GILEAD

CLINICAL STUDY PROTOCOL

Study Title:	A Phase 2, Open-Label Study Evaluating the Efficacy, Safety, Tolerability, and Pharmacodynamics of GS-9973 in Subjects with Relapsed or Refractory Hematologic Malignancies
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404
IND No.:	116416
Clinical Trials.gov Identifier:	NCT01799889
EudraCT No.	2013-001845-15
Indication:	Chronic Lymphocytic Leukemia and non-Hodgkin Lymphomas
Protocol ID:	GS-US-339-0102
Gilead Sciences Medical Monitor:	Name: PPD Telephone: PPD E-mail: PPD
Protocol Version/Date:	Original: 19 November 2012 Amendment 1: 11 January 2013 Amendment 2: 04 June 2013 Amendment 3: 04 November 2013 Amendment 4: 20 December 2013 Amendment 5: 06 June 2014 Amendment 6: 03 August 2015 Amendment 7: 13 November 2015 Amendment 8: 31 March 2017

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PROTOCOL SYNOPSIS
Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404

Study Title:	A Phase 2, Open-Label Study Evaluating the Efficacy, Safety, Tolerability, and Pharmacodynamics of GS-9973 in Subjects with Relapsed or Refractory Hematologic Malignancies
IND Number:	116416
Study Centers Planned:	Multiple centers in North America
Objectives:	The primary objective of this study is: • To evaluate the efficacy of GS-9973 in subjects with relapsed or refractory hematologic malignancies The secondary objectives of this study are: • To evaluate the safety and tolerability of GS-9973 in subjects with relapsed or refractory hematologic malignancies • To evaluate GS-9973 exposures in subjects with relapsed or refractory hematologic malignancies
Study Design:	Phase 2, open-label study evaluating the efficacy, safety and tolerability of GS-9973 administered twice daily (BID) over multiple 28-day cycles in subjects with relapsed or refractory hematologic malignancies. Historically the study planned to investigate 5 cohorts of Entospletinib in subjects with an chronic lymphocytic leukemia (CLL), mantle cell lymphoma (MCL), diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL), and a fifth cohort consisting of the non-FL indolent non-Hodgkin lymphomas (iNHL), ie, subjects with Lymphoplasmacytoid Lymphoma/ Waldenström macroglobulinemia (LPL/WM), Small Lymphocytic Lymphoma (SLL), or Marginal Zone Lymphoma (MZL), with a mono-methanesulfonate salt at 800 mg bid of the original mono-mesylate (MM) formulation. After completion of enrollment of the original CLL cohort the study was amended to include the addition of 3 CLL cohorts (1 dose finding prior BCR naïve), 2 prior BCR exposure [1 prior BTK inhibitor, and 1 prior PI3K inhibitor]); all 3 additional cohorts receive a new formulation of GS-9973 designated spray dried dispersion [GS-9973 SDD]. The SDD formulation had greater bioavilability and lesser drug-drug interactions (no H2 and reduce PPI). As of protocol amendment 8, subjects receiving GS-9973 MM formulation will be transitioned to the GS-9973 SDD formulation (Section 5.3.5).

The 2 CLL cohorts with prior B-Cell receptor (BCR) exposure enroll based on the most recent progression followed BCR-exposure. The BCR naïve patients cohort designated as CLL dose ranging cohort are randomly assigned to one of 3 doses evaluating 100 mg, 200 mg and 400 mg (200 mg x 2) BID dosing of GS-9973 SDD.

Cohort	Dose (BID)*	formulation
CLL	800mg Amendment 8: 400mg	MM Amendment 8: SDD
MCL	800mg Amendment 8: 400mg	MM Amendment 8: SDD
DLBCL	800mg Amendment 8: 400mg	MM Amendment 8: SDD
FL	800 mg Amendment 8: 400mg	MM Amendment 8: SDD
Other iNHL	800mg Amendment 8: 400mg	MM Amendment 8: SDD
CLL prior BCR inhibitor naïve	400mg 200mg 100mg	SDD SDD SDD
CLL Prior BTK inhibitor	400mg	SDD
CLL Prior PI3K inhibitor	400mg	SDD

*Note 800mg of MM is PK/PD equivalent of 400 mg SDD

For subjects with MCL, DLBCL, FL, CLL (except for the CLL dose ranging cohort), a Bayesian, continuous data review, which will be conducted independently, will be used to update the estimates of progression-free survival (PFS) rates at 16 weeks (CLL after BCR targeted therapy, MCL and DLBCL) or 24 weeks (CLL and FL), assessing the efficacy once each subject's primary endpoint becomes available for a cohort. Because it consists of 3 different histologies, accrual to the 'non-FL iNHL' cohort will continue to a maximum of 45 subjects without interim review. The continuous data review for MCL, DLBCL, FL and CLL cohorts (except for the CLL dose ranging cohort) will be conducted independently. Futility assessment will begin when the first eligible 10 subjects' primary endpoints become available.

Given the initial activity seen in the CLL cohort, which was treated with the original formulation, and improved PK of the new formulation, exploration of lower doses will be pursued in the 3 CLL cohorts {Sharman 2015}. Subjects who are treated at lower doses of GS-9973

SDD may have their dose escalated up to 400 mg (200 mg x 2) BID, if after 8 weeks there is less stable disease or at the time of disease progression, if the investigator feels it is in the subject's best interest.

Up to 40 subjects will be studied in each cohort of MCL, DLBCL, FL and CLL, up to 45 subjects will be enrolled in the non-FL iNHL cohort; up to 60 subjects will be enrolled in each cohort of CLL dose ranging, CLL prior BTK inhibitor exposure and CLL prior PI3K inhibitor exposure).

In the BCR targeted therapies cohorts, subjects who have progressed will be enrolled to either simple progression (Non-Richter's) or transformation (Richter's) to Richter's or Richter's-like disease. A biopsy is not required but encouraged if there is a clinical concern of possible transformation. In each BCR targeted therapies sub-cohort a) progression (Non- Richter's) or b) transformation (Richter's), a separate futility assessment will occur after the first 10 subjects are accrued in each sub-cohort. Thereafter, continuous data review may be conducted when a new primary endpoint becomes available.

- If the futility criterion is not met, subsequent subjects will be enrolled until a total number of 20 (Richter's) or 40 (Non-Richter's) subjects per cohort. The CLL subjects who were previously treated with BCR inhibitors will be recruited for a cohort dosed at 400 mg twice daily (BID) of GS-9973 SDD.
- The sponsor may consider terminating enrollment to that cohort, taking into account efficacy, drug exposure data, and subtype (for DLBCL) unless there are subjects who remain on treatment and have not yet reached 16 weeks (CLL who have failed prior BCR therapy, MCL and DLBCL) or 24 weeks (CLL and FL). In this case, enrollment will be suspended until the next on-going subject primary endpoint becomes available and another data review is conducted. If, after review of all available subjects, the futility boundary has still been crossed and low drug exposure or subtype (DLBCL) does not explain the lack of activity, enrollment to that malignancy will be terminated

Number of Subjects Planned:	185 to 385
Target Population:	Subjects with relapsed or refractory hematologic malignancies
Duration of Treatment:	Until progression of disease, unacceptable toxicity, or withdrawal of consent
Safety Review:	Safety data will be reviewed continuously during the course of the study.

Main Diagnosis and Eligibility Criteria:

(see Protocol for Details)

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
   a) Diagnosis of B-cell iNHL, DLBCL, MCL (mantle cell, nodal, diffuse or blastoid), or CLL, as documented by medical records and with histology based on criteria established by the World Health Organization. If the subject has DLBCL, subtyping is required. Submission of 15 unstained slides is required for subtyping if the subtype is not already known. Subjects for whom tissue is not available but the subtype is already known may be included if pathology report including the subtype is provided.
   b) If the subject has iNHL, the lymph node histology report confirms 1 of the following subtypes:
      i) FL Grade 1, 2, or 3a
      ii) SLL (ie, SLL/CLL histology with an absolute lymphocyte count of $< 5 \times 10^9$/L at diagnosis and on Screening laboratory assessment performed within 35 days prior to the start of study drug administration)
      iii) LPL/WM
      iv) MZL (splenic, nodal, or extranodal)
2) **For institutions that have Phase 3 or Phase 4 protocols studying idelalisib (Zydelig)**: subjects with malignancies being studied in these protocols must be a screen failure in the respective idelalisib protocol
3) Prior treatment for lymphoid malignancy and requiring treatment for progressive disease. Criteria for progressive disease is established Cheson criteria for NHL and by IWCLL criteria for CLL, and for LPL/WM patients per Update on Recommendations for Assessing Response from the Third International Workshop onWaldenström's Macroglobulinemia
4) (see Section 4 for details)
   a) Subjects with denovo DLBCL for whom there is no curative option with conventional treatment
   b) If the subject has MCL, iNHL, or BCR based therapy naïve CLL, the prior treatment must be comprised of at least 1 of the following:
      i) regimen containing a therapeutic antibody administered for ≥ 2 doses of antibody treatment
      ii) regimen containing ≥ 1 cytotoxic agent administered for ≥ 2 cycles of cytotoxic treatment

iii) regimen containing yttrium^{90}-ibritumomab tiuxetan or iodine^{131}-tositumomab

iv) experimental therapy as part of a clinical trial protocol

c) The previously BCR treated patients will be limited to subjects with CLL (other BCR targeted therapies may be accepted after approval of the medical monitor) only in the context of this cohort are Richter's transformation eligible.

i) CLL subjects whom have had more than 1 BCR targeted therapy will be enrolled into the cohort of the most recent treatment ibrutinib or idelalisib received prior to progression.

5) Presence of radiographically measurable progressive disease as defined using Cheson criteria for NHL, and iNHL and by IWCLL criteria for CLL; lymphadenopathy or extranodal lymphoid malignancy (defined as the presence of ≥ 1 lesion that measures ≥ 2.0 cm in the longest diameter [LD] and ≥ 1.0 cm in the longest perpendicular diameter [LPD] as assessed by CT or MRI) ;

a) Subjects with LPL/WM who do not have radiographically measurable progressive disease must have a monoclonal serum IgM ≥ 2x ULN, as verified by serum protein electrophoresis (SPEP) and with lymphoplasmacytic marrow involvement are eligible. LPL/WM enrollment is limited to those sites which have cryoglobulin analysis capabilities

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

7) Karnofsky performance status of ≥ 60

8) Life expectancy of at least 3 months

9) Required screening laboratory data (within 5 weeks prior to administration of study drug) as shown in the table below.
Note: Confirmation should be considered for out-of-range values to determine if the abnormality is real or artifactual. Values used for screening must be obtained within the screening period and should be the most recent measurement obtained. Subjects with any degree of neutropenia, thrombocytopenia, or anemia with documentation that it is due to malignancy may enroll.

Required Screening Laboratory Values

Organ System	Parameter	Required Value
Hematopoietic	ANC	≥ 0.5 x 10^9/L
	Platelets	≥ 50 x 10^9/L
	Hemoglobin	≥ 80 g/L (8.0 g/dL)
Hepatic	Serum total bilirubin	≤ 1.5 x ULN (unless elevated due to Gilbert's syndrome or hemolysis)
	Serum ALT	≤ 2.5 x ULN
	Serum AST	
Renal	Serum creatinine OR Estimated creatinine clearance	< 1.5 x ULN OR ≥ 60 ml/min as calculated by the Cockroft-Gault method
Coagulation	INR[a]	< 1.7
Pregnancy	β-HCG[b]	Negative
Infection	HIV	Negative HIV antibody
	HBV	Negative HBsAg and negative HBc antibody
	HCV	Negative viral RNA (if HCV antibody is positive)

a For subjects on anticoagulative therapy the required value is < 3.0
b For women of childbearing potential only; serum β-HCG must be negative during screening and serum β-HCG or urine dipstick pregnancy test must be negative at start of study therapy

10) For female subjects of childbearing potential, willingness to abstain from heterosexual intercourse or use a protocol-recommended method of contraception from the screening visit throughout the study treatment period and for 30 days following the last dose of GS-9973. ***See Section 7.11 for information regarding recommendations for contraception***

11) For male subjects of childbearing potential having intercourse with females of childbearing potential, willingness to abstain from heterosexual intercourse or use a protocol-recommended method of contraception from the start of study drug throughout the study treatment period and for 90 days following the last dose of GS-9973or GS-9973 SDD and to refrain from sperm donation from the start of study drug throughout the study treatment period and for 90 days following the last dose of GS-9973 or GS-9973 SDD . ***See Section 7.11 for information regarding recommendations for contraception***

12) Willingness to comply with scheduled visits, drug administration plan, imaging studies, laboratory tests, other study procedures, and study restrictions

13) Have the ability to understand and sign a written informed consent form, which must be obtained prior to initiation of any study specific procedures

Exclusion Criteria

Subjects who meet any of the following exclusion criteria are not eligible for study participation:

