and unused study drug supplies in accordance with that site's approved SOP. A copy of the site's approved SOP will be obtained for the electronic trial master file. If study drug is destroyed at the site, the investigator must maintain accurate records for all study drugs destroyed. Records must show the identification and quantity of each unit destroyed, the method of destruction, and the person who disposed of the study drug. Upon study completion, copies of the study drug accountability records must be filed at the site. Another copy will be returned to Gilead.

If the site does not have an appropriate SOP for drug destruction, used and unused study drug supplies are to be sent to the designated disposal facility for destruction. The study monitor will provide instructions for return.

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

For both disposal options listed above, the study monitor must first perform drug accountability during an on-site monitoring visit.

6. STUDY PROCEDURES

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

For subjects who discontinue idelalisib prior to IRC documented disease progression, every attempt should be made to keep the subject in the study and continue to perform regular assessments per the schedule of procedures (with the exception of PK sampling and CMV monitoring) until the subject meets criteria for study discontinuation (see Section 3.5.2).

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

Safety and tolerability assessments will include regular monitoring of AEs, changes from baseline in laboratory variables, physical examinations (PEs), vital signs, and special safety assessment like ECGs.

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

6.1. Study Procedure Descriptions

During the treatment period, all visits may be performed within the specified visit window as noted in the schedule of events (see Appendix 2).

6.1.1. Informed Consent

All subjects must sign and date the most recent IRB/IEC-approved informed consent form before any study procedures are performed.

6.1.2. Medical and Medication History

A complete medical and surgical history will be obtained during screening including disease history and prior therapies.

A history of all medication taken within the 3 months prior to screening and during the screening period will be obtained.

6.1.3. Physical Examination

A physical exam will be performed at screening and will include assessment of clinical signs and symptoms. The exam will be performed by a physician, a physician's assistant, or nurse practitioner qualified to perform assessments. Breast, genital, and rectal examinations are not required, unless warranted in the opinion of the healthcare provider.

A limited physical exam (consistent with standard institutional guidelines) should be performed at the following visits:

Subjects enrolled as of Protocol Amendment 5:

Weeks 12, 24, 36, 48, 60, and every 24 weeks thereafter.

Subjects enrolled prior to Protocol Amendment 5:

Weeks 8, 16, 24, 36, 48, 60, and every 24 weeks thereafter.

6.1.4. Vital Signs

At Screening, vital signs including oxygen saturation, systolic and diastolic blood pressure, heart rate, respiratory rate, temperature, and anthropometric measurements of height and weight will be measured by the investigator or qualified designee as per standard institutional guidelines.

6.1.5. Laboratory Assessments

Analytes to be tested are listed in Table 6-1. Specific instructions for processing, labeling, and shipping samples will be provided in a Central Laboratory Manual.

Blood samples for hematology and chemistry will be collected at each study visit. Additional clinic visits may be needed to monitor absolute neutrophil count (ANC) at Weeks 14, 18, and 22.

At screening, blood samples will also be obtained for serum pregnancy (if applicable), HBV, HCV, and HIV.

Blood samples for coagulation will be collected at screening, baseline, Weeks 8, 16, 32, 48, every 12 weeks thereafter.

Blood samples for Beta-2 microglobulin will be collected at screening, Weeks 24, 48, every 12 weeks thereafter, and at the End of Treatment (EOT) visit.

Blood samples for CMV will be collected at screening, Weeks 4, 8, 12, 16, 20, 24, and every 4 weeks thereafter throughout the course of study drug treatment, (including during drug interruptions due to toxicity or AEs), and at the EOT visit.

Blood sample for CMV serology (immunoglobulin [Ig]G, IgM) will be collected at baseline (Day 1) only.

Blood samples for immune-monitoring will be collected at Screening, Weeks 4, 12, 24, every 12 weeks thereafter, and at the EOT and EOS visits. Immune-monitoring samples include:

- Lymphocyte subset panel using flow cytometry (immunophenotyping)
- Quantitative immunoglobulins: IgG, IgM, IgA, IgE
- Serum CH50 level

At any time during the study, abnormal laboratory parameters that are clinically relevant (eg, lead to clinical symptoms or signs, require therapeutic intervention), and constitute an AE must be recorded in the eCRF.

A urine sample for urinalysis will be collected at screening only.

Table 6-1. Analytes

Chemistry	Hematology	Urinalysis	Other
Albumin Alkaline phosphatase ALT/SGPT AST/SGOT Bicarbonate Calcium Chloride Cholesterol Creatinine[b] GGT Glucose LDH Phosphorus Potassium Sodium Total bilirubin[a] Total protein Triglycerides Uric acid BUN	ANC RBC Hemoglobin Hematocrit Platelets WBC Differential Neutrophils Eosinophils Basophils Lymphocytes Monocytes Bands	pH Protein Glucose Ketones Bilirubin Urobilinogen Blood Nitrite Leukocyte esterase	Serum β-hCG or urine for pregnancy test HIV antibody Hepatitis B surface antigen Hepatitis B core antibody Hepatitis C antibody Hepatitis C viral RNA CMV PCR Anti-CMV IgG and IgM Immunophenotyping Serum CH50 level
	Coagulation PT/INR aPTT/PTT	**Quantitative Immunoglobulins** IgA IgE IgG IgM	Beta-2 microglobulin

a Includes direct bilirubin
b Estimated glomerular filtration rate will be calculated according to the Cockcroft-Gault formula for creatinine clearance. Creatinine clearance is only measured at screening.

6.1.5.1. Pregnancy Test

All females of childbearing potential (see Appendix 4) will have a serum pregnancy test at screening. Urine pregnancy tests will be performed at baseline, and every 4 weeks thereafter. The pregnancy testing is more frequent than regular clinic visits after Week 24. Urine pregnancy tests will also be performed at the EOT and EOS visits.

6.1.5.2. Pharmacokinetics

Blood samples will be collected for PK assessments at baseline, Weeks 2, 4, 6, 8, 10, 12, 16, 20, 24, 32, and 48 predose (within 1 hour prior to dose) and 1.5 hours (± 10 min) post dose in the morning. If prior scheduled dose was missed for any reason including due to planned "off-treatment" schedule, a predose PK sample is not needed. A single non-timed PK sample will also be collected at any unscheduled study visit through Week 48.

For subjects randomized to Arm C, study drug should not be taken on scheduled "off-treatment" days, regardless of prior missed doses, study drug interruptions for toxicity, or PK samples.

6.1.5.3. CCI

CCI

6.1.5.4. CCI

6.1.5.5. Evaluation for Gastrointestinal Events/Colitis

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, *Clostridium difficile* toxin, Rotavirus, Cytomegalovirus, 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 recommended. All biopsy samples should include immunohistochemistry and polymerase chain reaction (PCR) for CMV and adenovirus.
CCI

See Section 6.1.12.1 for additional requirements (ie, collection of information and physical exam) when an AE of diarrhea or colitis occurs.

6.1.5.6. Differentiation Between Small-Bowel and Large-Bowel Diarrhea

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

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

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

6.1.6. Electrocardiogram Assessment

A standard 12-lead ECG will be performed at screening as per standard institutional practice.

6.1.7. Radiology Assessment

Subjects will be imaged at neck, chest, abdomen, and pelvis with either PET-CT (diagnostic), contrast-enhanced CT, or gadolinium-enhanced MRI. If MRI is chosen, subjects will have an MRI of neck, abdomen, and pelvis, but will need a non-contrast enhanced CT of the chest. Chest x-ray, ultrasound, endoscopy, laparoscopy, 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 participation.

All relevant clinical and radiographic information required to make each assessment must be made available for source verification and for submission to the IRC.

Investigators will assess the status of each subject’s disease using standard response criteria.

If disease progression is suspected, the IRC will be notified and radiographic images will be submitted to the IRC.

The IRC will review radiographic and pertinent clinical data in order to provide a definitive interpretation. The findings of the IRC will be considered primary for analyses of efficacy endpoints. It is recommended that the investigator consults with the medical monitor if considering removing a subject from study prior to a definitive IRC assessment of progression.

Radiographic assessments will be performed at the following visits:

Subjects enrolled as of Protocol Amendments 5 and 6:

Screening, Weeks 12, 24, 36, 48, 60, and 84 until IRC documented disease progression, and at EOT (unless radiographic assessments performed within 4 weeks prior to EOT visit). After Week 84, radiographic assessments are performed at the discretion of the investigator. Screening CT/PET-CT/MRI may be performed within 6 weeks prior to first dose. Subsequent scans may be done within 1 week prior to clinic visit.

Subjects enrolled prior to Protocol Amendment 5:

Screening, Weeks 8, 16, 24, 36, 48, 60, and 84 until IRC documented disease progression, and at EOT (unless radiographic assessments performed within 4 weeks prior to EOT visit). After Week 84, radiographic assessments are performed at the discretion of the investigator. Screening CT/PET-CT/MRI may be performed within 6 weeks prior to first dose. Subsequent scans may be done within 1 week prior to clinic visit.

6.1.8. Bone Marrow Biopsy

For subjects in whom a radiologic CR is determined, a bone marrow biopsy may be required for complete assessment. In a subject who has a baseline or on-study bone marrow biopsy showing involvement with lymphoma or does not have a baseline bone marrow examination, declaration of an on-study CR requires bone marrow biopsy documentation of the absence of lymphoma. In a subject who has a baseline or on-study bone marrow biopsy showing no evidence of lymphoma, declaration of an on-study CR does not require bone marrow examination as long as other criteria for CR are met.

6.1.9. Performance Status

Performance status may be scored using the ECOG or Karnofsky Performance Status Scoring Systems at screening, Weeks 8, 16, 32, 48, every 12 weeks thereafter, and at the EOT and EOS visits.

6.1.10. Baseline Prognostic Factors, Ann Arbor Stage and FLIPI

At Screening, prognostic factors will be assessed. All subjects will have Ann Arbor stage assessments recorded (Appendix 3) and FLIPI factors assessed and scores calculated. FLIPI scores are a composite of 5 factors: age, number of nodal sites, Ann Arbor stage, hemoglobin level, and LDH level (Appendix 5).

6.1.11. Study Drug Dispensing and Dosing

Study drug will be dispensed at Baseline (Day 1), Weeks 4, 8, 12, 16, 20, 24, 32, 40, 48, and every 12 weeks thereafter until EOT. Drug may also be dispensed at unscheduled visits if necessary. Idelalisib will be administered as per Section 5.3.

6.1.12. Adverse Events

Adverse events will be assessed at all study visits. From the time of obtaining informed consent through the first administration of study drug, record all SAEs as well as any non-serious AEs related to protocol-mandated procedures on the AE eCRF. All other untoward medical occurrences observed during the screening period, including exacerbation or changes in medical history are to be captured on the medical history eCRF.

From the time of obtaining informed consent through 30 days post the last administration of study drug, record any AEs related to protocol-mandated procedures or study drug on the AE eCRF. SAEs should be captured on the SAE eCRF.

See Section 7 (Adverse Events and Toxicity Management) for additional details.

6.1.12.1. Assessment of Diarrhea/Colitis

A 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 must be obtained to identify possible diarrheogenic agents.

A physical examination including assessment for fever, dizziness, abdominal pain/cramping, and weakness (ie, evaluate for sepsis, bowel obstruction, dehydration) must be performed.

6.1.12.2. Prior and Concomitant Medications

Concomitant medications will be collected within the 3 months prior to screening and during the screening period. They will also be assessed at all study visits.

6.2. Posttreatment Assessments

The EOT and EOS visits may be performed on the same day, if the subject will be discontinuing study treatment and discontinuing the study at the same time (eg, withdrawal of consent).

For subjects who discontinue idelalisib prior to IRC documented disease progression, every attempt should be made to keep the subject in the study and continue to perform regular assessments per the schedule of procedures (with the exception of PK sampling and CMV monitoring) until the subject meets criteria for study discontinuation (see Section 3.5.2).

During the follow-up period, medical treatment of the subject is left to the investigator discretion.

6.3. Assessments for Premature Discontinuation from Study

If a subject discontinues idelalisib (for example, as a result of an AE) every attempt should be made to keep the subject in the study and continue to perform the required study-related follow-up and procedures. If this is not possible or acceptable to the subject or investigator, the subject may be withdrawn from the study. It is recommended that the investigator consults with the medical monitor prior to removing the subject from study for any reason except subject withdrawal of consent.

6.4. End of Treatment

EOT assessments will be performed when a subject permanently discontinues idelalisib. For subjects who discontinue idelalisib prior to IRC documented disease progression, every attempt should be made to keep the subject in the study and continue to perform regular assessments per the schedule of procedures (with the exception of PK sampling and CMV monitoring) until the subject meets criteria for study discontinuation (see Section 3.5.2).

6.5. 30-Day Follow-Up

A 30-day follow-up visit will be performed 30 days (± 5 days) following the EOT visit; however, this visit 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. Information may be gathered during a routine clinic visit, via telephone, or via another contact method.

6.6. End of Study

EOS assessments will be completed once it has been determined that the subject will discontinue the study. The EOT and EOS visits may be performed on the same day if the subject will be discontinuing study treatment and discontinuing the study at the same time (eg, withdrawal of consent).

6.7. Survival Follow-Up

Survival 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 anti-tumor treatment, secondary malignancies, survival status, and death details if applicable.

6.8. Unscheduled Visits

Unscheduled visits may occur at any time while the subject is enrolled on study. Vital signs, laboratory assessments, ECG, PE, and radiographic assessments may be conducted at these visits. If the unscheduled visit is to manage an AE of interest, PK samples may be included at these visits. Data generated during an unscheduled visit will be collected on the eCRF.

7. ADVERSE EVENTS AND TOXICITY MANAGEMENT

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

7.1.1. Adverse Events

An AE is any untoward medical occurrence in a clinical study subject administered a study drug, 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 study drug, whether or not the AE is considered related to the study drug. Adverse events may also include pretreatment or posttreatment complications that occur as a result of protocol-specified procedures, lack of efficacy, overdose, drug abuse/misuse reports, or occupational exposure.

An AE does not include the following:

- Medical or surgical procedures such as surgery, endoscopy, tooth extraction, and transfusion. The condition that led to the procedure may be an AE and must be reported
- Preexisting diseases, conditions, or laboratory abnormalities present or detected before the screening visit that do not worsen
- Situations where an untoward medical occurrence has not occurred (eg, hospitalization for elective surgery, social and/or convenience admissions)
- Overdose without clinical sequelae (see Section 7.6.1)
- Any medical condition or clinically significant laboratory abnormality with an onset date before the consent form is signed and not related to a protocol-associated procedure is not an AE, but rather considered to be preexisting and should be documented on the medical history case report form (CRF)

Preexisting events that increase in severity or change in nature after study drug initiation or during or as a consequence of participation in the clinical study will also be considered AEs.

7.1.2. Serious Adverse Events

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

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

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

7.1.2.1. Protocol-Specific Serious Adverse Event Definitions

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

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

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

7.2. Assessment of Adverse Events and Serious Adverse Events

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

7.2.1. Assessment of Causality for Study Drugs and Procedures

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

- **No:** Evidence exists that the AE has an etiology other than the study drug. For SAEs, an alternative causality must be provided (eg, preexisting condition, underlying disease, intercurrent illness, or concomitant medication).
- **Yes:** There is reasonable possibility that the event may have been caused by the study drug.

It should be emphasized that ineffective treatment should not be considered as causally related in the context of AE 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 AE has an etiology other than the study procedure.
- **Yes:** The AE occurred as a result of protocol procedures, (eg, venipuncture).

7.2.2. Assessment of Severity

The severity of AEs will be graded using the CTCAE, Version 5.0. For each episode, all increases in severity/grade should be reported.

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

Table 7-1. Grading of Adverse Event Severity

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

The distinction between the seriousness and the severity of an AE should be noted. Severe is a measure of intensity; thus, a severe reaction is not necessarily a serious reaction. 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 7.1.2.

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

All SAEs, regardless of cause or relationship, that occur after the subject first consents to participate in the study (ie, signing the informed consent) and throughout the duration of the study, including the protocol-required posttreatment follow-up period, must be reported in the eCRF database and Gilead PVE as instructed. This also includes any SAEs resulting from protocol-associated procedures performed from Screening onwards.

All AEs, regardless of cause or relationship, which occur from initiation of study drug until 30 days after last administration of study drug must be reported to the eCRF database as instructed.

All special situations including pregnancy, regardless of cause or relationship, until 30 days for females or 90 days for males after last administration of study drug(s) must be reported to the CRF/eCRF database as instructed.

Any SAEs and deaths that occur after the posttreatment follow-up visit but within 30 days of the last dose of the study drug, 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 determine that the subject's condition is stable. However, Gilead 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 study drug, he/she should promptly document and report the event to Gilead PVE.

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

7.3.1. Electronic Serious Adverse Event (eSAE) Reporting Process

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

If for any reason it is not possible to record the SAE information electronically, ie, the eCRF database is not functioning, record the SAE on the paper SAE reporting form and submit within

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

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

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

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

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

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

7.4. Gilead Reporting Requirements

Depending on relevant local legislation or regulations, including the applicable US FDA Code of Federal Regulations, 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, or SUSARs. In accordance with the EU Clinical Trials Directive (2001/20/EC), Gilead or a specified designee will notify worldwide regulatory agencies and the relevant IEC in concerned Member States of applicable SUSARs as outlined in current regulations.

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

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

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

Given the endpoints of the study, in order to maintain the integrity of the study, the following events that are assessed as unrelated to study drug will not be considered SAEs:

- Progression of FL
- Death related to progression of FL

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 unrelated events will be reported, as appropriate, in the final clinical study report (CSR) and in any relevant aggregate safety reports. The safety information from this study will also be reviewed by an independent DMC on an ongoing basis. The DMC can have access to partially blinded or unblinded data in order to determine if it is safe to continue the study according to the protocol.

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

7.5.1. Dermatological Events

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

For subjects who develop a Grade ≥ 3 rash for which an underlying etiology cannot be identified (eg, infection, co-suspect drug), study drug must be interrupted until Grade ≤ 1; idelalisib can then be resumed at the reduced dose level,100 mg twice daily or discontinued at the investigator's discretion.

Severe cutaneous reactions, including fatal events of Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug reaction with eosinophilia and systemic symptoms (DRESS) have been reported in subjects receiving idelalisib. Assessment of potential causal association between idelalisib and the occurrence of SJS or TEN has been confounded by the coadministration of antineoplastic agents (eg, bendamustine, rituximab) and/or other concomitant medications known to be associated with SJS or TEN (eg, allopurinol). If SJS, TEN, or DRESS is suspected, idelalisib and all coadministered medications associated with SJS, TEN, or DRESS should be interrupted and the subject treated accordingly.

Subjects should be monitored for the development of SJS, TEN, or DRESS and idelalisib treatment must be permanently discontinued if such events occur.

7.5.2. Progressive Multifocal Leukoencephalopathy

Cases of progressive multifocal leukoencephalopathy (PML) have been reported following the use of idelalisib within the context of prior or concomitant immunosuppressive therapies (including fludarabine and select anti-DC20 monoclonal antibodies [eg, rituximab]) that have been associated with PML. Investigators should consider PML in the differential diagnosis in subjects with new or worsening neurological, cognitive, or behavioral signs or symptoms. If PML is suspected, then appropriate diagnostic evaluations (referral to neurologist including MRI scan preferably with contrast, cerebrospinal fluid testing for John Cunningham viral DNA) should be undertaken and treatment needs to be suspended until PML is excluded.