1) Known histological transformation from iNHL or CLL to an aggressive form of NHL (ie, Richter transformation) except if the CLL patient is enrolling in the BCR previously treated cohort (see inclusion 3C). Subjects who have a history of iNHL or CLL with a subsequent confirmed high grade histology will be considered transformed for purpose of this study and excluded if they are not part of the CLL BCR previously treated cohort. ***Note: Biopsy documentation of the absence or presence of transformation is not required***
2) Known active central nervous system or leptomeningeal lymphoma. Note: Central nervous system imaging is only required in subjects with suspected lymphomatous involvement based on symptoms or signs
3) Presence of known intermediate- or high-grade myelodysplastic syndrome (ie, subjects are excluded who have ≥ 5 bone marrow blasts; karotypic abnormalities other than normal, Y deletion, 5q deletion, or 20q deletion; or ≥ 2 lineages of cytopenias) {Greenberg 1997}.
4) Because they are likely to interfere with GS-9973 absorption, current therapy with agents that reduce gastric acidity, including but not limited to proton pump inhibitors
5) History of any prior lymphoid malignancy other than registrational histology except for CLL subjects with prior BCR therapy
    a) Subjects with diagnoses other than CLL who were previously treated with a BCR inhibitor are excluded from this study.
6) History of 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 start of study therapy, other adequately treated Stage 1 or 2 cancer currently in complete remission, or any other cancer that has been in complete remission for ≥ 5 years

7) Evidence of ongoing systemic bacterial, fungal, or viral infection at the time of start of study drug. Note: Subjects with localized fungal infections of skin or nails are eligible.
8) Ongoing, drug-induced liver injury, chronic active Hepatitis C Virus (HCV), HIV, chronic active Hepatitis B Virus (HBV), alcoholic liver disease, non-alcoholic steatohepatitis, primary biliary cirrhosis, ongoing extrahepatic obstruction caused by cholelithiasis, cirrhosis of the liver, or portal hypertension
9) Ongoing (within the past 6 weeks) hepatic encephalopathy
10) Ongoing drug-induced pneumonitis
11) Ongoing inflammatory bowel disease
12) Ongoing alcohol or drug addiction as determined by investigator
13) Pregnancy or breastfeeding
14) History of prior allogeneic bone marrow progenitor cell or solid organ transplantation
15) Ongoing immunosuppressive therapy, including systemic corticosteroids for treatment of lymphoid malignancy. Concurrent use of methotrexate for rheumatologic conditions is permitted. ***Note: Subjects may use topical, enteric, or inhaled corticosteroids as therapy for comorbid conditions and systemic steroids for autoimmune anemia and/or thrombocytopenia. Ongoing use of low-dose systemic corticosteroids (≤ 5 mg/day of methylprednisolone or equivalent) for rheumatologic conditions is permitted. During study participation, subjects may receive systemic or other corticosteroids needed for treatment-emergent comorbid conditions. See next entry for exception related to steroids***
16) Concurrent participation in an investigational drug trial with therapeutic intent defined as prior study therapy within 21 days prior to study drug. Exception: the cohorts with relapsed CLL following BCR pathway inhibitors whom in the opinion of the investigators cannot have a 21 day washout period ≥5 half lives washout period will be allowed, along with up to 20 mg of prednisone at the start of the trial, for control of disease related symptoms, with planned taper over 2 weeks
17) Any other prior or ongoing condition that, in the opinion of the investigator, could adversely affect the safety of the subject or impair the assessment of study results

Cytokine and Chemokines:	To assess the biological effects of GS-9973, cytokine and chemokine levels will be measured in all assessable subjects.

Resistance Mechanisms:	To assess changes in the molecular signature of malignant cells following treatment with GS-9973 or GS-9973 SDD to explore mechanisms of resistance to GS-9973 or GS-9973 SDD, blood for circulating tumor cells will be obtained from SLL, CLL, and MCL subjects.
Test Product, Dose, and Mode of Administration:	Oral administration of up to 800 mg GS-9973 BID, taken fasting in the NHL and iNHL subsets. Oral administration of 100 mg, 200 mg or 400 mg (200 mg x 2) GS-9973 SDD BID, taken fasting in the CLL dose ranging cohort of subjects not previously treated with BTK inhibitors or PI3K inhibitors. Oral administration of 400 mg (200 mg x 2) GS-9973 SDD BID, taken fasting in the CLL cohorts of subjects refractory to or intolerant of BTK inhibitors or PI3K inhibitors
Criteria for Evaluation:	**Primary Endpoint** • Progression free survival (PFS) rate at 16 weeks (CLL after BCR targeted therapy, MCL and DLBCL) or 24 weeks (CLL and iNHL). PFS is defined as the interval from the first dose of GS-9973 or GS-9973 SDD to the earlier of the first documentation of definitive disease progression or death from any cause. **Secondary Endpoints** • Safety: all abnormal laboratory data, and AEs. Safety will be assessed by grading of laboratory values and AEs according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 • Tumor response: objective response rate (ORR), duration of response (DOR), and time to response (TTR). **Exploratory Endpoints** [redacted] CCI [redacted]

Statistical Methods: Analysis Methods

A Bayesian, continuous data review approach using Beta-Binomial model will be used to update the estimates of progression-free survival (PFS) rates at 16 weeks (CLL after BCR targeted therapy, MCL and DLBCL) or 24 weeks (CLL and FL), assessing the efficacy once each subject's primary endpoint becomes available for a malignancy. The response is defined as subject not experiencing progression or death by week 16 (CLL after BCR targeted therapy, MCL and DLBCL) and 24 (CLL and FL). In this Beta-Binomial model, a binomial likelihood for the data and a conjugate Beta (0.5, 1.5) prior distribution for response rate θ are assumed. Statistical inference and decision-making will be based on the posterior distribution of response rate θ, which is a Beta distribution with parameters $x+0.5$ and $n-x+1.5$, where x is the observed number of subjects who achieve the response and n is the total number of subjects who have a response result for a given malignancy.

For the primary analysis of the primary efficacy endpoint, PFS will be described using Kaplan-Meier methods in the full analysis set. Medians, ranges, the proportion of subjects who are progression-free at Week 16 (CLL after BCR targeted therapy, MCL and DLBCL) and 24 (CLL and iNHL) will be presented. Data for subjects with iNHL will be presented by histologic subtype (ie, FL, SLL, LPL, and MZL). Data in the CLL prior BTK inhibitor exposed and prior PI3K inhibitor exposed cohort will be represented separately. Data in the CLL dose ranging cohort will be presented by dose level. The findings of the Independent Review Committee (IRC) will be considered primary for analyses of PFS. The full analysis set includes all subjects who receive ≥ 1 dose of GS-9973/GS-9973 SDD.

Sample Size Calculation

With the decision rule employed, and assuming that enrollment will be terminated once the futility criterion is met, a sample size of 40 subjects in a cohort gives this design a high probability (~84%) of claiming futility when the true response rate is low (0.1). When the true response rate is high (0.5), this design has a low probability (0.15%) of claiming futility.

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

GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

°C	degrees Celsius
°F	degrees Fahrenheit
ADR	adverse drug reaction
AE	adverse event
ALC	absolute lymphocyte count
ALT	alanine aminotransferase
AM	Morning
ANC	absolute neutrophil count
AST	aspartate aminotransferase
ATP	adenosine triphosphate
AUC	area under the concentration versus time curve
AUC_{tau}	area under the plasma concentration versus time curve over the dosing interval (tau)
BAT	Basophil Activation Test
BCR	B-cell receptor
BCRP	breast cancer resistance protein (ABCG2 gene product)
BID	bis in die (twice a day)
BLNK	B-cell linker protein
BTK	bruton tyrosine kinase
BUN	blood urea nitrogen
C_{max}	maximum observed concentration of drug
CFR	(United States) Code of Federal Regulations
CI	confidence interval
CLL	chronic lymphocytic leukemia
cm/s	centimeter per second
CR	complete response
CRO	contract research organization
CT	computed tomography
CTA	clinical trial application
CTC	circulating tumor cells
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DLBCL	diffuse large B-cell lymphoma
DICOM	Digital Imaging and Communication in Medicine
dL	Deciliter
DNA	deoxyribonucleic acid
DOR	duration of response
DSPH	Drug Safety and Public Health
EC	ethics committee

EC50	50% effective inhibitory concentration
ECG	Electrocardiogram
eCRF	electronic case report form(s)
EDC	electronic data capture
EOS	end of study
EU	European
FDA	(United States) Food and Drug Administration
FL	follicular lymphoma
FLIPI	follicular lymphoma international prognostic index
FNA	Fine needle aspirate
FSH	follicle stimulating hormone
g	Gram
GCP	Good Clinical Practice (Guidelines)
G-CSF	granulocyte colony-stimulating factor
GM-CSF	granulocyte-macrophage colony-stimulating factor
GSI	Gilead Sciences, Inc.
h, hr	Hour
HBc	hepatitis B core
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
β-HCG	beta human chorionic gonadotropin
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HL	Hodgkin lymphoma
IB	investigator's brochure
IC	immune-complex
IC_{50}	concentration necessary to achieve 50% inhibition of target
ICF	informed consent form
ICH	International Conference on Harmonisation
ID	Identification
IEC	independent ethics committee
IFE	immunofixation electrophoresis
IND	Investigational New Drug (Application)
iNHL	indolent non-Hodgkin lymphoma
IRB	institutional review board
IRC	independent review committee
ITAM	immunoreceptor tyrosine-based activation motifs
IWCLL	International Workshop on Chronic Lymphocytic Leukemia
IxRS	Interactive Voice/Web Response System
K_2-EDTA	potassium-ethylenediaminetetraacetic acid

kg	Kilogram
L	Liter
LD	longest diameter
LDH	lactate dehydrogenase
LPD	longest perpendicular diameter
LPL	lymphoplasmacytoid lymphoma
LVD	longest vertical dimension
MAPK	mitogen-activated protein kinase
MCL	mantle cell lymphoma
mg	Milligram
mL	Milliliter
mm	Millimeter
MMRM	mixed model for repeated measures
MR	minor response
MRI	magnetic resonance imaging
mTOR	mammalian target of rapamycin
MZL	marginal zone lymphoma
NCI	National Cancer Institute
ND	no disease
NE	not evaluable
ng	Nanogram
NHL	non-Hodgkin lymphoma
nM	Nanomolar
NOAEL	no observable adverse effect level
OATP1B1/3	organic anion transporting polypeptide 1B1/3 (SLCO1B1/3 gene products)
OS	overall survival
ORR	objective response rate
PBMC	peripheral blood mononuclear cells
PD	progressive disease
PET	positron-emission tomography
PFS	progression-free survival
P-gp	multidrug resistance protein 1 (P-glycoprotein, MDR1, ABCB1 gene product)
PI	principal investigator
PI3K	phosphatidylinositol 3-kinase
PK	pharmacokinetic(s)
PM	evening
PPD	product of the perpendicular diameters
PR	partial response
pSYK	phospho-spleen tyrosine kinase
QD	once-daily

REB	research ethics board
RNA	ribonucleic acid
SD	stable disease
SDD	spray-dried dispersion tablets
STD	standard deviation
SADR	serious adverse drug reaction
SAE	serious adverse event
SLL	small lymphocytic lymphoma
SOP	standard operating procedure
SPD	sum of the products
SPEP	serum protein electrophoresis
SUSAR	Suspected Unexpected Serious Adverse Reaction
SYK	spleen tyrosine kinase
T_{max}	time (observed time point) of C_{max}
$t_{½}$	an estimate of the terminal elimination half-life of the drug, calculated by dividing the natural log of 2 by the terminal elimination rate constant (λ_z)
TNF	tumour necrosis factor
TNF-α	tumour necrosis factor-α
TTF	time to treatment failure
TTR	time to response
UGT1A1	uridine 5'-diphospho-glucuronosyltransferase 1 family, polypeptide A1
ULN	upper limit of the normal range
US	United States
VGPR	very good partial response
WHO	World Health Organization
WM	Waldenström macroglobulinemia
αIgM	anti-IgM
β	population mean slope
λ_z	terminal elimination rate constant, estimated by linear regression of the terminal elimination phase of the concentration of drug versus time curve

1. INTRODUCTION

1.1. Background

B-cell lymphoid malignancies comprise the most common hematologic malignancies {Surveillance Epidemiology and End Results (SEER) Program 2011}. These cancers arise in organs such as blood, bone marrow, spleen, and liver from the accumulation of monoclonal B lymphocytes in lymph nodes. Among the variants of these cancers are non-Hodgkin lymphomas (NHL) – including diffuse large B-cell lymphoma (DLBCL), indolent non-Hodgkin lymphoma (iNHL), and mantle cell lymphoma (MCL) - and chronic lymphocytic leukemia (CLL). These disorders are characterized by lymphadenopathy that is frequently disturbing for patients and can sometimes induce life-threatening organ dysfunction; patients may also have constitutional symptoms (fevers, night sweats, and/or weight loss) and fatigue {Diehl 2004, Dighiero 2008, Salles 2007, Williams 2010}.

The goal of therapy for these diseases is to induce tumor regression and delay tumor progression in order to control disease-related complications and potentially extend life. Patients who require treatment are commonly given chemotherapeutic and/or immunotherapeutic agents {Eichhorst 2010, Friedberg 2011, Gribben 2011, Jost 2007, Wierda 2010, Zelenetz 2011}. Among patients with iNHL, CLL, and MCL, front-line combination therapies can be effective in providing durable remissions {Hallek 2010, Lenz 2005, Recher 2011, Santoro 1987, Schulz 2007}. In DLBCL such front-line regimens can be curative in the majority of patients {Kuruvilla 2009, Recher 2011, Santoro 1987}. However, most treated patients with iNHL, CLL, and MCL will eventually experience disease relapse. Some patients with DLBCL or NHL will experience recurrent disease even with initial induction therapy and later salvage therapy. For any of these cancers, further sequential therapies are given in an attempt to control disease manifestations. However, progressive resistance to treatment develops despite the use of agents with differing mechanisms of action. Patients with relapsed progressive disease have a poor prognosis; median survival for these groups of patients is generally ≤ 2 years {Di Bella 2010, Friedberg 2011, Goy 2005, Hess 2009, Keating 2002a, Moskowitz 2009, Wierda 2010}. Agents with novel mechanisms of action are needed to offer additional treatment options for patients with lymphoid malignancies who are experiencing progressive lymphadenopathy or symptoms due to disease progression.

1.2. Chronic Lymphocytic Leukemia

CLL is a neoplasm resulting from the progressive accumulation of functionally incompetent monoclonal B lymphocytes in blood, bone marrow, lymph nodes, spleen, and liver {Dighiero 2008}. CLL constitutes the most commonly occurring leukemia in Europe and the United States {Sant 2010, Surveillance Epidemiology and End Results (SEER) Program 2011}. While some patients never require treatment, many will need therapy for disfiguring or obstructing lymphadenopathy, debilitating constitutional B symptoms (fevers, night sweats, fatigue, weight loss) {Sant 2010}, or recurrent cytopenias and infections {Keating 2002b, Perkins 2002}. CLL is largely a disease of the elderly; at diagnosis, 70% of patients are ≥ 65 years of age and the median age is 72 years {Surveillance Epidemiology and End Results (SEER) Program 2011}.

In younger and relatively healthy patients with CLL, chemoimmunotherapy regimens that include the anti-CD20 monoclonal antibody, rituximab, are commonly employed to control disease manifestations {Gribben 2011}. However, in elderly patients or in those with comorbid conditions, such regimens are associated with less efficacy and greater toxicity {Eichhorst 2009, Tam 2008, Thurmes 2008}.

These health constraints in older or compromised patients have prompted noncytotoxic approaches to therapy. Alternative immunotherapeutics have been developed, such as monoclonal antibodies: alemtuzumab (targeting CD52 on mature lymphocytes) {Keating 2002a}or ofatumumab (inhibiting CD20 necessary for early stage B-cell activation) {Wierda 2010}. At the time the disease is first identified, ~25% of patients with CLL do not meet conventional criteria for participation in clinical studies containing cytotoxic agents {Thurmes 2008, Zelenetz 2011}, or ofatumumab (inhibiting CD20 necessary for early stage B-cell activation) {Wierda 2010}. Addition of high-dose methylprednisone to rituximab can extend median PFS to 12 months, but this combination is commonly associated with severe hyperglycemia and frequent life-threatening or fatal infections {Bowen 2007, Zelenetz 2011}. While single-agent rituximab use can offer palliative benefit with good tolerability in some patients with previously treated CLL, tumor control is not lasting, especially in patients with bulky adenopathy {Gentile 2010}. New noncytotoxic, well-tolerated, and convenient therapies are needed in order to enhance and prolong tumor control in patients with comorbid conditions. Richter's syndrome (RS) is characterized by the development of high-grade non-Hodgkin's lymphoma (NHL) in a patient with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma, associated with typically unfavorable clinical response to standard therapies.

1.3. Non-Hodgkin Lymphoma

NHL comprises a diverse group of malignancies arising in lymphoid tissue. The neoplasms represent a progressive clonal expansion of B cells, T cells, or natural killer cells arising from the accumulation of genetic lesions that affect proto-oncogenes or tumor suppressor genes, resulting in cell immortalization {Friedberg 2008b}. A B-cell origin is documented in 80% to 85% of cases. Chromosomal translocations that reduce lymphocyte apoptosis are typical. In the United States, NHL is the sixth most common cancer; it is estimated that during the year 2010, ~66,000 new patients were diagnosed and ~20,000 patients died of NHL {Jemal 2010}. In Europe, it is anticipated that ~74,000 new cases occurred, leading to ~31,000 deaths {Ferlay 2010}. As mortality due to other causes has declined, the incidence of lymphoma has increased; almost exclusively a disease of adulthood, diagnosis most commonly occurs in patients between 50 and 70 years of age {Friedberg 2008b}

Of the B-cell NHLs, 4 subtypes (follicular lymphoma [FL], small lymphocytic lymphoma [SLL], lymphoplasmacytoid lymphoma [LPL] [also known as Waldenström macroglobulinemia], and marginal zone lymphoma [MZL]) have differing pathological features {Campo 2011}, but are generally included among those characterized as indolent in nature because they have common clinical presentations, show a slowly progressive natural history, and generally require similar treatments {Pileri 2004}. Patients with iNHL typically present with painless and gradually progressive peripheral adenopathy {Friedberg 2008b, Salles 2007}. Some patients may experience primary extra-nodal involvement or B symptoms (ie, temperature > 38°C, night sweats, or weight loss > 10% from baseline within 6 months). As the disease advances, fatigue

is often noted. Bone marrow involvement is common and may result in cytopenias. Patients with iNHL commonly have splenomegaly and hepatomegaly. Elevated serum levels of lactate dehydrogenase (LDH) reflect general tumor burden. Abnormal transaminase values may indicate hepatic involvement or chronic lymphoma-related inflammation.

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 2010}. Positron-emission tomography (PET) is sometimes used to identify occult sites of disease in patients who appear to have localized iNHL based on CT and bone marrow biopsy {Seam 2007}. The Ann Arbor staging system categorizes patients by whether they have a single site of involvement (Stage 1), ≥ 2 sites of disease on the same side of the diaphragm (Stage 2), sites of disease on both side of the diaphragm (Stage 3), or disseminated disease (Stage 4) {Lister 1989}. 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 LDH above normal. Patients are scored as low risk (≤ 1 factor), intermediate risk (2 factors), or high risk (≥ 3 factors). While a protracted course is common in iNHL, life expectancy varies by the types of factors represented in the FLIPI score; median survival is ~4 to > 10 years from diagnosis depending upon such prognostic characteristics {Solal-Celigny 2004}. Patients are at risk of transformation of iNHL to aggressive DLBCL at a rate of 2% to 3% per year {Bastion 1997, Montoto 2007}; such transformation is usually associated with a poor clinical outcome.

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 2010}. Watchful waiting is possible but patients are generally treated if they have lymphoma-related symptoms or end-organ dysfunction, bulky disease, cytopenias, persistent disease progression, or a strong preference for immediate therapy. 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 the progression-free interval.

For older or infirm patients, single-agent rituximab or alkylating agents such as cyclophosphamide or chlorambucil may be administered {Zelenetz 2010}. Most patients receive chemoimmunotherapy in which rituximab is given together with cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) {Buske 2009, Hiddemann 2005} or cyclophosphamide, vincristine, prednisone (R-CVP) {Marcus 2005, Marcus 2008}. Alternative regimens include rituximab with the alkylating agent, bendamustine, or fludarabine- or mitoxantrone-based therapy that may include an alkylating agent {Herold 2007, Zinzani 2004}. Meta-analysis data from randomized trials indicate that the addition of rituximab to chemotherapy not only improves tumor control, but also extends overall survival (OS) in previously untreated patients {Schulz 2007}. Based on controlled trials, rituximab has formal regulatory approval for use as a component of front-line chemoimmunotherapy of iNHL. In addition, maintenance or consolidation therapy with rituximab or yttrium^{90}-ibritumomab tiuxetan has been shown to prolong PFS {Morschhauser 2008, van Oers 2006, Vidal 2009}.

Despite the chemosensitivity of iNHL to front-line therapy, existing systemic therapies for iNHL are not typically curative. Some patients will be refractory to initial therapy and most patients will ultimately relapse. Several treatments have received regulatory approval in the United States and/or Europe for treatment of refractory or relapsed disease, including rituximab, yttrium^{90}-ibritumomab tiuxetan, iodine^{131}-tositumomab, and bendamustine. The principal support for use in these settings has comprised non-randomized single-arm trials that have focused on documenting treatment-related tumor responses in populations of patients with disease that has become resistant to either alkylating agents or rituximab immunotherapy {Friedberg 2008a, Kaminski 2005, Maloney 1997, Vose 2000, Witzig 2002}. Yttrium^{90}-ibritumomab tiuxetan and iodine^{131}-tositumomab use has been limited because of medical and practical restrictions on the use of these agents; these drugs are contraindicated in patients with substantial pre-existing myelotoxicity or bone marrow lymphoma involvement. The use of these agents is constrained by the complexity of dosimetry calculations and drug preparation, the need for administration by specifically trained clinicians at specially equipped sites, protracted Grade 3-4 hematological toxicity that commonly results in infectious complications and impedes subsequent therapy, and long-term risks of hypothyroidism.

Other clinical approaches that have been reported include alkylating agent monotherapy, alkylating-agent-based combination therapy (CVP, CHOP), or administration of purine analogues (fludarabine, cladribine) {Zelenetz 2010}. Similarly, patients have also been treated with bortezomib or lenalidomide {Di Bella 2010, Goy 2009, Witzig 2002}.

Due to the acquisition of drug resistance, progressively less activity is observed, particularly when administering previously used therapies; the disease course is characterized by a continuous decrease in the quality and the duration of tumor response with each subsequent treatment {Salles 2007}. Patients face the burden of cumulative myelosuppressive toxicity, a problem that has been documented with fludarabine {Janikova 2009} and commonly limits continued therapy with cytotoxic agents such as bendamustine {Friedberg 2008a, Kahl 2010}. In addition, there is a well-documented risk of myelodysplasia and/or acute myelogenous leukemia associated with use of alkylating agents, doxorubicin, fludarabine, iodine^{131}-tositumomab, and Y^{90}-ibritumomab tiuxetan {Friedberg 2006}. Consequently, new therapies with novel mechanisms of action are needed to offer additional treatment options for patients with iNHL. The need is especially acute in those patients whose disease has become refractory to existing chemoimmunotherapeutic approaches, particularly in those with lymphoma that is refractory to both rituximab and alkylating agents.

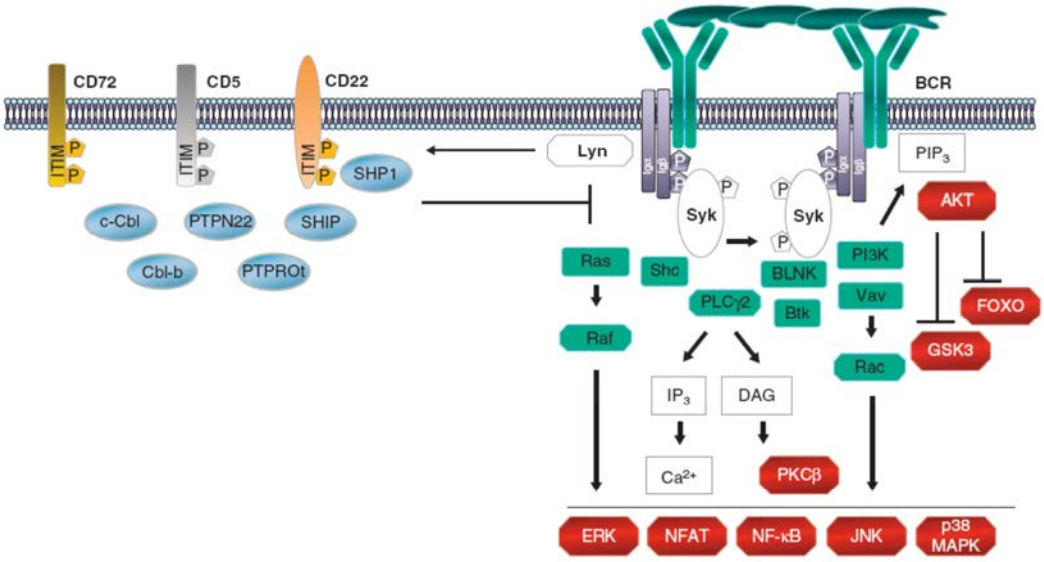
1.4. Spleen Tyrosine Kinase

1.4.1. Spleen Tyrosine Kinase in Hematologic Malignancies

Spleen tyrosine kinase (SYK) is a non-receptor cytoplasmic tyrosine kinase that is primarily expressed in cells of hematopoietic lineage. It is an important mediator of immunoreceptor signaling in macrophages, neutrophils, mast cells, and B cells. SYK contains 2 adjacent SH2 domains that bind to immunoreceptor tyrosine-based activation motifs (ITAMs) to autophosphorylate and activate the enzyme. This allows SYK to phosphorylate its specific substrates including other enzymes and adaptor proteins, orchestrating a complex series of cellular responses such as cell proliferation, differentiation, survival, and phagocytosis.