7.5.3. 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 must be permanently discontinued in subjects who experience bowel perforation.

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.

For subjects who develop persistent diarrhea, obtain history of onset and duration of diarrhea and perform a physical exam per Section 6.1.12.1.

For Grade ≥ 2 diarrhea/colitis causes may relate to concomitant medications or gastrointestinal infections. Stool collection is required per Section 6.1.5.5. Differentiate between small-bowel and large-bowel diarrhea on a clinical basis. If unclear, consider upper and lower tract endoscopy with biopsy. Refer to Section 6.1.5.6 for additional information. 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. Ensure good hydration status. 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 SAEs. Withhold idelalisib for subjects with Grade 3 diarrhea and monitor at least weekly until Grade ≤ 1, then the subject may resume idelalisib at the reduced dose level, 100 mg twice daily. Discontinue idelalisib permanently for Grade 4 diarrhea.

7.5.4. Hepatic Events

Transaminase Elevations: Consistent with observations in a dog toxicology study, reversible asymptomatic alanine aminotransferase (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 elevations must be managed by withholding idelalisib. After resolution to ≤ 1 x upper limit of normal, idelalisib may be resumed at the reduced dose level, 100 mg twice daily. Discontinue idelalisib permanently for Grade 4 elevation. 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. Monitor ALT, AST, and bilirubin at least weekly until all abnormalities are Grade ≤ 1.

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 SAEs.

7.5.5. Hematological and Immunological Events

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

Treatment-emergent Grade 3 or 4 neutropenia events, including 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 Grade 3 neutropenia, maintain idelalisib dose and blood counts must be monitored at least weekly until ANC ≤ Grade 2. For subjects who develop Grade 4 neutropenia, idelalisib must be interrupted and blood counts monitored at least weekly until ANC ≤ Grade 2. Idelalisib may be resumed at the reduced dose level, 100 mg twice daily, when ANC ≤ Grade 3. Neutropenia should be managed according to established clinical guidelines.

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

7.5.6. Infectious Events

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

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

CMV surveillance for active disease (quantitative PCR) must be conducted approximately every 4 weeks throughout the course of idelalisib treatment, including during drug interruptions due to toxicity or AEs. 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.

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.

7.5.7. Pulmonary Events

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

Given the potential for infectious or drug-related pulmonary AEs, clinicians should be particularly observant for evidence of respiratory events in subjects participating in this study. 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 (eg, asymptomatic), withhold idelalisib until resolution to baseline. Idelalisib may be resumed at the reduced dose level, 100 mg twice daily or discontinued at investigator discretion. For subjects with suspected Grade ≥ 2 pneumonitis (eg, onset of cough, dyspnea, hypoxia and/or a diffuse interstitial pattern or ground-glass opacities on chest imaging without obvious infectious etiology), idelalisib must be discontinued permanently and therapy initiated as clinically appropriate.

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

7.5.8. Secondary Malignancies

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

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

7.5.9. Tumor Lysis Syndrome

Tumor lysis syndrome is very uncommonly associated with idelalisib monotherapy.

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

7.5.10. Pregnancy, Lactation, and Reproduction

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

Given the potential risks to a fetus or infant as a result of exposure to idelalisib, women of reproductive potential entering this study must have a negative serum pregnancy test at baseline and must not be breastfeeding. Males and females of childbearing potential should abstain from sexual intercourse or use an effective form of contraception (see Appendix 4). If a female study participant becomes pregnant or decides to breastfeed during the course of the study, all study therapy must be discontinued.

7.5.10.1. PJP Prophylaxis Precautions in 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 aerosolized pentamidine 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 aerosolized pentamidine can cause fetal harm when administered to a pregnant woman. Aerosolized pentamidine should be given to a pregnant woman only if clearly needed. It is not known whether aerosolized pentamidine is excreted in human milk. Aerosolized pentamidine should not be given to a nursing mother unless the potential benefits are judged to outweigh the unknown risks.

7.5.11. Ultraviolet Exposure

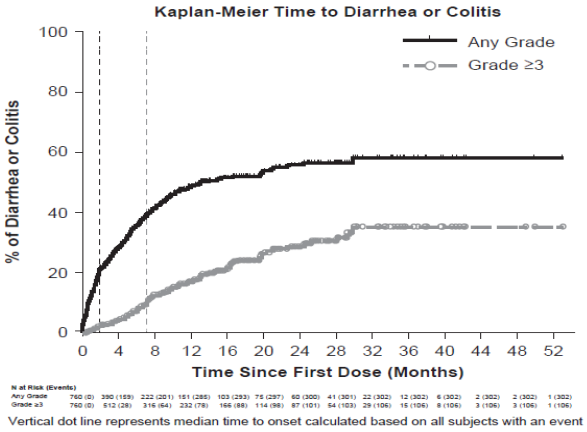
In vitro studies indicate enhanced cytotoxicity when embryonic murine fibroblasts treated with GS-563117 (the major metabolite of idelalisib) are simultaneously exposed to ultraviolet light. While nonclinical findings suggest the hypothetical potential for phototoxicity in humans, available clinical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

7.5.12. Investigation for Idelalisib Late Onset or Severe Diarrhea/Colitis

See CTCAE Version 5.0 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 7-1 {Coutre 2015}.

Figure 7-1. 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}.

7.5.13. Further Safety Information

Further safety information regarding the study drug may be found in the IB for idelalisib. The idelalisib IB contains information related to toxicity management that is not covered in Section 5.3.2. The dose modification guidelines in the current idelalisib IB may be slightly different than those listed in Section 5.3.2 because different recommended dose modifications were used in prior clinical studies.

7.6. Special Situations Reports

7.6.1. Definitions of Special Situations

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

- A pregnancy report is used to report any pregnancy in female subjects 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 labeling (as it applies to the daily dose of the subject in question). In cases of a discrepancy in drug accountability, overdose will be established only when it is clear that the subject has taken the excess dose(s). Overdose cannot be established when the subject cannot account for the discrepancy except in cases in which the investigator has reason to suspect that the subject has taken the additional dose(s).

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

7.6.2. Instructions for Reporting Special Situations

7.6.2.1. 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 PVE using the pregnancy report form within 24 hours of becoming aware of the pregnancy. Refer to the eCRF completion guidelines for full instructions on the mechanism of pregnancy reporting.

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

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

A spontaneous abortion is always considered to be an SAE and will be reported as such. Furthermore, any SAE occurring as an adverse pregnancy outcome post study must be reported to Gilead PVE.

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

Pregnancies of female partners of male study subjects exposed to Gilead study drug must also be reported and relevant information should be submitted to Gilead PVE using the pregnancy outcome report form 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 PVE.

Gilead PVE contact information is as follows: Email: PPD and Fax: PPD.

Refer to Appendix 4 for Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Recommendations.

7.6.2.2. Reporting Other Special Situations

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

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

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

8. STATISTICAL CONSIDERATIONS

8.1. Analysis Objectives and Endpoints

8.1.1. Analysis Objectives

The primary objective of this study is as follows:

- Establish a safe and effective dosing regimen of idelalisib in subjects with relapsed or refractory FL who have no other therapeutic options

The secondary objectives of this study are as follows:

- Evaluate the ORR
- Evaluate the PFS, DOR, and OS
- Evaluate the overall safety profile of idelalisib
- Determine the PK of idelalisib and its major metabolite (GS-563117)

The exploratory objective of this study is as follows:

- CCI [redacted]

8.1.2. Primary Endpoints

The primary endpoints are as follows:

- ORR, defined as the proportion of subjects who achieve a PR or CR
- Incidence of Grade ≥ 4 TEAEs

8.1.3. Secondary Endpoints

The secondary endpoints are as follows:

- DOR, defined as the interval from the first documentation of CR or PR to the earlier of the first documentation of disease progression by IRC or death from any cause
- ORR by Week 24, defined as the proportion of subjects who achieve a PR or CR by Week 24
- Overall safety profile of idelalisib, including the incidence of AEs and clinically significant laboratory abnormalities, severity, timing, and relationship to idelalisib of any AEs; SAEs; or AEs leading to interruption, reduction, or discontinuation of idelalisib

- Time to onset of AEIs, defined as the interval from the start of idelalisib treatment to the first documentation of start of AEI
- PFS, defined as the interval from randomization to the earlier of the first documentation of disease progression by IRC or death from any cause
- OS, defined as the interval from randomization to death from any cause
- Idelalisib trough (predose) and peak (1.5-hour samples) plasma concentrations assessed by validated bioanalytical method

8.1.4. Other Endpoints of Interest

The exploratory endpoint is as follows:

- CCI [redacted]

8.2. Analysis Conventions

The primary study analysis will be conducted when all enrolled subjects have discontinued the study or been on treatment for at least 48 weeks and completed response assessment of Week 48.

8.2.1. Analysis Sets

8.2.1.1. Intent-to-Treat (ITT) Analysis Set

The ITT Analysis Set will include all subjects who are randomized regardless of whether subjects receive any study drug. Treatment assignment will be designated according to a subject's initial randomization. This analysis set will be used in the analysis of subject characteristics and efficacy.

8.2.1.2. Safety Analysis Set

The Safety Analysis Set will include data from subjects who receive at least 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.

8.2.1.3. Pharmacokinetics Analysis Set

The PK Analysis Set will include data from all subjects in the Safety Analysis Set who have received the study drug and have at least 1 sample with detectable drug concentration.

8.3. Data Handling Conventions

The baseline value used in each analysis will be the last (most recent) pretreatment value before or on the first dosing date of study drug. 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. Data will be described and summarized by relevant treatment arm, analysis set, and time point. As appropriate, changes from baseline to each subsequent time point will be described and summarized by treatment arm.