Recent studies have suggested a role for the dysregulation of the tyrosine kinase SYK in B-cell malignancies. SYK is expressed in B-cells and is essentially involved in multiple signal transduction pathways downstream of the B-cell receptor (BCR). In this process, SYK trans-autophosphorylates, and activates effector molecules such as PLCγ, PI3K, and mitogen-activated protein kinase (MAPK) and their associated signaling pathways, to induce a variety of responses including: proliferation, survival, differentiation, anergy, and apoptosis (Figure 1-1). In B-cells, GS-9973 effectively blocks BCR-mediated activation and proliferation (data on file). Additionally, the BCR can deliver antigen-independent signals that have also been postulated to require SYK activity. Both antigen-dependent and independent signals have been implicated in the pathogenesis of several common B-cell malignancies, including CLL, DLBCL, FL, MCL, MZL, and B-lineage acute lymphoblastic leukemia (B-ALL) {Efremov 2011}. As a result, inhibitors of SYK activity are an attractive therapeutic option for hematopoietic B-cell lymphomas and other NHL varieties where SYK inhibition would prevent B-cell receptor-mediated signaling and therefore the uncontrolled growth of lymphoma cells.

Figure 1-1. Positive and Negative Regulators of Antigen-dependent BCR Signaling



Source: {Efremov 2011}

1.4.2. Clinical Experience in Hematologic Malignancies treated with SYK Inhibitors

Positive results have been reported from a Phase 2 clinical trial with the putative SYK inhibitor fostamatinib showing objective anti-tumor responses in CLL and DLBCL patients {Friedberg 2010}. These responses occurred despite off target toxicities that limited drug exposure. GS-9973 is a highly selective inhibitor of SYK and hence has the potential for an improved efficacy and tolerability profile in patients with hematologic malignancies (see Section 1.6).

1.4.3. Mechanism of action of SYK Target Inhibition

1.4.3.1. Circulating Tumor Cells (CTC)

Determining levels of target inhibition is a key element in the evaluation of new agents. In vitro experiments demonstrated that treatment of malignant B-cell lines with GS-9973 inhibited the phosphorylation of key BCR signaling related nodes including pSYK, pBTK, pAKT, pS6, pMEK, pERK, and pNF-kB among others. GS-9973 inhibited basophil activation and SYK phosphorylation in peripheral blood from healthy subjects receiving the study drug (see Section 1.5.5). We have detected pSYK expression in circulating lymphocytes from patients with CLL that could be inhibited by in vitro exposure to GS-9973. Circulating malignant cells were also identified from 2 of 5 patients with MCL but evaluation of pSYK expression in these cells has not yet been carried out.

1.4.3.2. Systemic Cytokines and Chemokines

In hematologic malignancies, disease-related perturbations in inflammatory status can be clinically overt and patients often develop bothersome B symptoms (fevers, night sweats, and weight loss) that are characteristic of excessive systemic inflammation. In addition, chemokines and cytokines that are markers of aberrant B-cell trafficking or perturbations in inflammation are over-expressed by malignant and stromal cells and circulate in plasma. In vitro cell culture experiments demonstrated that SYK inhibition by GS-9973 or GS-9973 SDD reduced the levels of the secreted chemokines and cytokines (CCL3, CCL4, and others) by DLBCL, MCL, and B-ALL cell lines. To evaluate the downstream effects of SYK inhibition by GS-9973 in Study GS-US-339-0102 we will assess the baseline and on treatment systemic levels of disease related cytokines and chemokines. These will include at a minimum, but will not be limited to: CCL3, CCL4, CXCL12, CXCL13, tumor necrosis factor-α, and C-reactive protein.

1.4.3.3. Hypothesis-driven assessments

The hypothesis-driven molecular mechanisms of resistance to GS-9973 to be tested in this study are based on established molecular drivers behind each of the specific hematologic malignancies investigated and their known interactions with SYK signaling pathways (see Figure 1-1). These hypotheses fall into the following categories:

1.4.3.3.1. p110α gene amplification and/or other PI3K pathway related alterations

Circulating tumor cells from subjects with SLL, CLL, or MCL will be assessed at a minimum for pSYK, pBtk, pPLCγ1/2, pErk, pP38, pAkt, pS6, pNFκB, and PTEN and PI3K mutations and amplifications to evaluate changes in protein expression and in signaling pathway activation that may have developed in resistant tumors. To increase our understanding of GS-9973 activity and tumor resistance, other key signaling nodes may also be evaluated for alterations that are related to malignant B-cell proliferation, migration, and survival.

1.4.3.3.2. Mutations/alterations in pathways related to apoptosis evasion (eg bcl-2, TP53, ATM) in the presence of high c-myc expression/signaling

Once tumor cells are forced to re-enter the circulation through the inhibition of BCR and chemokine signaling by GS-9973, they cannot receive trophic and anti-apoptotic stimuli from the solid tissue microenvironment (including BAFF) to sustain their survival in the presence of high c-myc expression. Thus, it is possible that the presence of tumor cell clones with additional mutations/alterations (eg, ATM, TP53, bcl-2, etc.) that suppress apoptosis in the presence of high c-myc signaling may lead to clonal escape and repopulation of the lymph nodes.

We will assess circulating tumor cells for mutations/alterations of ATM, TP53, bcl-2 and other proteins that are directly related to apoptosis regulation.

1.4.3.3.3. ZAP-70 over-expression

Hypermutation of IgVH genes is a prognostic marker for outcome in CLL: patients with unmutated IgVH genes have shorter survival rates and more rapid disease progression than patients with mutated IgVH genes. A small subset of genes was found differentially expressed in VH-mutated versus unmutated cases. ZAP-70 was found to be the most discriminating gene between the 2 subsets of CLL, with higher expression of ZAP-70 present in unmutated IgVH B-CLL cells.

Importantly, defects in BCR signaling in SYK-deficient B cells can be reconstituted by the expression of ZAP-70. This raises the important question whether SYK inhibition alone will be sufficient to suppress BCR signaling in ZAP-70 over-expressing cells. To address this question in this study we will assess ZAP-70 protein levels and P38 phosphorylation status in circulating tumor cells.

1.4.3.4. Genomics Assessments

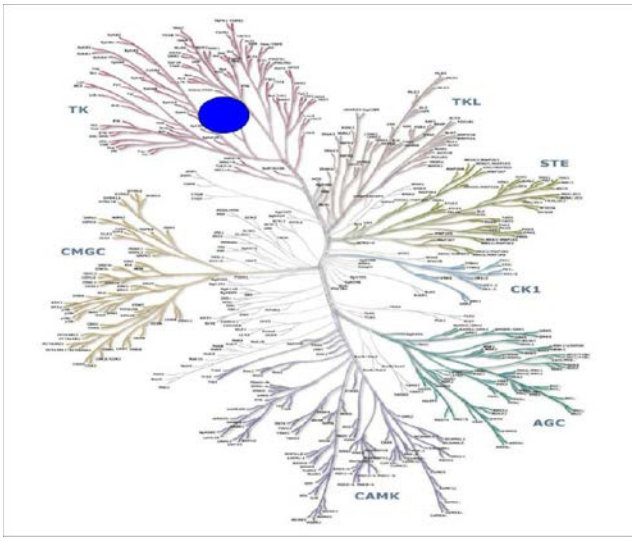
In addition to the specific biomarker assessments outlined above, a genomics approach will also be used to generate new leads for better understanding of resistance to BCR targeted agents in B-cell malignancies. These new leads may increase our understanding of the mechanisms of resistance and pathophysiology of B-cell malignancies for informing the design of future rational drug combinations.

1.5. GS-9973

1.5.1. Nonclinical Pharmacology

GS-9973 is an adenosine triphosphate (ATP) competitive inhibitor of SYK with an IC_{50} of 8.5 ± 3.6 nM. GS-9973 binds in the ATP pocket of the SYK active site and disrupts the kinase activity of the enzyme. Kinase selectivity profiling showed a > 14-fold selectivity of GS-9973 for SYK versus 359 nonmutant kinases. Furthermore, there was < 50% binding of GS-9973 at 1 μM to any of a panel of 67 ion channels, transporters, and receptors. Therefore, GS-9973 demonstrated at least 14-fold selectivity against a total of 426 biological targets tested (See Figure 1-2).

Figure 1-2. GS-9973 Kinome Scan



The cellular activity of GS-9973 was evaluated in 2 anti-IgM (αIgM)-stimulated CD86 expression assays in human peripheral and mouse splenic B-cells. GS-9973 potently inhibited αIgM-stimulated CD86 expression with a mean EC_{50} of 125.0 ± 78.2 nM and 94.5 ± 19.6 nM in human peripheral and murine splenic B-cells, respectively. Additionally, GS-9973 was evaluated in vitro in an FcεRI-triggered αIgE-stimulated β–hexosaminidase release assay in mouse bone marrow derived mast cell (BMMC) cultures. GS-9973 inhibited the FcεRI-stimulated hexosaminidase release into the media with a mean EC_{50} of 159.3 ± 14.8 nM. GS-9973 was evaluated in vitro in an immune-complex (IC)-stimulated TNFα release assay in primary human monocytes. GS-9973 inhibited the IC-stimulated TNFα release with a mean EC_{50} of 147.0 ± 15.6 nM. These data support the concept that SYK inhibition blocks with similar potency, B-cell, αIgE, and Fcγ receptor signaling in vitro.

The potency of GS-9973 was evaluated in human whole blood by an αIgE-stimulated CD63 expression assay in human basophils. GS-9973 inhibited the αIgE-stimulated CD63 expression on $CD123^{+}/HLADR^{-}$ human basophils with a mean EC_{50} ± SD of 0.387 ± 0.220 μM. Additionally, GS-9973 inhibited the pervanadate-induced autophosphorylation of SYK at phospho-SYK(Y_{525}) in whole blood with a mean EC_{50} ± SD of 830 ± 560 nM. These data support the concept that SYK inhibition can block SYK activity in whole blood as determined by functional inhibition of CD63 expression and direct target inhibition of SYK autophosphorylation.

GS-9973 was evaluated in a battery of safety pharmacology studies. The IC_{50} for the inhibitory effect of GS-9973 on human ether-à-go-go-related gene (hERG) potassium current in vitro was estimated to be greater than 1 μM. Because GS-9973 is 97.3% protein bound in human plasma and the total plasma concentrations of GS-9973 are in the 1 to 3 micromolar range, with a corresponding range of free GS-9973 of 27 to 81 nM, it is unlikely that a clinically relevant

effect on QT interval would occur. No GS-9973-related effects were noted on neurological or respiratory function in rats at doses up to 1000 mg/kg, the highest dose tested. In dogs, GS-9973 caused small increases in heart rates (during the night cycle) at doses ≥ 15 mg/kg but had no effects on electrocardiograms (ECGs) or blood pressure at up to 150 mg/kg, the highest dose evaluated.

GS-9973 is a potent and selective SYK inhibitor and disrupts the kinase activity of the enzyme. No significant off target or adverse pharmacological effects of clinical relevance were noted in preclinical evaluations.

Further information on the nonclinical pharmacology of GS-9973 is available in the Investigator's Brochure.

1.5.2. Nonclinical Drug Metabolism and Pharmacokinetics

Despite high plasma protein binding, GS-9973 had a moderate volume of distribution, close to that of total body water. The systemic clearance was low in rats, moderate in dogs, and moderate to high in monkeys.

Single-day dose escalation of GS-9973 administered orally to rats, dogs, and monkeys showed a less than dose proportional increase in GS-9973 systemic exposure in all species over the dose ranges tested.

Consistent with the moderate to high bioavailability seen in nonclinical species, GS-9973 showed high forward permeability across Caco-2 monolayers and low potential for efflux.

GS-9973 showed good metabolic stability with human hepatic material in vitro. In humans, clearance through metabolism is therefore expected to be low. The primary routes of metabolism of GS-9973 involved oxidative opening of the morpholine ring as well as further oxidation or conjugation. In humans, CYP2C9, CYP3A, and CYP1A2 were shown to oxidize GS-9973.

Metabolism followed by biliary excretion is likely to be the major route of elimination of GS-9973 and its metabolites, as < 5% of the radiolabeled dose administered orally to rats was recovered in urine.

GS-9973 will be unlikely to cause clinical drug interactions through inhibition of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A. GS-9973 is an inhibitor of UGT1A1 and may transiently inhibit UGT1A1 activity in vivo at the expected clinical concentrations. The effect may be mitigated by the high plasma protein binding of GS-9973 (> 97%).

GS-9973 is an inhibitor of the uptake transporters OATP1B1 and OATP1B3 as well as the efflux transporters P-gp and BCRP with an IC_{50} value of approximately 2 μM for each of these transporters. GS-9973 may affect the activity of these transporters in vivo at the expected clinical concentrations and could transiently affect the disposition of other drugs. The high plasma protein binding of GS-9973 (> 97%) may mitigate some of the potential drug-drug interactions at clinically relevant doses.

GS-9973 is not expected to be a clinically relevant inducer of cytochrome P450 enzymes CYP1A2 or CYP3A4 and other drug metabolizing enzymes or transporters through activation of either the aryl hydrocarbon receptor (AhR) or pregnane-X-receptor (PXR).

Further information on the nonclinical drug metabolism and pharmacokinetics of GS-9973 is available in the Investigator's Brochure.

1.5.3. Nonclinical Toxicology

GS-9973 was well tolerated in single-dose studies at doses of 1000 mg/kg in dogs and cynomolgus monkeys. GS-9973 was well tolerated in rats for 14 days up to 1000 mg/kg/day and for 4 weeks at 50 mg/kg/day. In dogs, GS-9973 was well tolerated for 7 days at 50 mg/kg/day and at 10 mg/kg/day for 4 weeks. GS-9973 was well-tolerated in cynomolgus monkeys for 14 days or 13 weeks at 100 mg/kg/day, the highest dose tested. The highest feasible dose in cynomolgus monkeys was 100 mg/kg/day, as no increase in exposure was achieved by higher doses.