In general, for data summaries involving continuous variables, data tables will typically contain the following statistics: N (number in analysis set), n (number with data), mean, standard deviation (StD), 95% CIs on the mean, median, minimum, and maximum. For categorical variables, the following statistics will typically be presented: 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.

Tumor response status and progression will be assessed by the IRC using standard response criteria. The findings of the IRC will be considered primary for analyses of the primary efficacy endpoint and other tumor control endpoints.

8.4. Demographic Data and Baseline Characteristics

Subject characteristics will be listed and summarized by treatment arm in the ITT Analysis Set using standard descriptive methods. Demographic summaries will include sex, race/ethnicity, and age. Baseline characteristics data will include a summary of body weight, height, ECOG performance status score, Ann Arbor stage assessments, and FLIPI factors.

8.5. Efficacy Analysis

8.5.1. Primary and Supportive Analysis for Primary Endpoint

For the primary efficacy analysis, ORR will be evaluated by treatment arm using the IRC assessments in the ITT Analysis Set. The estimation may also be done for subgroups including potential predictors of response. Subjects who do not have sufficient baseline or on-study tumor assessment to characterize response status will be counted as non-responders. Estimates and the corresponding 95% CIs based on the Clopper-Pearson exact method will be provided.

The potential impact of subject baseline characteristics and treatment response rates may be explored with logistic regression modeling.

8.5.2. Analysis for Secondary Endpoints

The ORR by Week 24 and corresponding 95% CIs will be evaluated by treatment arm using the IRC assessments in the ITT Analysis Set.

The time-to-event efficacy endpoints including PFS, DOR, and OS will be analyzed using the Kaplan-Meier method in the ITT Analysis Set, and the analysis of DOR will include subjects who achieve a PR or CR. Analyses may also be performed for subgroups defined by potential predictors of response.

8.6. Safety Analysis

Safety will be assessed via AEs, clinical laboratory tests, and concomitant medications. Safety data collected on or after the date that idelalisib was first administered up to the date of last dose of study drug plus 30 days will be summarized by treatment arm.

8.6.1. Extent of Exposure

Descriptive information will be provided by treatment arm regarding the duration of exposure to study drug, and the number and timing of dose interruptions and reductions.

8.6.2. Adverse Events

All AEs will be listed. The focus of AE summarization will be on treatment-emergent AEs. A treatment-emergent AE is defined as any AE with onset date on or after the date of first dose of study drug up to 30 days after permanent study drug discontinuation or any AEs leading to premature study drug discontinuation.

AEs will be classified using Medical Dictionary for Regulatory Activities with descriptions by system organ class (SOC), high-level group term, high-level term, preferred term (PT), and lower-level term. The severity of AEs will be graded by the investigator according to the CTCAE, Version 5.0, whenever possible. If a CTCAE criterion does not exist for a specific type of AE, the grade corresponding to the appropriate adjective will be used by the investigator to describe the intensity of the AE: Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), Grade 4 (life threatening), or Grade 5 (fatal). The relationship of the AE to the study drug will be categorized as related or unrelated.

For the primary safety endpoint, the number and percentage of subjects who experienced at least one Grade ≥ 4 TEAE will be listed and summarized by SOC and PT, and by treatment arm in the Safety Analysis Set. The severity, timing, relationship to study drug, drug interruptions, reductions, and discontinuations for Grade ≥ 4 TEAEs will be summarized.

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

Separate summaries will be prepared for the following types of TEAEs:

- Idelalisib-related AEs
- AEs that are Grade ≥ 4 in severity

- AEs that are Grade ≥ 3 in severity
- AEs leading to study drug interruption, reduction, or discontinuation
- SAEs

Additional analysis on AEIs will be performed. The AEIs include: Grade ≥ 3 diarrhea/colitis, rash, febrile neutropenia, infection, and any grade of the following: pneumonitis, bowel perforation, progressive multifocal leukoencephalopathy (PML), PJP, CMV infection, and organizing pneumonia. The frequency, severity, timing, and drug interruptions for AEIs will be summarized by treatment arm using descriptive statistics. Time to first onset of AEIs and time to resolution will be summarized using the Kaplan-Meier method.

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

Hematological and serum biochemistry data will be programmatically graded according to CTCAE severity grade, when applicable. Hematological and serum biochemistry and their changes from baseline will be summarized by treatment and by visit. Summary tables will be presented for each relevant assay to show the number of subjects by CTCAE severity grade with corresponding percentages. For parameters for which a CTCAE scale does not exist, the frequency of subjects with values below, within, and above the normal ranges will be summarized. Subjects will be characterized only once for a given assay, based on their worst severity grade observed during a period of interest (eg, during the study or from baseline to a particular visit). Shift tables for hematology and serum biochemistry will also be presented by showing change in CTCAE severity grade from baseline to the worst grade post baseline. Separate listings and summaries will be prepared for laboratory abnormalities that are Grade ≥ 3 in severity.

8.7. Pharmacokinetic Analysis

Plasma concentrations of idelalisib/metabolite will be listed and summarized by treatment arm and visit using descriptive statistics (eg, sample size, arithmetic mean, geometric mean, % coefficient of variation, StD, median, minimum, and maximum).

Additionally, a population PK model using a nonlinear mixed-effect modeling technique may be used to characterize the PK of idelalisib and GS-563117. Idelalisib exposure-response relationship between efficacy, safety, and idelalisib and/or GS-563117 exposure may be explored.

A logistic regression model may be used to explore the correlation between drug exposure and efficacy or safety.

8.8. Sample Size

The planned sample size is approximately 266 subjects: approximately 120 subjects in Arm A, approximately 26 subjects in Arm B, and approximately 120 subjects in Arm C. As of Protocol Amendment 5, Arm B enrollment was closed after enrollment of approximately 26 subjects into Arm B and approximately 26 subjects into Arm A.

As of Protocol Amendment 5, subjects will be randomized to 2 arms (Arm A and C) with a 1:1 ratio until the enrollment target of 120 subjects in each arm is met. The ORR was approximately 56% for subjects with FL in Study 101-09. If the underlying true ORR is 56% for subjects in this study, the chance to observe 60 or more responders out of 120 subjects (observed ORR ≥ 50%) is 92%. With 120 subjects in each arm, the half-width of a two-sided 95% CI of ORR is ≤ 10% for an observed ORR in the range of 40%-60%, and the half-width of a two-sided 95% CI of ≥ Grade 4 TEAEs incidence rate is ≤ 10% for an observed AE rate in the range of 20%-40%.

The sample size was originally planned to include 240 subjects randomized to Arm A and Arm B with a 1:1 ratio. The previous sample size calculation is based on the rate of Grade ≥ 3 diarrhea/colitis approximately 15% in the prior idelalisib studies. A sample size of 120 subjects per arm would provide 73% chance to detect a reduction of 10% (ie, 15% incidence in the 150 mg twice daily arm versus 5% incidence in the 100 mg twice daily arm) using a 2-sided Chi-square test with alpha level of 0.05.

8.9. Data Monitoring Committee

An external multidisciplinary DMC will review the progress of the study and perform interim reviews of safety data at regular intervals until all blinded subjects are either unblinded or off the study. The DMC will provide recommendations to Gilead as to whether the nature, frequency, and severity of adverse effects associated with study treatment warrant the early termination of the study in the best interests of the study participants, whether the study should continue as planned, or whether the study should continue with modifications.

The DMC's specific activities will be defined by a mutually agreed charter, which will define the DMC's membership, conduct, and meeting schedule.

CCI [redacted]

9. RESPONSIBILITIES

9.1. Investigator Responsibilities

9.1.1. Good Clinical Practice

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

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

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

9.1.2. Institutional Review Board (IRB)/Independent Ethics Committee (IEC) Review and Approval

The investigator (or sponsor as appropriate according to local regulations) will submit this protocol, informed consent form, and any accompanying material to be provided to the subject (such as advertisements, subject information sheets, or descriptions of the study used to obtain informed consent) to an IRB/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 any modifications made to the protocol or any accompanying material to be provided to the subject after initial IRB/IEC approval, with the exception of those necessary to reduce immediate risk to study subjects.

9.1.3. Informed Consent

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

9.1.4. Confidentiality

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

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

9.1.5. Study Files and Retention of Records and 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, CRF and query forms, IRB/IEC, and governmental approval with correspondence, informed consent, drug records, staff curriculum vitae and authorization forms, and other appropriate documents and correspondence.

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

- Subject identification (name, date of birth, gender);
- Documentation that subject meets eligibility criteria, ie, history, 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 study (including study number);
- Study discussed and date of informed consent;
- Dates of all visits;
- Documentation that protocol specific procedures were performed;
- Results of efficacy parameters, as required by the protocol;
- Start and end date (including dose regimen) of study drug, including dates of dispensing and return;
- Record of all AEs and other safety parameters (start and end date, and including causality and severity);
- Concomitant medication (including start and end date, dose if relevant; dose changes);
- Date of study completion and reason for early discontinuation, if it occurs.

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

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

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

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

9.1.6. Case Report Forms

For each subject consented, an eCRF will be completed by an authorized study staff member whose training for this function is documented according to study procedures. eCRF should be completed as per site contract, to enable the sponsor to perform central monitoring of safety data. The Eligibility Criteria eCRF should be completed only after all data related to eligibility have been received. Subsequent to data entry, a study monitor will perform source data verification within the electric data capture system. Original entries as well as any changes to data fields will be stored in the audit trail of the system. Prior to database lock (or any interim time points as described in the clinical data management plan), the investigator will use his/her log in credentials to confirm that the forms have been reviewed, and that the entries accurately reflect the information in the source documents. The eCRF capture the data required per the protocol schedule of events and procedures. System-generated or manual queries will be issued to the investigative site staff as data discrepancies are identified by the monitor or internal Gilead staff, who routinely review the data for completeness, correctness, and consistency. The site coordinator is responsible for responding to the queries in a timely manner, within the system, either by confirming the data as correct or updating the original entry, and providing the reason for the update (eg, data entry error). At the conclusion of the trial, Gilead will provide the site with a read-only archive copy of the data entered by that site. This archive must be stored in accordance with the records retention requirements outlined in Section 9.1.5.

9.1.7. Idelalisib Accountability and Return

Where possible, study drug should be destroyed at the site. If the site has an appropriate SOP for drug destruction as determined by Gilead, the site may destroy used (empty or partially empty) and unused study drug supplies in accordance with that site's approved SOP. A copy of the site's approved SOP will be obtained for central files. If study drug is destroyed on site, the investigator must maintain accurate records for all study drug destroyed. Records must show the identification and quantity of each unit destroyed, the method of destruction, and the person who disposed of the study drug. Upon study completion, copies of the study drug accountability records must be filed at the site. Another copy will be returned to Gilead.

If the site does not have an appropriate SOP for drug destruction, used and unused study drug supplies are to be sent to the designated disposal facility for eventual destruction. The study monitor will provide instructions for return.

9.1.8. Inspections

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

9.1.9. Protocol Compliance

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

9.2. Sponsor Responsibilities

9.2.1. Protocol Modifications

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

9.2.2. Study Report and Publications

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

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

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

9.3. Joint Investigator/Sponsor Responsibilities

9.3.1. Payment Reporting

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

9.3.2. Access to Information for Monitoring

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

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

9.3.3. Access to Information for Auditing or Inspections

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

9.3.4. Study Discontinuation

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

9.4. 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. 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. The findings of the IRC will be considered primary for the primary efficacy endpoint, and other tumor control endpoints.

10. REFERENCES

Cheson BD, Fisher RI, Barrington SF, Cavalli F, Schwartz LH, Zucca E, et al. Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification. J Clin Oncol 2014.

Cheson BD, Pfistner B, Juweid ME, Gascoyne RD, Specht L, Horning SJ, et al. Revised response criteria for malignant lymphoma. J Clin Oncol 2007;25 (5):579-86.

Coutre SE, Barrientos JC, Brown JR, de Vos S, Furman RR, Keating MJ, et al. Management of adverse events associated with idelalisib treatment - expert panel opinion. Leuk Lymphoma 2015:1-20.

Dreyling M, Geisler C, Hermine O, Kluin-Nelemans HC, Le Gouill S, Rule S, et al. Newly diagnosed and relapsed mantle cell lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-updagger. Ann Oncol 2014;25 Suppl 3:iii83-iii92.

Gilead Sciences Inc. ZYDELIG® (idelalisib) tablets, for oral use. U.S. Prescribing Information. Foster City, CA. July 2014:

Mills EJ, Barnighausen T, Negin J. HIV and aging--preparing for the challenges ahead. N Engl J Med 2012;366 (14):1270-3.

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Non-Hodgkin's Lymphomas. July, 2014.

Okkenhaug K, Vanhaesebroeck B. PI3K-signalling in B- and T-cells: insights from gene-targeted mice. Biochemical Society transactions 2003;31 (Pt 1):270-4.

Raanani P, Gafter-Gvili A, Paul M, Ben-Bassat I, Leibovici L, Shpilberg O. Immunoglobulin prophylaxis in chronic lymphocytic leukemia and multiple myeloma: systematic review and meta-analysis. Leuk Lymphoma 2009;50 (5):764-72.

Solal-Celigny P, Roy P, Colombat P, White J, Armitage JO, Arranz-Saez R, et al. Follicular lymphoma international prognostic index. Blood 2004;104 (5):1258-65.

Tsang RW, Gospodarowicz MK. Radiation therapy for localized low-grade non-Hodgkin's lymphomas. Hematol Oncol 2005;23 (1):10-7.

Vanhaesebroeck B, Ali K, Bilancio A, Geering B, Foukas LC. Signalling by PI3K isoforms: insights from gene-targeted mice. Trends Biochem Sci 2005;30 (4):194-204.

Wilder RB, Jones D, Tucker SL, Fuller LM, Ha CS, McLaughlin P, et al. Long-term results with radiotherapy for Stage I-II follicular lymphomas. International journal of radiation oncology, biology, physics 2001;51 (5):1219-27.

Zelenetz AD, Abramson JS, Advani RH, Andreadis CB, Bartlett N, Bellam N, et al. Non-Hodgkin's lymphomas. J Natl Compr Canc Netw 2011;9 (5):484-560.

11. APPENDICES

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Appendix 1. Investigator Signature Page

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

STUDY ACKNOWLEDGEMENT

Dose Optimization Study of Idelalisib in Follicular Lymphoma

GS-US-313-1580, Amendment 6, 18 March 2021

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

PPD

Gilead Sciences Medical Monitor

PPD

Signature

17 MARCH 2021

Date

INVESTIGATOR STATEMENT

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

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

Principal Investigator Name (Printed)

Signature

Date

Site Number

Appendix 2. Study Procedures Table

Period	Screen	Baseline	Treatment																					Follow up	
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**lab**	**9**	**lab**	**10**	**lab**	**11**	**lab**	**12**	**13**	**14**	**lab**	**15**	**lab**	**16+**	**EOT**	**EOS**	**30 days**	**Survival**
Week		**0**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**20**	**22**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**60+ (Q12 wks)**				
Cycle		**C1 D1**	**C1 D15**	**C2 D1**	**C2 D15**	**C3 D1**	**C3 D15**	**C4 D1**	**C4 D15**	**C5 D1**	**C5 D15**	**C6 D1**	**C6 D15**	**C7 D1**	**C8 D1**	**C9 D1**	**C10 D1**	**C11 D1**	**C12 D1**	**C13 D1**	**C14 D1**	**C16D1 +(Q3 cycles)**				
Study Day	**Within 28 days**	**1**	**15**	**29**	**43**	**57**	**71**	**85**	**99**	**113**	**127**	**141**	**155**	**169**	**197**	**225**	**253**	**281**	**309**	**337**	**365**				**Within +30 days [a]**	**Annual for 5 years**
Visit Window			**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±5**	**±3**		**±5**	**±4 weeks**
Written Informed Consent	X																									
Medical History	X																									
Medication History	X																									
Physical Examination	X					X[q]		X[r]		X[q]				X			X			X		X[b]				
Vital Signs [c]	X																									
Performance Status	X					X				X						X				X		X	X	X		
Ann Arbor Staging	X																									
FLIPI	X																									
Chemistry	X	X	X	X	X	X	X	X		X		X		X		X	X	X		X		X	X	X		
Hematology	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X		X		X	X	X		
Coagulation	X	X				X				X						X				X		X				
Urinalysis	X																									

Period	Screen	Baseline	Treatment																					Follow up	
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**lab**	**9**	**lab**	**10**	**lab**	**11**	**lab**	**12**	**13**	**14**	**lab**	**15**	**lab**	**16+**	**EOT**	**EOS**	**30 days**	**Survival**
Week		**0**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**20**	**22**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**60+ (Q12 wks)**				
Cycle		**C1 D1**	**C1 D15**	**C2 D1**	**C2 D15**	**C3 D1**	**C3 D15**	**C4 D1**	**C4 D15**	**C5 D1**	**C5 D15**	**C6 D1**	**C6 D15**	**C7 D1**	**C8 D1**	**C9 D1**	**C10 D1**	**C11 D1**	**C12 D1**	**C13 D1**	**C14 D1**	**C16D1 +(Q3 cycles)**				
Study Day	**Within 28 days**	**1**	**15**	**29**	**43**	**57**	**71**	**85**	**99**	**113**	**127**	**141**	**155**	**169**	**197**	**225**	**253**	**281**	**309**	**337**	**365**				**Within +30 days [a]**	**Annual for 5 years**
Visit Window			**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±5**	**±3**		**±5**	**±4 weeks**
Serum β-hCG (women of childbearing potential)	X																									
Urine Pregnancy Test (women of childbearing potential) [d]		X		X		X		X		X		X		X	X	X	X	X	X	X	X	X	X	X		
Hepatitis B Screening/Testing	X																									
Hepatitis C Screening	X																									
HIV Screening	X																									
CMV testing [l]	X	X		X		X		X		X		X		X	X	X	X	X	X	X	X	X	X			
Beta-2 Microglobulin	X													X						X		X	X			
Labs for Immune monitoring [n]	X			X				X						X			X			X		X	X	X		
[redacted]																										