The target organ(s) of toxicity identified in rats was the duodenum, and in rabbits and dogs were predominantly the gastrointestinal tract and lymphoid organs. No target organs were identified in the cynomolgus monkey. Additional organs potentially affected in individual dogs at higher doses included gallbladder, pancreas (rabbits and dogs), urinary bladder, and epididymis. The gastrointestinal tract toxicity presented as enteropathy in the duodenum in rats, and hemorrhage and/or inflammation in rabbits and dogs. Gastrointestinal tract toxicity in rats, rabbits, and dogs was associated with decreased food consumption and/or decreased body weight or body weight gain. However, decreased food consumption and body weight changes also occurred in rabbits and dogs at doses below those which caused histological evidence of gastrointestinal toxicity.

Assessments in the clinical program will include monitoring for signs and symptoms of gastrointestinal distress and changes in clinical pathology parameters (changes in red cell mass, neutrophils, lymphocytes, liver enzymes, and total and indirect bilirubin) that could occur after GS-9973 administration. Because evidence of lymphoid tissue depletion was noted in rabbits and dogs at high doses, clinical assessments will also include monitoring for signs and symptoms of infection.

Increases in total and/or indirect bilirubin in rats, rabbits, and dogs at ≥ 30 mg/kg/day may have been due to the inhibition of the enzyme UGT1A1. GS-9973 inhibits this uridine glucuronyl transferase enzyme with an IC_{50} of 2 μM. This enzyme is involved in glucuronidation of bilirubin, and inhibitors of UGT1A1 have the potential to produce increased levels of total and indirect (unconjugated) bilirubin in the circulation {Zhang 2005}. As no histological evidence of hepatobiliary toxicity was noted concurrently with bilirubin increases in GS-9973-treated rats or dogs, and GS-9973 levels above the IC_{50} for UGT1A1 were achieved in serum, this seems a plausible mechanism for the noted increases in bilirubin.

Hemorrhage and/or sinus erythrocytosis in lymph nodes with decreases in red cell mass in individual animals was noted in rabbits and dogs, but not rats or cynomolgus monkeys. Although the mechanism for these changes is not clear, SYK deficiency in rodents and rodents with SYK-deficient bone marrow have been associated with hemorrhage, the latter in the presence of normal bleeding times and therefore suggesting normal platelet function {Turner 2000}. No evidence of altered coagulation parameters were noted at any dose level in the GS-9973 nonclinical studies and no biologically relevant effects were noted in an in vitro study of platelet aggregation. Other inhibitors of SYK have been found to have no effect on platelet function at efficacious dose levels in patients with rheumatoid arthritis as determined by ex vivo assays, and similarly, SYK inhibition has not been found to affect bleeding time in rodents {Braselmann 2006}. Evidence of hemorrhage and/or decreases in red cell mass will be monitored during clinical studies.

Adverse effects on lymphoid tissues including spleen, lymph nodes, and/or the thymus were noted in rabbits and dogs, but not in rats or cynomolgus monkeys, despite higher exposures achieved in both the rat and monkey. Recently published data demonstrated that species-specific lymphoid changes can occur in dogs but not rats, cynomolgus monkeys, or humans treated with small molecule kinase inhibitors that inhibit pathways that overlap with SYK signaling pathways; rabbits were not evaluated {Morris 2010}. Lymphoid toxicity occurs in dogs treated with p38α MAPK inhibitors, but not in rats or cynomolgus monkeys despite higher exposure levels achieved in these species. There has not been evidence of significant immunotoxicity in numerous clinical trials with p38α MAPK inhibitors. The relevance of the findings in rabbits and dogs to humans is unknown.

GS-9973 was negative in the bacterial mutation, in vitro chromosomal aberration, and rat micronucleus assays. GS-9973 can be considered non-genotoxic. Dose-range finding embryo-fetal developmental toxicity studies have been completed in the rat and rabbit. Maternal toxicity was demonstrated by dose-dependent decreases in the body weight gains of the dams. Dose-dependent developmental findings included increased incidence of early and late fetal resorptions at 500 mg/kg/day (rat only) and reduced fetal weights (500 and ≥ 15 mg/kg/day; rat and rabbit, respectively) which correlated with the maternal toxicity.

Further information on the nonclinical toxicology of GS-9973 is available in the Investigator's Brochure.

1.5.4. Clinical Trials of GS-9973

GS-9973 has been studied in single and multiple ascending dose studies in 304 healthy subjects, 7 subjects with rheumatoid arthritis who were on stable doses of methotrexate, 80 subjects with CLL and 95 subjects with NHL. Of these subjects, 460 received GS-9973 and 26 received placebo. In pharmacokinetics studies at steady state in healthy subjects, GS-9973 was well tolerated when given in a fasted state for 7 days at doses of 25, 75, 200, 600, 900, and 1200 mg BID (GS-US245-0101) and when given in a fed state for 6 days at doses of 100 and 900 mg BID (GS-US-245-0106), for 4 days at doses of 200 and 600 mg BID (GS-US-339-0101), and at 1200 mg BID for 5 days (GS-US-339-0109) see Figure 1-3 and Figure 1-4. Exposure, as measured by AUC and maximum concentration C_{max}, did not increase appreciably at doses of 600 mg and above under fasted condition.

To provide a margin for inter-patient variability, a dose of 900 mg BID was chosen for the study of subjects with rheumatoid arthritis receiving stable doses of methotrexate in Study GS-US-245-0101. A dose of 900 mg GS-9973 BID was given in a fasted state for 26 days in 7 subjects. The median AUC_{tau} in these subjects was similar to that of the healthy subjects. In general, this dose was well tolerated. One subject developed reversible, Grade 2 alkaline phosphatase and transaminase elevations starting 7 days after her last dose of GS-9973, concurrent with new onset of a bronchopneumonia. One other subject reported not feeling well and experienced hot flashes, fever, shivers, rash, headache, dizziness, and fainting 1 day after her last dose of GS-9973 with reversible Grade 1 alkaline phosphatase and Grade 3 transaminase elevations which peaked 1 week later. While these events are potentially confounded by concurrent illnesses, hepatic enzymes will be closely monitored during this study.

Consistent with the known inhibition of UGT1A1 by GS-9973, 8 of the 178 healthy subjects developed asymptomatic indirect bilirubin elevations (6 Grade 1, 1 Grade 2 and 1 Grade 3) that resolved following discontinuation of the drug. Three of the 7 subjects with rheumatoid arthritis who received GS-9973 for 26 days developed asymptomatic indirect bilirubin elevations (2 Grade 1, 1 Grade 3) which improved despite continued dosing.

Figure 1-3. GS-9973 AUC_{tau} at Steady State

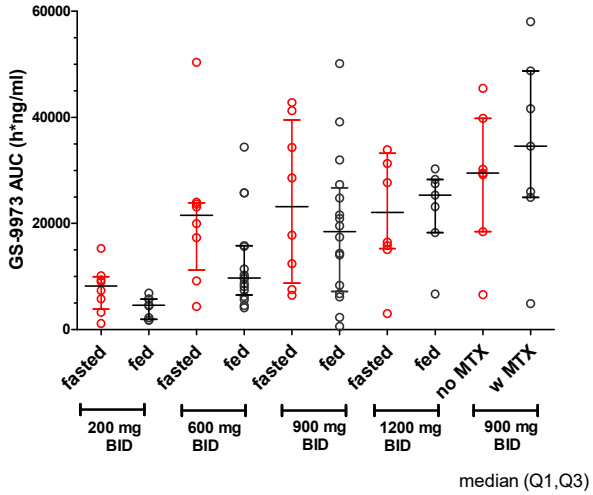
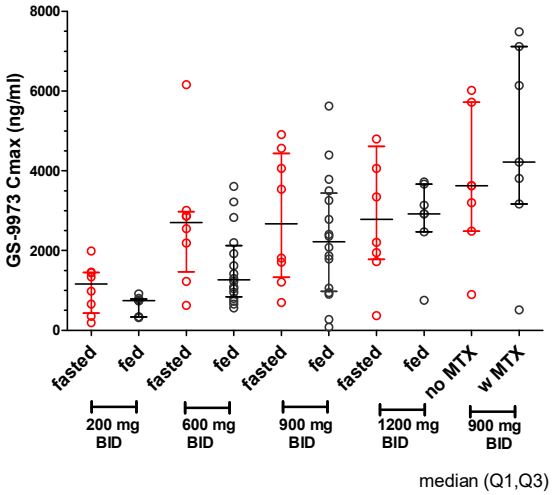


Figure 1-4. GS-9973 C_{max} at Steady State



1.5.5. GS-9973 Target Drug Concentrations

In healthy subjects, SYK inhibition, as measured by the ability to inhibit CD63 basophil activation and pSYK activation was evaluated in peripheral blood mononuclear cells (PBMCs) at multiple doses and schedules of GS-9973. Plasma GS-9973 exposures were correlated with the degree of SYK inhibition. GS-9973 inhibited SYK as measured by ex-vivo basophil activation (see Figure 1-5) and pSYK (see Figure 1-6) assays with EC_{70}s of 923 and 275 ng/mL, respectively.

Figure 1-5. Inhibition of Basophil Activation

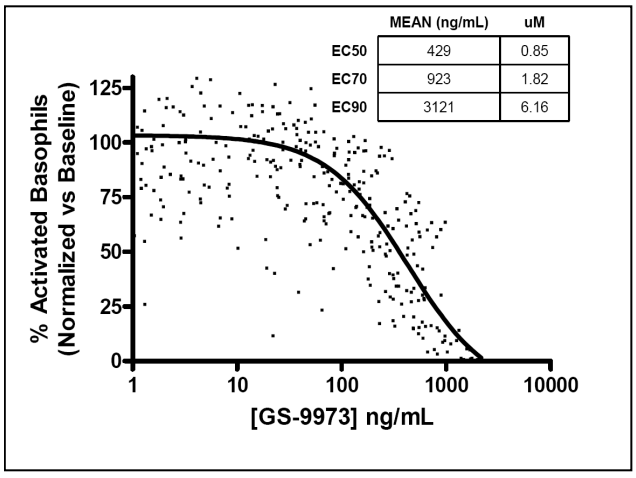
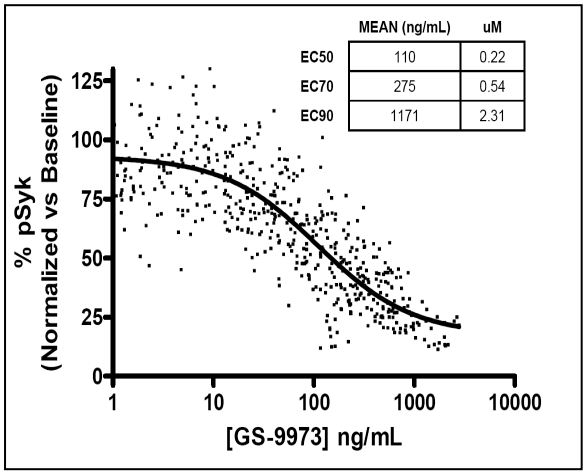


Figure 1-6. Inhibition of pSYK



1.5.6. Use of Concomitant Medications with GS-9973

In vivo and in vitro data indicates that GS-9973 is a substrate of CYP2C9 and CYP3A. Co-administration of CYP2C9 or CYP3A inducers may decrease GS-9973 exposure. As such, co-administration of strong CYP3A and CYP2C9 inducers and moderate CYP2C9 inducers are prohibited in this study. Caution should be exercised when co-administering drugs that are moderate or strong inhibitors of CYP2C9 (eg fluconazole, voriconazole or amiodarone) as they may increase GS-9973 exposure. Administration of strong CYP3A and CYP2C9 inducers or moderate CYP2C9 inducers should be avoided for 2 weeks prior to study drug administration.

Studies in healthy volunteers have demonstrated a significant reduction in GS-9973 exposure when proton pump inhibitors are co-administered. Therefore, proton pump inhibitors are prohibited in combination with GS-9973. Use of a proton pump inhibitor should be avoided for 1 week prior to study drug administration. Examples of medicines that are prohibited in this study are provided in Section 5.5.1 Table 5-5.

In vitro data indicates that GS-9973 has the potential to inhibit several transporters and the metabolizing enzyme UGT1A1, which may affect the plasma concentrations of substrates of these transporters and/or enzyme. Caution should be exercised when co-administering medications that are transported by OATP1B1, OATP1B3, MATE1, P-gp and BCRP or metabolized by UGT1A1; dose adjustment or switching to an alternative medication may be necessary if clinically indicated.

In a study in healthy volunteers, GS-9973 400 mg twice daily (SDD formulation) increased rosuvastatin exposure by approximately 3.8-fold, which may theoretically increase the risk of rhabdomyolysis. In reviewing the safety of subjects whom have received a statin with GS-9973 there have been no reports of rhabdomyolysis nor a different adverse events profile, but in the interest of caution, restrictions apply to the use of HMG-CoA reductase inhibitors with GS-9973 in this study. These restrictions are included in Section 5.5.1.

1.6. Rationale for the Current Study and Design

The purpose of this study is to obtain data on the efficacy, safety, tolerability, and pharmacodynamics of GS-9973 in subjects with hematologic malignancies. The initial malignancies to be studied are CLL, iNHL, MCL, and DLBCL. A new spray dried dispersion (SDD) formulation is being introduced in the study known as GS-9973 SDD which has favorable PK and reduced DDI with proton pump inhibitors. Due to the improved bioavailability of the new formulation a dose ranging cohort will be introduced into the study in order to evaluate doses between 100 to 400 mg BID. As significant clinical activity was noted in the initial CLL cohort treated with GS-9973, the decision was made to increase the number of CLL subjects treated with GS-9973 SDD through the addition of 2 CLL cohorts consisting of patients who were previously treated with ibrutinib or idelalisib and whom had disease progression at a dose that will approximate the target coverage seen with GS-9973. A Bayesian approach will be used to establish boundary rules that identify progression-free survival (PFS) rates at 16 weeks (CLL after BCR targeted therapy, MCL and DLBCL) or 24 weeks (CLL and iNHL) that are not sufficiently promising to warrant further development (ie, < 20%). For each malignancy, if, after at least 10 subjects are evaluated for response, the observed PFS rate for a given malignancy crosses the futility boundary, further accrual to that malignancy may be terminated taking into account efficacy, drug exposure, and subtype (for DLBCL). Since the non-FL iNHL cohort of 45 subjects consists of 3 histologies (LPL, SLL, and MZL), a Bayesian interim analysis will not be applied to this cohort.

1.6.1. Rationale for the Dose Selection

As noted above, in fed and fasted healthy subjects, GS-9973 has been well tolerated for 4 to 7 days at up to 1200 mg BID. In these subjects, drug exposure, as measured by AUC at steady state, plateaued at doses ≥600 mg BID. Target coverage, as measured by basophil activation and pSYK inhibition was consistently achieved at this dose level (See Figure 1-5 and Figure 1-6). Further, 7 subjects with rheumatoid arthritis receiving stable doses of methotrexate tolerated GS 9973 at a dose of 900 mg BID for 26 days. To account for variability in exposure, the dose of GS-9973 to be evaluated initially in subjects with CLL, iNHL, MCL, and DLBCL is 800 mg BID under fasted conditions. As of protocol amendment 8, subjects receiving GS-9973 MM formulation will be transitioned to the GS-9973 SDD formulation (Section 5.3.5).

A PK study of the new bis-MSA spray-dried formulation evaluating dose-exposure demonstrated improved PK parameters and improved target coverage at trough. Given data from GS-US-339-0111, “Open-Label, Adaptive Study of Novel GS-9973 Tablet Formulations to Evaluate the Effect of Acid Reducing Agents and Food on GS-9973 Pharmacokinetics, and Relative Bioavailability of the Novel GS-9973 Tablet Formulations” the magnitude of GS-9973 exposure upon coadministration with omeprazole was less than reduction observed in Study GS-US-245 0106 of the original formulation. Even though the new formulation did not completely annul the DDI effect of a coadministered PPI agent, the interaction of GS-9973 new Formulation with an H2 receptor antagonist (H2RA) is not considered clinically meaningful

1.6.2. Rationale for Dose Exploration in GS-9973 Sensitive Malignancies

The GS-9973 dose of 800 mg BID was chosen to provide maximum drug exposure for subjects with malignant disease. As noted above, this dose and schedule resulted in consistent target coverage in normal subjects. However, it is possible that this dose and schedule results in drug exposure that exceeds what is required for maximum target coverage. If GS-9973 demonstrates promising anti-cancer activity in a cohort, exploration of lower doses may be required before further studies are pursued. If these 2 conditions are met, additional cohorts of 40 subjects with that malignancy may be studied to evaluate the safety profile, pharmacodynamic parameters and anti-tumor activity at lower GS-9973 doses. GS-9973 doses of 200 or 400 mg given once daily or BID will be studied in the additional cohort(s) and will be selected based upon the emerging pharmacodynamic, pharmacokinetic and anti-tumor data from the subjects already studied. Subjects who are treated at lower doses of GS-9973 should have their dose escalated up to 800 mg BID at the time of disease progression if the investigator feels it is in the subject's best interest. As of protocol amendment 8, subjects receiving GS-9973 MM formulation will be transitioned to the GS-9973 SDD formulation (Section 5.3.5).

Transaminase Elevations Following Treatment with GS-9973

ALT and AST elevations have occurred in 13 of 109 subjects evaluated on this study; all subjects received GS-9973 800 mg BID. The ALT elevations were generally higher than the AST elevations, consistent with a hepatic origin. The distribution of highest ALT elevations were 1 Grade 1, 0 Grade 2, 6 Grade 3 and 5 Grade 4. GS-9973 dosing was continued for Grade 1 and 2 elevations and these subjects did not develop Grade 3 or 4 transaminase elevations. Dosing was interrupted for Grades 3 and 4 elevations. In the 4 subjects for whom GS-9973 was interrupted, in each case the ALT and AST values were lower at the next determination and returned to Grade 1 or less after 7, 12 and 21 days (Grade 3's) and after 27 days (Grade 4). Two subjects were subsequently re-started on GS-9973 at 600 mg BID without recurrence of the ALT elevation. Based upon this experience, we have provided specific guidance in the protocol for the management of Grade 3 and 4 transaminase elevations.

1.7. Rationale for Amendment 5

1.7.1. Initial Clinical Experience with GS-9973 in Subjects with CLL

The CLL cohort for this study has completed accrual. The initial results were presented at the 2013 American Society of Hematology Annual Meeting {Sharman 2013}. The results were later updated in the GS-9973 Investigator's Brochure Fourth Edition dated 14-March-2014. GS-9973 was generally well tolerated; adverse events regardless of cause that occurred in more than 10% of subjects are listed in Table 1-1. Transient grade 3 or 4 transaminase elevations, which declined upon holding GS-9973, occurred in 11 of 109 (10.1%) of subjects. Four subjects were re-challenged and remain on study without recurrence of the transaminase elevation, 1 withdrew consent 1 developed a Grade 2 rash and went off study and the remaining 3 were waiting for resolution prior to re-challenge.

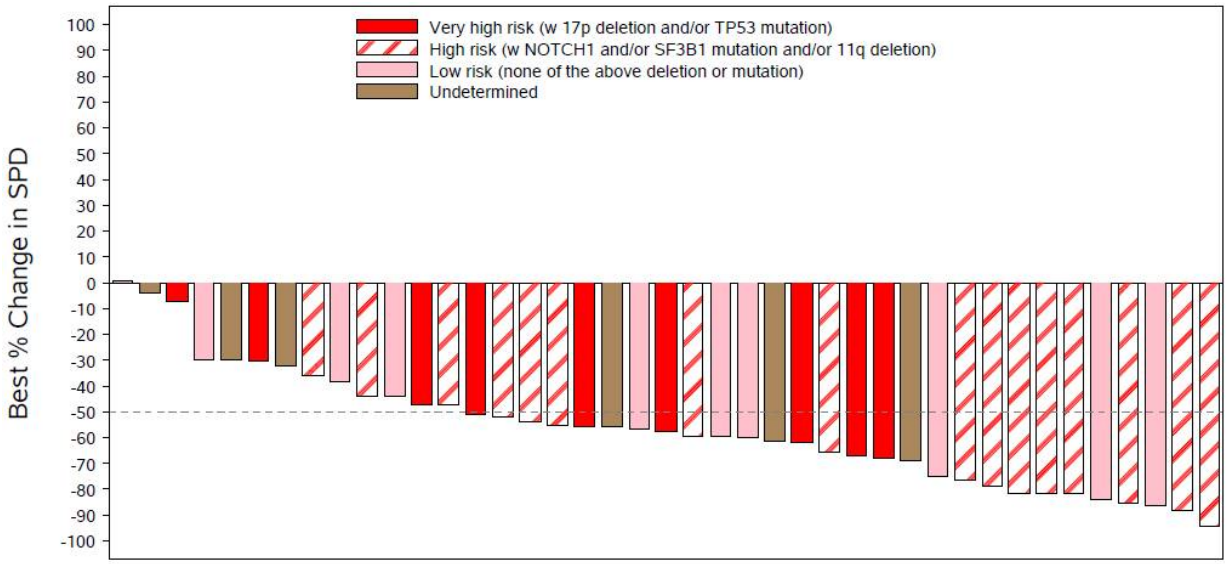
Table 1-1. GS-339-0102: Treatment-Emergent Non-hematologic Adverse Events Occurring in ≥ 10% of Subjects, N=109*

	Grade 1	Grade 2	Grade 3	Grade 4	All Grades
Any event					**106 (97.2%)**
Fatigue	20 (18.3%)	22 (20.2%)	9 (8.3%)		51 (46.8%)
Nausea	26 (23.9%)	10 (9.2%)	3 (2.8%)		40 (36.7%)
Diarrhoea	33 (30.3%)	5 (4.6%)	1 (0.9%)		39 (35.8%)
Decreased appetite	16 (14.7%)	9 (8.3%)			25 (22.9%)
Headache	21 (19.3%)	3 (2.8%)	1 (0.9%)		25 (22.9%)
Constipation	14 (12.8%)	8 (7.3%)	2 (1.8%)		24 (22%)
Dizziness	21 (19.3%)	1 (0.9%)			22 (20.2%)
Pyrexia	13 (11.9%)	7 (6.4%)	2 (1.8%)		22 (20.2%)
Cough	11 (10.1%)	5 (4.6%)	1 (0.9%)		17 (15.6%)
Oedema peripheral	12 (11%)	5 (4.6%)			17 (15.6%)
Insomnia	10 (9.2%)	5 (4.6%)			15 (13.8%)
Dyspepsia	6 (5.5%)	8 (7.3%)			14 (12.8%)
Vomiting	10 (9.2%)	2 (1.8%)	1 (0.9%)		14 (12.8%)
Dyspnoea	3 (2.8%)	4 (3.7%)	6 (5.5%)		13 (11.9%)
ALT increased	1 (0.9%)		6 (5.5%)	5 (4.6%)	12 (11%)
AST increased	1 (0.9%)	1 (0.9%)	7 (6.4%)	2 (1.8%)	11 (10.1%)

* Information in table is based on IB Edition 4

GS-9973 demonstrated promising results in subjects with CLL, producing a 68% nodal partial response (Figure 1-7).

Figure 1-7. GS-339-0102: Investigator Assessed Nodal Responses in CLL (n=41)



1.7.2. Rationale for addition of three CLL cohorts

1.7.2.1. CLL Subjects Whom are Intolerant, Develop Progressive Disease, or Transformation While Receiving Ibrutinib or Idelalisib

Ibrutinib is an inhibitor of Bruton's Tyrosine Kinase (BTK), a kinase that is closely associated with B-cell receptor signaling, that has reported an overall response rate of 71% and 2-year progression free survival of 75% in subjects with CLL {Byrd 2013}. Idelalisib is an inhibitor of PI3K-delta, a kinase that is also closely associated with B-cell receptor signaling. Idelalisib, when combined with rituximab, increased PFS and OS compared to rituximab alone in subjects previously treated CLL. This study was terminated at the first interim analysis due to the overwhelming activity of the combination arm and the results have recently been presented at the 2013 American Society of Hematology Annual Meeting {Furman 2013}. It is desirable to obtain preliminary data on the activity of GS-9973 in CLL subjects who have been previously treated with ibrutinib or idelalisib or other BCR targeted therapies whose disease has progressed. These subjects will be studied in 2 separate cohorts.

1.7.2.2. Study GS-US-339-0111 of GS-9973 New Formulation

GS-9973 Formulation

Among subjects treated with GS-9973 formulation 1 (N = 28), one subject (3.6%) reported an SAE of cholecystitis following treatment with GS-9973 plus famotidine. AEs resulting in study drug discontinuation were reported for 7 subjects (25.0%). Overall, 25 subjects (89.3%) reported an AE. The most common AEs were the following: headache (11 subjects, 39.3%); back pain and nausea (8 subjects each, 28.6%); diarrhea (6 subjects, 21.4%); alanine aminotransferase (ALT) increased, aspartate aminotransferase (AST) increased, constipation, and rash (4 subjects each, 14.3%); and

abdominal distension, abdominal pain, dizziness, pruritus, and vomiting (3 subjects each, 10.7%). Grade 3 AEs were reported for 2 subjects (7.1%) and included the following terms: cholecystitis, hyperbilirubinemia, idiosyncratic drug reaction, and pyrexia; no Grade 4 AEs were reported.

GS-9973 Formulation SDD

Among subjects treated with GS-9973 formulation 2 (N = 28), no subjects reported an SAE. AEs resulting in study drug discontinuation were reported for 3 subjects (10.7%). Overall, 19 subjects (67.9%) reported an AE. The most common AEs included the following: headache (11 subjects, 39.3%); back pain and nausea (6 subjects each, 21.4%); ALT increased, rash, and pruritus (4 subjects each, 14.3%); and AST increased and constipation (3 subjects each, 10.7%). No Grade 3 or 4 AEs were reported.