Period	Screen	Baseline	Treatment																					Follow up	
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**lab**	**9**	**lab**	**10**	**lab**	**11**	**lab**	**12**	**13**	**14**	**lab**	**15**	**lab**	**16+**	**EOT**	**EOS**	**30 days**	**Survival**
Week		**0**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**20**	**22**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**60+ (Q12 wks)**				
Cycle		**C1 D1**	**C1 D15**	**C2 D1**	**C2 D15**	**C3 D1**	**C3 D15**	**C4 D1**	**C4 D15**	**C5 D1**	**C5 D15**	**C6 D1**	**C6 D15**	**C7 D1**	**C8 D1**	**C9 D1**	**C10 D1**	**C11 D1**	**C12 D1**	**C13 D1**	**C14 D1**	**C16D1 +(Q3 cycles)**				
Study Day	**Within 28 days**	**1**	**15**	**29**	**43**	**57**	**71**	**85**	**99**	**113**	**127**	**141**	**155**	**169**	**197**	**225**	**253**	**281**	**309**	**337**	**365**				**Within +30 days [a]**	**Annual for 5 years**
Visit Window			**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±5**	**±3**		**±5**	**±4 weeks**
PK Sample [g]		X	X	X	X	X	X	X		X		X		X		X				X						
12-Lead ECG	X																									
Radiology (PET-CT/CT/MRI)[h]	X					X[q]		X[r]		X[q]				X			X			X		X	X			
Tumor Response [i]	X					X[q]		X[r]		X[q]				X			X			X		X	X			
Bone Marrow Biopsy [j]	X					X[q]		X[r]		X[q]				X			X			X		X	X	X		
Randomization[s]		X																								
Idelalisib Dispensing		X		X		X		X		X		X		X		X		X		X		X				
Idelalisib Administration [k]		X	X	X	X	X	X	X		X		X		X		X				X						
PJP prophylaxis [o]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
CD4+ T-cell count [p]																							X	X	X	
Adverse Events [m]	X	X	X	X	X	X	X	X		X		X		X		X	X	X		X		X	X	X	X	
Concomitant Medication	X	X	X	X	X	X	X	X		X		X		X		X	X	X		X		X	X	X	X	
Survival Follow-Up																										X

a Occurs 30-days following EOT.
b To be performed every 24 weeks.
c At Screening, vital signs including oxygen saturation, systolic and diastolic blood pressure, heart rate, respiratory rate, temperature, and anthropometric measurements of height and weight will be measured by the investigator or qualified designees as per standard institutional guidelines.
d For females of childbearing potential, urine pregnancy tests will be done every 4 weeks on study.
e CCI
f CCI
g Pre-AM dose (within 1 hour prior to dose) and 1.5 hours post-AM dose (± 10 min) in the morning. Additional PK samples (single, non-timed) will be collected at unscheduled study visits (between Week 0 and Week 48).
h Screening CT/PET-CT/MRI may be performed within 6 weeks prior to first dose and subsequent scans may be done within 1 week prior to clinic visit. Scans to be performed at Weeks 60 and 84 until documented IRC progressive disease, and at EOT (unless radiographic assessments performed within 4 weeks prior to EOT visit). After Week 84, radiographic assessments are performed at the discretion of the investigator.
i Both Investigator and IRC to perform response assessments.
j To be performed at baseline to confirm laboratory eligibility due to lymphoma involvement of the marrow. To be performed on-study to assess for a potential CR in a subject who had lymphoma involvement of the marrow at baseline or did not have a baseline bone marrow biopsy. After CR is determined, there is no need for any further bone marrow biopsy assessments.
k Idelalisib morning dose to be administered in clinic after PK CCI . For subjects randomized to Arm C, study drug should not be taken on scheduled "off-treatment" days, regardless of prior missed doses, study drug interruptions for toxicity, or PK/biomarker samples. If prior scheduled dose was missed for any reason including due to planned "off-treatment" schedule, a predose PK sample is not needed.
l CMV testing must be done at screening and every 4 weeks throughout the course of study drug treatment, including during drug interruptions due to toxicity or AEs, requiring clinic visits after Week 24. CMV serology (anti-CMV IgG and IgM) testing will be done at baseline (Day 1) only.
m For an AE of Diarrhea/Colitis: (1) Obtain history of onset and duration of diarrhea, including description of number of stools and stool composition, travel history, dietary changes and a medication review to identify possible diarrheogenic agents, and (2) Perform physical examination including assessment for fever, dizziness, abdominal pain/cramping, and weakness.
n The immune monitoring labs at all indicated timepoints include lymphocyte subset panel using flow cytometry (immunophenotyping), quantitative immunoglobulins IgG, IgM, IgA, IgE, and Serum CH50 level.
o PJP prophylaxis: per Section 7.5.6 ("Infectious Events") subjects must receive trimethoprim-sulfamethoxazole or other established prophylaxis for PJP throughout the course of idelalisib treatment and must continue for a minimum of 2 months after idelalisib discontinuation and should last for a period of 2-6 months. Prophylaxis may stop within the 2-6 months after idelalisib discontinuation when the CD4+ T-cell count is documented to be >200 cells/mcL. Subjects must permanently discontinue idelalisib upon diagnosis of PJP.
p CD4+ T-cell count is needed to determine when PJP prophylaxis may end as specified in Section 7.5.6 ("Infectious Events").
q Subjects enrolled prior to Protocol Amendment 5 only.
r Subjects enrolled as of Protocol Amendment 5 only.
s 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.

Appendix 3. Ann Arbor Lymphoma Staging System

Area of Involvement	Stage
Single lymph node group or lymph node region	1
Two or more node regions on same side of diaphragm	2
Lymph node regions on both sides of the diaphragm	3
Multiple extra-nodal sites or lymph nodes and extra-nodal sites	4

Additional Anatomic Factors	Designation
Confined to lymph nodes	N
Site of bulky disease (> 10 cm in diameter)	X
Extra-nodal extension or single isolated site of extra-nodal disease	E
Hepatic	H
Lung	L
Bone marrow	M
Spleen	S
Pleura	P
Bone	O
Skin	D

Additional Symptomatic Factors	Designation
No symptoms	A
Symptoms of weight loss > 10% within 6 months, fever, night sweats	B

Appendix 4. Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Requirements

1) Definitions

a. Definition of Childbearing Potential

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

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

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

a) Definition of Male Fertility

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

2) Contraception Requirements for Female Subjects

a. Study Drug Effects on Pregnancy and Hormonal Contraception

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

b. Contraception Requirements for Female Subjects of Childbearing Potential

The inclusion of female subjects of childbearing potential requires the use of highly effective contraceptive measures with a failure rate of < 1% per year. They must also not rely on hormonal contraceptives as a form of birth control during the study. They must have a negative serum pregnancy test at screening and a negative pregnancy test on Day 1 prior to randomization. Pregnancy tests will be performed at monthly intervals thereafter until the end of contraception requirement.

Duration of required contraception for female subjects in this clinical trial should start from the Screening visit until 30 days post last dose of study drug.

Female subjects must agree to use 1 of the following contraceptive methods:

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

Or

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

- Non-hormonal intrauterine device (IUD)
- Bilateral tubal occlusion (upon medical assessment of surgical success)
- Vasectomy in the male partner (upon medical assessment of surgical success)

Inclusion of methods of contraception in this list of permitted methods does not imply that the method is approved in any country or region. Methods should only be used if locally approved.

Female subjects must also refrain from egg donation and in vitro fertilization during treatment and until the end of contraception requirement. If needed, female subjects should be advised to seek advice about egg donation and cryopreservation of germ cells prior to treatment.

3) Contraception Requirements for Male Subjects

It is theoretically possible that a relevant systemic concentration of study drug may be achieved in a female partner from exposure to the male subject's seminal fluid and poses a potential risk to an embryo/fetus. Therefore, male subjects with female partners of childbearing potential must use condoms during treatment until 90 days after last dose of study drug. If the female partner of childbearing potential is not pregnant, use of locally approved contraceptive methods should also be considered.

Male subjects must also refrain from sperm donation during treatment and until the end of contraception requirement.

4) Unacceptable Birth Control Methods

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

5) Procedures to be Followed in the Event of Pregnancy

Female subjects will be instructed to notify the investigator if they become pregnant or suspect they are pregnant at any time from start of the study to 30 days post last study drug dose. Study drug must be discontinued immediately.

Male subjects whose partner has become pregnant or suspects she is pregnant from start of study to 90 days post last study drug dose must also report the information to the investigator. Instructions for reporting pregnancy, partner pregnancy, and pregnancy outcome are outlined in Section 7.6.2.1.

Appendix 5. Follicular Lymphoma International Prognostic Index

Follicular Lymphoma International Prognostic Index (FLIPI) Scoring System

Parameter	Value	Point Score
Age	> 60 years of age	1
Ann Arbor stage	Stage III or IV	1
Hemoglobin level	< 120 g/L (12.0 g/dL or 6.37 mmol/L)	1
Serum LDH	> ULN	1
Number of Nodal Sites	> 5	1

Risk Group by FLIPI Total Point Score

Risk Group	Total Point Score
Low	≤ 1
Intermediate	2
High	≥ 3

{Mills 2012}

Appendix 6. Efficacy Assessments

Tumor Status Assessments

The determination of lymphoma response and progression will be based on standardized criteria {Cheson 2007} as specifically modified for this study to reflect the biology of the diseases under study and the pharmacology of idelalisib and the methods to be used in evaluation. During the course of the study, investigators will periodically assess the status of each subject's lymphoma. If progression is suspected, the IRC will be notified and will review radiographic and pertinent clinical data in order to provide expert interpretation. Treatment decisions by the investigator in this study will be based, in part, on these assessments. The findings of the IRC will be considered primary for analyses of ORR and other tumor control endpoints.

Method of Assessment

In addition to clinical examination, imaging-based evaluation will be used in this study in all subjects enrolled. CT scan is the preferred method for radiographic tumor assessment. MRI scanning may be used at the investigator's discretion in subjects for whom this may be a preferred alternative to CT scanning; however, if MRI is performed, a non-contrast CT of the chest should also be performed. Contrast-enhanced scanning is preferred, but contrast material may be omitted in subjects for whom use of a contrast agent would be medically contraindicated. If available, PET scan data will be considered in response and progression assessment; however, PET scanning will not be a required component of assessment in this study. As appropriate, study treatment dosing delays, bone marrow aspirate/biopsy information (eg, for confirmation of CR) and lymph node biopsy information (eg, for documentation of disease transformation to an aggressive histology) will also be considered.

For radiographic assessments, 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, while on study drug treatment and during the open-label extension. Furthermore, the use of intravenous (IV) contrast should be consistent across time points. In the event that the screening/baseline CT scan of the neck, chest, abdomen, and pelvis is performed without IV contrast, follow-up time points should also be performed without IV contrast.