Laboratory Abnormalities seen in Study GS-US-339-0111

Study drug dosing was suspended and the study was terminated before Part B was initiated, because the protocol defined stopping rule of 3 or more subjects having a Grade 3 treatment emergent drug-related AE or laboratory abnormality was met. Seven of 28 subjects (25.0%) administered GS-9973, and 4 of 28 subjects (14.3%) administered GS-9973 SDD had Grade 3 laboratory abnormalities during Part A of the study. The most frequently reported Grade 3 laboratory abnormalities for subjects administered GS-9973 were blood in urine associated with menstrual flow (3 of 28 subjects, 10.7%), ALT increased (2 of 28 subjects, 7.1%), and bilirubin increased (2 of 28 subjects, 7.1%). For subjects administered GS-9973 SDD, the most frequently reported Grade 3 laboratory abnormalities were LDL cholesterol increased (2 of 28 subjects, 7.1%) and blood in urine associated with menstrual flow (2 of 28 subjects, 7.1%).

2. OBJECTIVES AND ENDPOINTS

2.1. Objectives

The primary objective of this study is:

- To evaluate the efficacy of GS-9973 in subjects with relapsed or refractory hematologic malignancies

The secondary objectives of this study are:

- To evaluate the safety and tolerability of GS-9973 in subjects with relapsed or refractory hematologic malignancies
- To evaluate GS-9973 exposures in subjects with relapsed or refractory hematologic malignancies

2.2. Endpoints

Primary Endpoints

- PFS rate at 16 weeks (CLL after BCR targeted therapy, MCL and DLBCL) or 24 weeks (CLL and iNHL) as established for each malignancy. PFS is defined as the interval from the first dose of GS-9973 to the earlier of the first documentation of definitive disease progression or death from any cause. The findings of the IRC will be considered primary for analyses of PFS rate.

Secondary Endpoints:

- Safety: abnormal laboratory data, adverse events (AEs) and treatment-emergent AEs. Safety will be assessed by grading of laboratory values and AEs according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

Efficacy:

- Objective response rate (ORR). ORR will be determined from the subjects' best response during GS-9973 therapy and will include complete response (CR) or partial response (PR) [or very good partial response (VGPR) or minor response (MR) for subjects with LPL/WM].
- Duration of response (DOR). DOR will be defined as time from the first response (CR or PR [or VGPR or MR for subjects with LPL/WM]) is achieved until the earlier of the first documentation of definitive disease progression or death from any cause.
- Time to response (TTR). TTR will be defined as time from the first dose of GS-9973 to the first time the response (CR or PR [or VGPR or MR for subjects with LPL/WM]) is achieved.

The findings of the IRC will be considered primary for analyses of secondary efficacy endpoints.

Exploratory Endpoints:

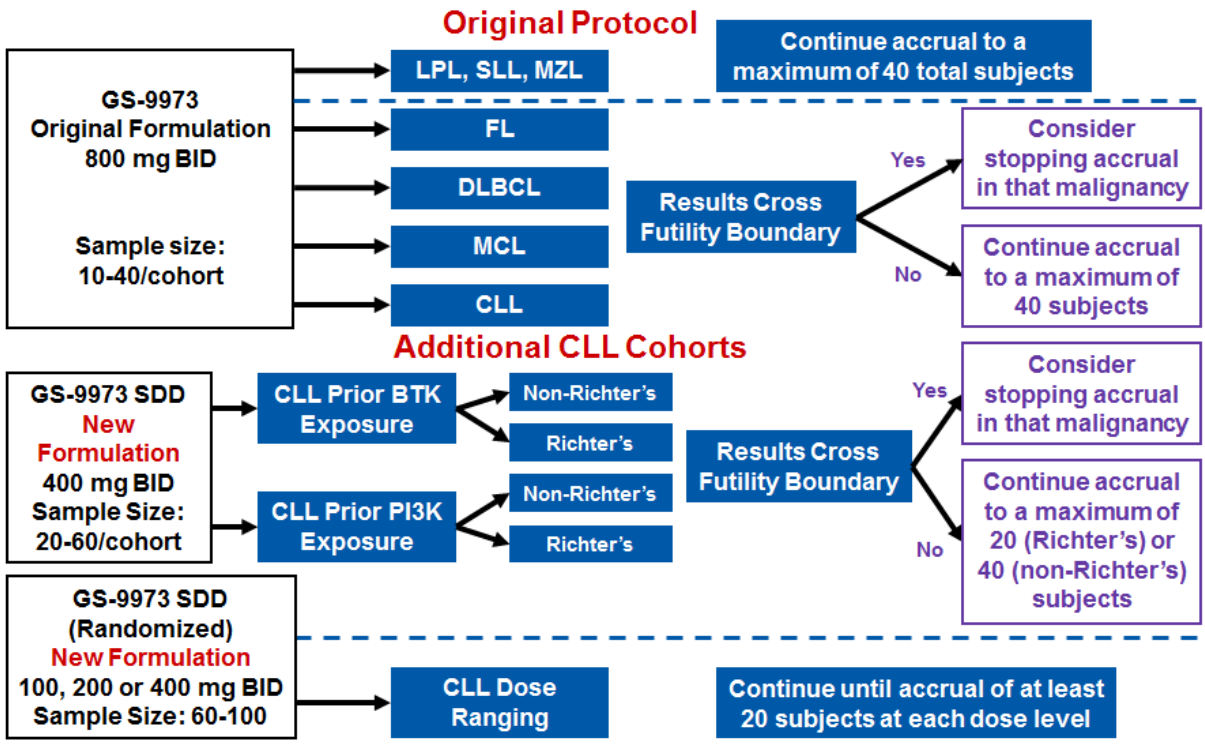
- [redacted]
- [redacted]

3. STUDY DESIGN

3.1. Overview

This protocol describes a Phase 2, open-label study evaluating the efficacy, safety, tolerability, pharmacokinetics and pharmacodynamics of GS-9973/GS-9973 SDD in subjects with relapsed or refractory hematologic malignancies. Eight separate cohorts consisting of subjects with CLL, iNHL, MCL, or DLBCL will be studied concurrently. Subjects with iNHL will be studied in 2 cohorts: 1 consisting of only subjects with FL and the other consisting of subjects with LPL/WM, SLL, and MZL. Two additional cohorts have been added to the study under amendment 4, consisting of subjects with CLL who have previously been treated with ibrutinib or idelalisib and now have progressive disease (CLL prior BTK inhibitor exposure and CLL prior PI3K inhibitor exposure, respectively). A dose ranging cohort consists of 100 mg, 200 mg and 400 mg (200 mg x 2) new formulation of GS-9973 SDD are added under amendment 5. (See Figure 3-1). As of protocol amendment 8, subjects receiving GS-9973 MM formulation will be transitioned to the GS-9973 SDD formulation (Section 5.3.5).

Figure 3-1. Study Schema



3.1.1. CLL, FL, DLBCL, MCL

A Bayesian, continuous data review approach will be used to update the estimates of PFS rates at 16 weeks (CLL after BCR targeted therapy, MCL and DLBCL) or 24 weeks (CLL and iNHL) as each subject's primary endpoint becomes available for a malignancy. The criterion used for the futility boundary is defined as highly likely (>90%) that the PFS rates at 16 weeks (CLL after BCR targeted therapy, MCL and DLBCL) or 24 weeks (CLL and iNHL) are less than 0.2 given the available subjects' efficacy data.

Futility assessment begins when the first 10 subjects' primary endpoints become available. Thereafter, continuous data review will be conducted when a new primary endpoint becomes available.

- If the futility criterion is not met, subsequent subjects will be enrolled until a total of pre-defined number of subjects are recruited for a cohort.

- If the futility criterion is met, the sponsor will consider terminating enrollment to that malignancy, taking into account efficacy, drug exposure and subtype (for DLBCL), unless there are subjects who remain on treatment and have not yet reached 16 weeks (CLL after BCR targeted therapy, MCL and DLBCL) or 24 weeks (CLL and FL). In this case, enrollment will be suspended until the next on-going subjects' primary endpoint becomes available, and another data review is conducted. If, after review of all available subjects, the futility boundary has still been crossed and the lack of drug exposure or for DLBCL, subtype does not explain the lack of activity, enrollment to that malignancy will be terminated.

The futility boundary is provided in Figure 3-2 with details in Section 8.6. The boundary is represented in terms of the total number of subjects and the number of progression-free subjects at Week 16 (CLL after BCR targeted therapy, MCL and DLBCL) or Week 24 (CLL and FL). Subjects who withdraw or are lost to follow-up before Week 16 (CLL after BCR targeted therapy, MCL and DLBCL) or week 24 (CLL and FL) will be considered as not achieving PFS for the analysis.

At each data review, if the observed ratio of the number of PFS at Week 16 (CLL after BCR targeted therapy, MCL and DLBCL) or Week 24 (CLL and FL) over the total number of subjects is at or below the futility boundary, then the futility criterion has been met.

The data review for the CLL prior BTK inhibitor exposure and CLL prior PI3K inhibitor exposure cohorts will be conducted independently for Richter's and non-Richter's.

3.1.2. CLL Dose Ranging Cohort

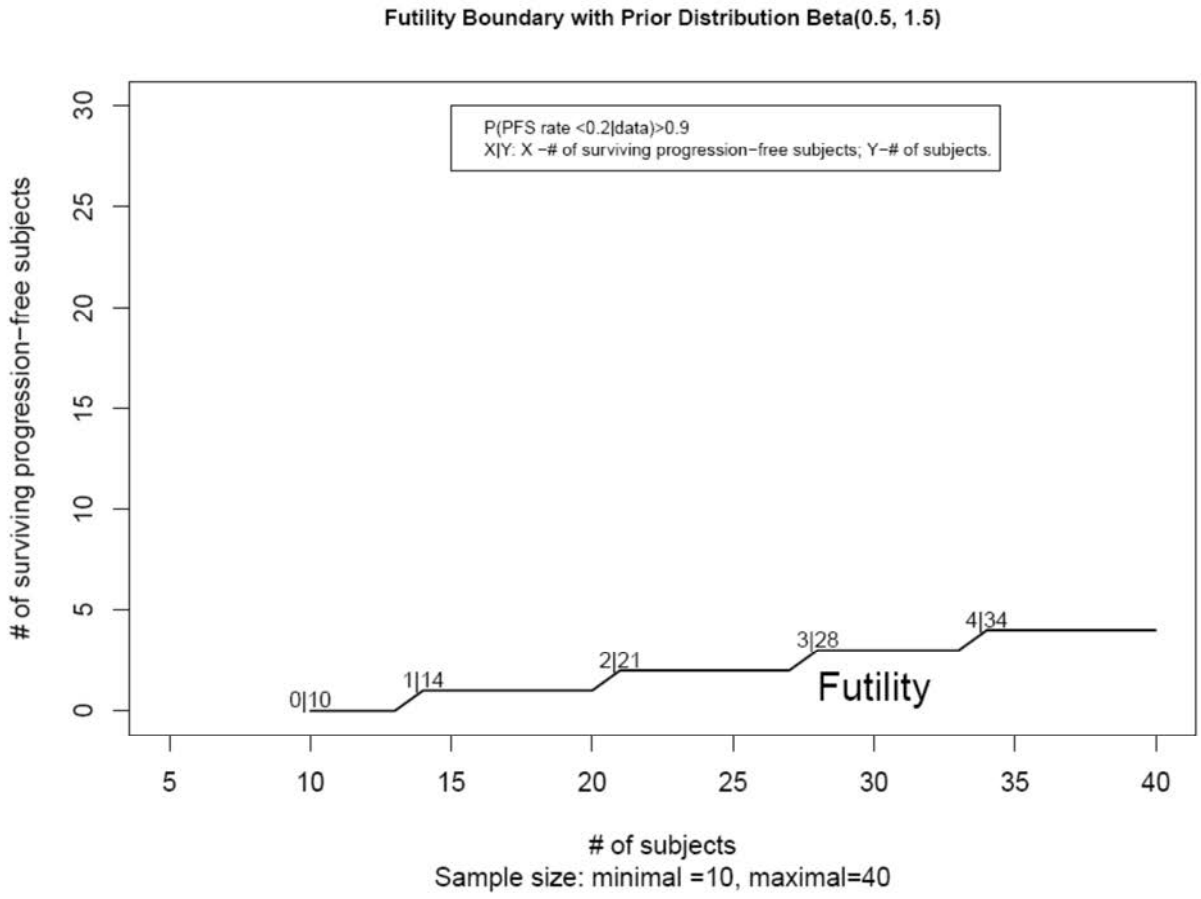
For the CLL dose ranging cohort, subjects enrolled will be randomized 1:1:1 to receive 100 mg, 200 mg or 400 mg (200 mg x 2) of GS-9973 SDD BID. Therefore 20 subjects are treated at each of the three dose levels.

Because the CLL dose raging cohort consists of 3 different dose levels each with approximately 20 subjects, the continuation data review of futility will not be conducted for this cohort.

3.1.3. LPL, SLL, MZL

Because the 'other non-FL iNHL' cohort consists of 3 different histologies, accrual will continue to a maximum of 45 subjects without a Bayesian analysis.