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

Timing of Assessments

During screening, clinical and imaging-based tumor assessments should be performed within the specified screening period. On-study PET-CT/CT/MRI tumor assessments should be performed at as indicated in Appendix 2. An end-of-study PET-CT/CT/MRI tumor assessment should be performed unless the subject already has radiographic confirmation of disease progression ≤4 weeks prior to study discontinuation. If a subject permanently discontinues study drug prior to objective documentation of lymphoma progression, investigators should continue further follow-up until lymphoma progression is documented by the IRC.

Timing of Assessments − Subjects enrolled Prior to Protocol Amendment 5

Subjects randomized to 100 mg twice daily idelalisib with SD or PD will be unblinded and dose escalated to 150 mg twice daily. Subjects randomized to 150 mg with SD will be unblinded. The subjects should continue PET-CT/CT/MRI tumor assessments as indicated in Appendix 2, until lymphoma progression is documented by the IRC. Subjects with PD on the 150 mg twice daily arm will be discontinued from study.

Identification and Follow-up of Tumor Lesions and Organomegaly

Index Lesions

Up to 6 lesions (eg, lymph nodes, liver or spleen nodules, and/or other circumscribed extra-nodal masses) should be selected as index lesions that will be used to quantitate the status of the disease during study. Ideally, the index lesions should be located in disparate regions of the body and include mediastinal, abdominal, and retroperitoneal areas of disease whenever these sites are involved.

Index lesions will be measured and recorded at baseline and at the stipulated intervals. The cross-sectional dimensions (the largest cross-sectional diameter, ie, the longest diameter [LD] × the longest perpendicular diameter [LPD]) will be recorded (in cm) for each index lesion. Using the LD and LPD, the product of the perpendicular diameters (PPD) for each index lesion will be calculated. The sum of the products (SPDs) for all index lesions will be calculated and recorded. The baseline SPDs will be used as references by which objective tumor response will be characterized during treatment. The nadir LDs of individual lesions and the nadir SPDs will be used as references by which objective tumor progression will be characterized during study. All PPD and SPD measurements will be reported in centimeters squared.

Nodal Index Lesions

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 >1.5 cm regardless of the LPD. If a lymph node lesion has a LD of 1.1 to 1.5 cm it should only be considered abnormal if its LPD is more than 1.0 cm.

Abnormal, measurable nodal lesions will be subcategorized as either large or small.

- Large nodal lesions have an LD that is > 1.5 cm and an LPD that is ≥1.0 cm.
- Small nodal lesions have an LD that is > 1.0 cm and ≤ 1.5 cm and an LPD that is > 1.0 cm.

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

At follow-up time points, 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).

New or enlarging nodal lesions that are still ≤ 1.0 cm by ≤ 1.0 cm will not be considered to represent recurrent disease or PD. A new node that measures > 1.5 cm in any diameter or a new node that measures > 1.0 cm to ≤ 1.5 cm in the LD and measures > 1.0 cm in the LPD will be considered PD.

In cases in which a large lymph node mass has split into multiple components, only those elements that are > 1.0 cm in at least 1 diameter will be considered abnormal and used in calculating the SPD. Components that are ≤ 1.0 cm in the LD are assumed to be normal lymph node structures. PD will not be based on the growth of a lesion sub-component until it meets the criteria for abnormal. Lesion sub-components that are abnormal (> 1.0 cm in ≥ 1 diameter) will have the true PPDs calculated with the result used only for calculating an accurate nadir. Lesion sub-components that are normal (≤ 1.0 cm in the LD) will have the default PPD of 1.0 cm^2 (1.0 cm x 1.0 cm) stored only for the purposes of calculating the nadir value.

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.

Extra-Nodal Index Lesions

An extra-nodal mass may be selected as an index lesion if it is both abnormal and measurable at baseline. An extra-nodal mass of any size is considered abnormal. It is considered measurable at baseline if it has 2 perpendicular diameters that can be accurately measured in cross section with the LD being ≥ 1.0 cm and the LPD also being ≥ 1.0 cm.

At follow-up time points, the PPD of each single extra-nodal index lesion and the SPD of all extra-nodal index lesions will be considered. Because extra-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. If an extra-nodal lesion is no longer clearly visible, it will be considered resolved and its PPD will be defined as 0 cm^2.

If an extra-nodal lesion that had resolved (ie, had a PPD of 0 cm^2) subsequently reappears unequivocally, the subject will be considered to have PD. A new unequivocal extra-nodal lesion of any size that appears at a site that was not previously involved with lymphoma and is discernible to the radiologist by CT scan will be considered PD.

Non-Index Lesions

Any other measurable and abnormal nodal or extra-nodal lesions not selected for quantitation as index lesions may be considered non-index lesions. In addition, non-measurable evidence of lymphoma such as abnormal, non-measurable nodal lesions, extra-nodal lesions with both diameters < 1.0 cm, 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, or lesions with artifacts may be considered as non-index disease.

If present at baseline, up to 6 non-index lesions should be recorded. Measurements are not required.

Non-index disease will be used as a general reference to further characterize regression or progression of lymphoma during assessments of the objective tumor response during treatment. These lesions should be followed as "present", "absent" or "progressed."

Spleen and Liver

Qualitative assessments of the sizes of the spleen and liver will be performed. In addition, the presence or absence of splenic and/or hepatic nodules will be recorded.

Bone Marrow

Bone marrow assessments will be based on morphologic evaluation of bone marrow biopsies. Immunohistochemistry may be used to assess response if the sample is indeterminate by morphology.

In a subject who has a baseline bone marrow biopsy showing bone marrow lymphoma or does not have a baseline bone marrow examination, declaration of an on-study CR requires bone marrow biopsy documentation of the absence of bone marrow lymphoma. In a subject who has a baseline bone marrow biopsy showing no evidence of lymphoma, declaration of an on-study CR does not require bone marrow examination as long as other criteria for CR are met.

Biopsy and Cytology

During study participation, a subject who has a biopsy or cytology indicating a new site of disease or transformation to an aggressive lymphoma will be considered to have PD even in the absence of other evidence of PD. If the subject has no earlier objective documentation of PD, the date of the biopsy or cytology will be considered the date of lymphoma progression.

Definitions of Tumor Response and Progression

Responses will be categorized as complete response (CR), very good partial response, partial response (PR), stable disease (SD), or progressive disease (PD). In addition, a response category of not evaluable (NE) is provided for situations in which there is inadequate information to otherwise categorize response status. A response category of no disease (ND) is included for situations in which there is no evidence of tumor 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 study drug until PD/recurrence (taking as reference for PD the smallest measurements recorded since study drug started). Subjects with a best overall response of NE or ND will be included in the denominators in calculations of tumor response rate.

Response Categories

Complete Response

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

- No evidence of new disease
- Regression of all index nodal lesions to normal size (≤ 1.5 cm in the LD for nodes that were considered large at baseline and ≤ 1.0 cm in the LD and ≤ 1.0 cm in the LPD for nodes that were considered small at baseline) Regression to normal of all nodal non-index disease
- Disappearance of all detectable extra-nodal index and non-index disease
- Normal spleen and liver size by imaging studies, no hepatic or splenic lymphoma nodules, and no new liver or spleen enlargement
- Morphologically negative bone marrow based on an adequate unilateral core biopsy (> 20 mm unilateral core); if the sample is indeterminate by morphology, it should be negative by immunohistochemistry. After the subject meets radiographic CR, the window for bone marrow biopsy is within 30 days from the date that CR was met.
- If PET performed (not required), no evidence of residual disease

Partial Response

To satisfy criteria for PR, all of the following criteria must be met as noted below:

- No evidence of new disease
- A ≥ 50% decrease from baseline in the SPD of the index lesions
- No increase in the size of non-index disease

- No increase in the size of the liver or spleen and no new liver or spleen enlargement
- Persistence of bone marrow involvement in a subject who meets other criteria for CR based on the disappearance of all nodal and extra-nodal masses
- If PET performed (not required):
  - Typically fluorodeoxyglucose (FDG)-avid lymphoma: if no baseline PET scan or if the PET scan was positive before initiating study drug(s), the on-treatment PET is positive in ≥1 previously involved site. If baseline PET was performed and was negative, there is no new PET evidence of disease
  - Variably FDG-avid lymphoma/FDG-avidity unknown: if no pretreatment PET scan or if the pretreatment PET scan was negative for lymphoma, CT criteria should be used in assessing the tumor during study. If the PET scan was positive before initiating study drug(s), the on-treatment PET is positive in ≥1 previously involved site.

Stable Disease

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

- No evidence of new disease
- Neither sufficient tumor shrinkage from baseline to qualify for PR nor sufficient evidence of tumor growth to qualify for PD

Progressive Disease

The occurrence of any of the following events indicates progressive disease (PD):

- Evidence of any new disease that was not present at baseline:
  - A new node that measures > 1.5 cm in LD and > 1.0 cm in the LPD.
  - A new node that measures > 1.0 cm to ≤ 1.5 cm in the LD and > 1.0 cm in the LPD
  - Unequivocal reappearance of an extra-nodal lesion that had resolved (ie, had previously been assigned a PPD of 0 cm^2)
  - A new unequivocal extra-nodal lesion of any size
  - New non-index disease (eg, effusions, ascites, or other organ abnormalities) of any size unequivocally attributable to lymphoma (usually requires PET, biopsy, cytology, or other non-radiologic confirmation to confirm disease attributable to lymphoma).
    Note: Isolated new effusions, ascites, or bone lesions are not sufficient evidence alone of PD unless histologically confirmed. In subjects with no prior history of pulmonary lymphoma, new lung nodules identified by CT are usually benign. Thus, a declaration of PD should not be made if this is the only manifestation of an apparently new lesion.

- New or recurrent bone marrow involvement with lymphoma if the last prior bone marrow biopsy performed as part of the study (baseline or on-study) was negative for lymphoma

- Evidence of worsening of nodal or extra-nodal index lesions:
  - 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

- Unequivocal increase in the size of non-index disease

- Transformation to a more aggressive NHL histology as established by lymph node biopsy

- If PET performed (not required):
  - The appearance of any new lesion compatible with lymphoma with confirmation by other radiographic or histological modalities
  - The reappearance of any activity in a pre-existent lesion that meets size criteria for a new lesion on CT

Note: If there is uncertainty regarding whether there is definitive lymphoma progression, the subject should continue study drug(s) and remain under close observation (eg, evaluated at scheduled intervals) pending confirmation of progression status by the IRC. In particular, worsening of constitutional symptoms in the absence of objective evidence of worsening lymphoma will not be considered definitive disease progression; in such subjects, both lymphoma-related and non-lymphoma-related causes for the constitutional symptoms should be considered. Transient worsening of disease during temporary interruption of study drug(s) (eg, for intercurrent illness) may also not indicate definitive disease progression. In these instances, PET-CT/CT/MRI should be attempted in order to document whether definitive disease progression has occurred. If subsequent evaluations suggest that the subject has experienced persistent definitive disease progression, then the date of progression will be the time point at which progression was first objectively documented.

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.

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.

No Disease

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

- Index disease absent at both baseline and on-study.
- Non-index disease absent at both baseline and on-study.
- Enlargement of the liver and spleen absent at both baseline and on-study.

Appendix 7. Cockcroft-Gault Method for Estimating Creatinine Clearance

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

Serum Creatinine Units	Gender	Formula
mg/dL	Males	$\text{eCcr [mL/min]} = \dfrac{(140\text{-subject age [years]}) \times \text{subject weight [kilograms]} \times 1}{72 \times \text{subject serum creatinine [mg/dl]}}$
	Females	$\text{eCcr [mL/min]} = \dfrac{(140\text{-subject age [years]}) \times \text{subject weight [kilograms]} \times 0.85}{72 \times \text{subject serum creatinine [mg/dl]}}$
µmol/L	Males	$\text{eCcr [mL/sec]} = \dfrac{(140\text{-subject age [years]}) \times \text{subject weight [kilograms]}}{[(72 \text{ x serum creatinine (µmol /L) x } 0.6786]}$
	Females	$\text{eCcr [mL/sec]} = \dfrac{(0.85 \text{ x } (140\text{-subject age [years]}) \times \text{subject weight [kilograms]}}{[(72 \text{ x serum creatinine (µmol /L) x } 0.6786]}$

eC_{cr}=estimated creatinine clearance

Appendix 8. Pandemic Risk Assessment and Mitigation Plan

During an ongoing pandemic, potential risks associated with subjects being unable to attend study visits have been identified for this study.

These potential risks and mitigation plans can be summarized as follows:

1) Subject screening and enrollment

   a) Prior to screening and enrolling any new subjects, the site monitor will confirm

      i) The site is able to perform protocol-required procedures and data collection by delegated/trained staff.

      ii) The site is able to adequately manage the subject's safety in light of COVID-19; and they should only proceed with screening if there are no known issues that may impact the ability for the subject to attend study visits.

      iii) The principal investigator (PI) deems study participation and onsite visits outweigh the risk of COVID-19 exposure.

2) Study drug supplies to subjects and sites

   a) Subjects may be unable to return to the site for a number of visits to get the study drug, or the site may be unable to accept any subject visits. Without study drugs, the subject would not be able to stay on the study drug as planned per protocol.

      Mitigation plan:

      i) Study drug supplies may be provided to the subject from the site without a clinic visit, once it is confirmed that the subject may safely continue on study drug as determined by the PI.

      ii) A virtual study visit, via phone or video conferencing, must be performed prior to remote study drug resupply. At the earliest opportunity, the site will schedule in-person subject visits and return to the protocol's regular schedule of assessments.

      iii) A qualified courier may be utilized to ship the study drug from sites to study subject's home if permitted by local ethic committee (EC)/institutional review boards (IRB)/Regulatory Authority as applicable and with sponsor's approval.

      iv) Obtain subject's consent verbally (eg, by phone) to ship investigational medicinal product (IMP) from site to the subject's home and to provide the subject's address to the courier service responsible for delivering the IMP. The date and time that the consent was obtained must be documented in the subject's source documents.

      v) Ensure IMP documentation is complete for the shipment from site to subject.

vi) Utilize same day or overnight shipping with tracking information. Provide a clear chain of custody.

b) Shipments of study drug could be delayed because of transportation issues. Without study drug subject would not be able to stay on the study drug as planned per protocol.

Mitigation plan The study drug supply lookout window was increased to 90 days for all drug shipments to mitigate the risk of insufficient study drug supply or shipment delays from the depot to the study site.

i) All sites with active subjects to confirm capacity to store the extra supply of study drug prior to shipment.

ii) The sites' study drug inventory should be closely monitored. Site staff should notify the sponsor or delegate if they foresee shortage in study drug inventory or if there is any interruption in local shipping service.

iii) The sponsor will continue to monitor inventory at the study drug depot and study sites. Manual shipments will be triggered as necessary.

3) Subject safety monitoring and follow-up:

a) Subjects may be unable or unwilling to come to the study site for their scheduled study visits as required per protocol.

Mitigation plan: For subjects who may be unable or unwilling to visit the study site for their scheduled study visits as required per protocol, the PI or qualified delegate will conduct a virtual study visit, via phone or video conferencing, to assess the subject within target visit window date whenever possible. During the virtual study visit, the following information at minimum will be reviewed:

i) Confirm if subject has experienced any adverse events (AEs)/serious adverse events (SAEs)/special situations (including pregnancy) and follow-up on any unresolved AE/SAEs.

ii) Review current list of concomitant medications and document any new concomitant medications.

iii) Confirm if subject dosing diary questionnaires is completed.

iv) Confirm subject’s study drug supply is sufficient to last until the next planned visit date. If study drug resupply is needed it will be provided as described above in (2).

v) Remind subject to maintain current dosing and to keep all dispensed study drug kits for return at the next on-site visit.

vi) If more than one visit will be missed, and other local labs or alternatives are not possible, please discuss ongoing subject participation with the medical monitor.

b) Subjects may be unable or unwilling to travel to the site for planned assessments (eg, safety blood draws); hence samples may not be sent for central lab analyses.

Mitigation plan: Local labs may be utilized as appropriate to monitor subject safety until the subject can return to the site for their regular follow-up per protocol. Any laboratory assessments conducted at a local lab due to the pandemic will be documented accordingly. Pregnancy testing may be performed using a home urine pregnancy test if local lab pregnancy testing is not feasible. A positive urine pregnancy test must be immediately confirmed with a serum pregnancy test. If serum pregnancy test is positive, please see instructions for reporting pregnancy in Section 7.6.2.1 of this document.

c) Subjects may be unable or unwilling to attend the study visit to sign an updated informed consent form version.

Mitigation plan: The site staff will follow their approved consent process and remain in compliance with local EC/IRB and national laws and regulations. Remote consent will be allowed if it has been approved by the local EC/IRB. The consent process will be documented and confirmed by normal consent procedure at the earliest opportunity.

d) The safety of trial participants is important and testing of COVID-19 infection will be based on local clinical guidelines for testing based on signs/symptoms and or suspected exposure to COVID-19.

Mitigation Plan: If subject becomes infected with COVID-19 while on study, please inform the Contract Research Organization and Gilead immediately. If test results are positive for COVID-19, consider discontinuing or interrupt idelalisib until patient has clinically recovered. Discuss with the medical monitor prior to resuming study drug or if subject becomes COVID-19 negative.

COVID-19 infections including asymptomatic infections or positive tests for COVID-19, should have this recorded as an AE. Any AEs attributed to COVID treatments should also be recorded in the electronic data capture, regardless of causality.

4) Protocol and monitoring compliance:

a) Protocol deviations may occur, in case scheduled visits cannot occur as planned per protocol.

Mitigation plan: If it is not possible to complete a required procedure, an unscheduled visit should be conducted as soon as possible when conditions allow. The situation should be recorded and explained as a protocol deviation. Any missed subject visits or deviation to the protocol due to the pandemic must be reported in the eCRF and described in the

clinical study report. Any virtual study visits that are conducted in lieu of clinic visits due to the pandemic will be documented as a protocol deviation related to the pandemic.

b) Study monitors may be unable to carry out source data review or source data verification (SDV), or study drug accountability or assess protocol and Good Clinical Practice compliance. This may lead to delays in SDV, an increase in protocol deviations, or under reporting of AEs.

Mitigation plan: The study monitor is to remain in close communication with the site to ensure data entry and query resolution. Remote SDV may be arranged if allowed. The study monitor is to reference the Clinical Management Plan for guidance on how to conduct a remote monitoring visit. The study staff is to save and document all relevant communication in the study files. The status of sites that cannot accept monitoring visits and/or subjects on site, must be tracked centrally and updated on a regular basis.

5) Missing data and data integrity:

a) There may be an increased amount of missing data due to subjects missing visits/assessments. This could have an impact on the analysis and the interpretation of clinical trial data.

Mitigation plan: Implications of a pandemic on methodological aspects for the study will be thoroughly assessed and documented, and relevant actions will be taken as appropriate (ie, modification of the statistical analysis plan) and in compliance with Regulatory Authorities' guidance. Overall, the clinical study report will describe the impact of the pandemic on the interpretability of study data.

Risks will be assessed continuously, and temporary measures will be implemented to mitigate these risks as part of a mitigation plan, as described above. These measures will be communicated to the relevant stakeholders as appropriate and are intended to provide alternate methods that will ensure the evaluation and assessment of the safety of subjects who are enrolled in this study.

Since these potential risks are considered mitigated with the implementation of these measures, the expected benefit-risk assessment of idelalisib in study subjects remains unchanged.