Figure 3-2. Futility Boundary with Prior Distribution Beta (0.5, 1.5)



3.2. Treatment Regimen

Initially subjects with iNHL and NHL will receive treatment with 800 mg GS-9973 BID (under fasted conditions (as defined in Section 5.5.10). As of protocol amendment 8, subjects receiving GS-9973 MM formulation will be transitioned to the GS-9973 SDD formulation (Section 5.3.5).

GS-9973 SDD doses of 100, 200 or 400 mg given BID will be studied in the additional cohorts. A specific dosing regimen will be selected based upon the emerging pharmacodynamic, pharmacokinetic and anti-tumor data from the CLL dose ranging subjects and all cohorts will be transition to the dose level of GS-9973 SDD.

Initially subjects in the CLL prior BTK inhibitor exposure or CLL prior PI3K inhibitor exposure cohorts will receive GS-9973 SDD 400 mg twice daily (BID). Subjects in the CLL dose ranging cohorts will receive the GS-9973 SDD at the dose level assigned in the randomization.

For study purposes, a cycle is considered to be 28 days. In the absence of toxicity requiring a drug holiday (as defined in Section 8.10), dosing will be continuous without interruption. Subjects will have evaluations for safety and provide blood for drug levels and pharmacodynamic monitoring prior to starting treatment and then 1.5 hours thereafter per the following schedule: at initial dose, weekly during Cycle 1, every 2 weeks during Cycle 2, and then once each cycle thereafter. Additional PK samples will be collected at 4 hours after dosing on Cycle 1 Day 1 and Cycle 1 Day 8. Subjects will undergo a radiographic assessment to determine their tumor response to treatment every 8 weeks during the first 24 weeks and then every 12 weeks thereafter for all diagnoses, except LPL/WM who did not have measurable disease at the time of the study and who are not suspected to have measurable disease at the time of progression. For those LPL/WM patients, the reassessments will consist of bone marrow evaluation, serum monoclonal IgM, done by same technique as used in screening, and cryoglobulin. A bone marrow must be done at PD if that is the only source of the PD and at CR to confirm the CR to determine their tumor response to treatment every 8 weeks during the first 24 weeks and then every 12 weeks thereafter.

Treatment with GS-9973 or GS-9973 SDD may continue in the absence of disease progression or unacceptable toxicity.

4. SUBJECT POPULATION

4.1. Number of Subjects and Subject Selection

Subjects with one of the designated malignancies who meet the eligibility criteria will be studied. Up to 60 subjects for the CLL dose ranging cohort and CLL BCR targeted therapy cohorts (CLL prior BTK inhibitor exposure and CLL prior PI3K inhibitor exposure, respectively), up to 40 subjects for each of the other cohorts and up to 8 cohorts (385 subjects in total) will be studied.

Subjects with a documented diagnosis of histologically or cytologically confirmed CLL and selected types of B-cell NHL, with progressive disease are eligible for the study:

- CLL as established by the International Workshop on CLL (IWCLL) {Hallek 2008}. Subjects with atypical immunophenotype must lack t(11;14) translocation or cyclin D1 over-expression.
- B-cell NHL of the following subtypes as defined by the World Health Organization (WHO) Lymphoma Classification:
  - MCL
  - DLBCL
  - iNHL

4.2. Eligibility Criteria

4.2.1. Inclusion Criteria

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

1) Male or female ≥ 18 years of age

   a) Diagnosis of B-cell iNHL, DLBCL, MCL (mantle cell, nodal, diffuse or blastoid), or CLL as documented by medical records and with histology based on criteria established by the World Health Organization. If the subject has DLBCL, subtyping is required. Submission of 15 unstained slides is required for subtyping if the subtype is not already known. Subjects for whom tissue is not available but the subtype is already known may be included if pathology report including the subtype is provided.

   b) If the subject has iNHL, the lymph node histology report confirms 1 of the following subtypes:

      i) FL Grade 1, 2, or 3a

ii) SLL (ie, SLL/CLL histology with an absolute lymphocyte count of < 5 x 10^9/L at diagnosis and on Screening laboratory assessment performed within 35 days prior to the start of study drug administration)

iii) LPL/WM

iv) MZL (splenic, nodal, or extranodal)

2) **For institutions that have Phase 3 or Phase 4 protocols studying idelalisib (Zydelig)**: subjects with malignancies being studied in these protocols must be a screen failure in the respective idelalisib protocol

3) Prior treatment for lymphoid malignancy and requiring treatment for progressive disease. Criteria for progressive disease is established Cheson criteria for NHL and by IWCLL criteria for CLL

a) LPL/WM patients do not need to have progressive disease but need to meet criteria of needing treatment per Update on Recommendations for Assessing Response from the Third International Workshop onWaldenström's Macroglobulinemia

4) (see Section 4 for details)

a) Subjects with denovo DLBCL for whom there is no curative option with conventional treatment

b) If the subject has MCL, iNHL, or BCR based therapy naïve CLL, the prior treatment must be comprised of at least 1 of the following:

i) regimen containing a therapeutic antibody administered for ≥ 2 doses of antibody treatment

ii) regimen containing ≥ 1 cytotoxic agent administered for ≥ 2 cycles of cytotoxic treatment

iii) regimen containing yttrium^{90}-ibritumomab tiuxetan or iodine^{131}-tositumomab

iv) experimental therapy as part of clinical trial protocol

c) The previously BCR treated patients will be limited to subjects with CLL (other BCR targeted therapies may be accepted after approval of the medical monitor) only in the context of this cohort are Richter's transformation eligible.

i) CLL subjects whom have had more than 1 BCR targeted therapy will be enrolled into the cohort of the most recent treatment ibrutinib or idelalisib received prior to progression.

5) Presence of radiographically measurable progressive disease as defined using Cheson criteria for NHL, and iNHL and by IWCLL criteria for CLL; lymphadenopathy or extranodal lymphoid malignancy (defined as the presence of ≥ 1 lesion that measures ≥ 2.0 cm in the longest diameter [LD] and ≥ 1.0 cm in the longest perpendicular diameter [LPD] as assessed by CT or MRI) ;

   a) Subjects with LPL/WM who do not have radiographically measurable progressive disease must have a monoclonal serum IgM ≥ 2x ULN as verified by serum protein electrophoresis (SPEP) and with lymphoplasmacytic marrow involvement are eligible. LPL/WM enrollment is limited to those sites which have cryoglobulin analysis capabilities

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

7) Karnofsky performance status of ≥ 60

8) Life expectancy of at least 3 months

9) Required screening laboratory data (within 5 weeks prior to administration of study drug) as shown in Table 4-1. ***Note: Confirmation should be considered for out-of-range values to determine if the abnormality is real or artifactual. Values used for screening must be obtained within the screening period and should be the most recent measurement obtained. Subjects with any degree of neutropenia, thrombocytopenia, or anemia with documentation that it is due to malignancy may enroll.***

Table 4-1. Required Screening Laboratory Values

Organ System	Parameter	Required Value
Hematopoietic	ANC	≥ 0.5 x 10^9/L
	Platelets	≥ 50 x 10^9/L
	Hemoglobin	≥ 80 g/L (8.0 g/dL)
Hepatic	Serum total bilirubin	≤ 1.5 x ULN (unless elevated due to Gilbert's syndrome or hemolysis)
	Serum ALT	≤ 2.5 x ULN
	Serum AST	
Renal	Serum creatinine OR Estimated creatinine clearance	< 1.5 x ULN OR ≥ 60 ml/min as calculated by the Cockroft-Gault method
Coagulation	INR[a]	< 1.7
Pregnancy	β-HCG[b]	Negative
Infection	HIV	Negative HIV antibody
	HBV	Negative HBsAg and negative HBc antibody
	HCV	Negative viral RNA (if HCV antibody is positive)

a For subjects on anticoagulative therapy the required value is < 3.0

b For women of childbearing potential only; serum β-HCG must be negative during screening and serum β-HCG or urine dipstick pregnancy test must be negative at start of study therapy

10) For female subjects of childbearing potential, willingness to abstain from heterosexual intercourse or use a protocol-recommended method of contraception from the screening visit throughout the study treatment period and for 30 days following the last dose of GS-9973. ***See Section 7.11 for information regarding recommendations for contraception***

11) For male subjects of childbearing potential having intercourse with females of childbearing potential, willingness to abstain from heterosexual intercourse or use a protocol-recommended method of contraception from the start of study drug throughout the study treatment period and for 90 days following the last dose of GS-9973 or GS-9973 SDD and to refrain from sperm donation from the start of study drug throughout the study treatment period and for 90 days following the last dose of GS-9973 or GS-9973 SDD. ***See Section 7.11 for information regarding recommendations for contraception***

12) Willingness to comply with scheduled visits, drug administration plan, imaging studies, laboratory tests, other study procedures, and study restrictions

13) Have the ability to understand and sign a written informed consent form, which must be obtained prior to initiation of any study specific procedures

4.2.2. Exclusion Criteria

Subjects who meet any of the following exclusion criteria are not eligible for study participation:

1) Known histological transformation from iNHL or CLL to an aggressive form of NHL (ie, Richter transformation) if the CLL patient has not had ibrutinib or idelalisib as their immediately prior therapy. CLL patients who were treated with a BCR inhibitor as the most recent therapy and who experience a transformation of their tumor, will not be excluded. Subjects who have a history of iNHL or CLL with a subsequent confirmation high grade histology will be considered transformed for purpose of this study. ***Note: Biopsy documentation of the absence or presence of transformation is not required***

2) Known active central nervous system or leptomeningeal lymphoma. ***Note: Central nervous system imaging is only required in subjects with suspected lymphomatous involvement based on symptoms or signs***

3) Presence of known intermediate- or high-grade myelodysplastic syndrome (ie, subjects are excluded who have ≥ 5 bone marrow blasts; karotypic abnormalities other than normal, Y deletion, 5q deletion, or 20q deletion; or ≥ 2 lineages of cytopenias) {Greenberg 1997}

4) Because they are likely to interfere with GS-9973 absorption, current therapy with agents that reduce gastric acidity, including but not limited to proton pump inhibitors

5) History of any prior lymphoid malignancy other than registrational histology except for CLL subjects with prior BCR therapy

    a) Subjects with diagnoses other than CLL who were previously treated with a BCR inhibitor are excluded from this study.

6) History of 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 start of study therapy, other adequately treated Stage 1 or 2 cancer currently in complete remission, or any other cancer that has been in complete remission for ≥ 5 years

7) Evidence of ongoing systemic bacterial, fungal, or viral infection at the time of start of study drug. ***Note: Subjects with localized fungal infections of skin or nails are eligible.***

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

9) Ongoing (within the past 6 weeks) hepatic encephalopathy

10) Ongoing drug-induced pneumonitis

11) Ongoing inflammatory bowel disease

12) Ongoing alcohol or drug addiction as determined by investigator

13) Pregnancy or breastfeeding

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

15) Ongoing immunosuppressive therapy, including systemic corticosteroids for treatment of lymphoid malignancy. Concurrent use of methotrexate for rheumatologic conditions is permitted. Note: Subjects may use topical, enteric, or inhaled corticosteroids as therapy for comorbid conditions and systemic steroids for autoimmune anemia and/or thrombocytopenia. Ongoing use of low-dose systemic corticosteroids (≤ 5 mg/day of methylprednisolone or equivalent) for rheumatologic conditions is permitted. During study participation, subjects may receive systemic or other corticosteroids needed for treatment-emergent comorbid conditions. See next entry for exception related to steroids.

16) Concurrent participation in an investigational drug trial with therapeutic intent defined as prior study therapy within 21 days prior to study drug. Exception: the cohorts with relapsed CLL following BCR pathway inhibitors whom in the opinion of the investigators cannot have a 21 day washout period ≥5 half lives washout period will be allowed, along with up to 20 mg of prednisone at the start of the trial, for control of disease related symptoms, with planned taper over 2 weeks

17) Any other prior or ongoing condition that, in the opinion of the investigator, could adversely affect the safety of the subject or impair the assessment of study results

5. INVESTIGATIONAL MEDICINAL PRODUCTS

5.1. Enrollment

It is the responsibility of the Investigator to ensure that the subjects are eligible for the study prior to enrollment. Once eligibility is confirmed subjects will be assigned a unique subject number. In this open-label study all subjects will receive up to 800 mg GS-9973 BID or one of 3 doses (100 mg, 200 mg or 400 mg) of GS-9973 SDD BID under fasted conditions (as defined in Section 5.5.10). As of protocol amendment 8, subjects receiving GS-9973 MM formulation will be transitioned to the GS-9973 SDD formulation (Section 5.3.5). All baseline tests and procedures must be completed prior to the administration of the first dose of study drug on Day 1. Once a subject number is assigned to a subject, it will not be reassigned to another subject.

5.2. Description and Handling of GS-9973 and GS-9973 SDD

5.2.1. Formulation

GS-9973 tablet is available as 200 mg strength tablets. The tablets contain commonly used excipients including lactose monohydrate, microcrystalline cellulose, crospovidone, povidone, sodium lauryl sulfate, silicon dioxide, magnesium stearate, polyethylene glycol, polyvinyl alcohol, talc, titanium dioxide, and FD&C blue #2 aluminum lake. The 200 mg GS-9973 tablets are capsule-shaped, plain-faced, film-coated blue tablets.

GS-9973 SDD (ENTO) tablets, 100 mg and 200 mg strength, are available as blue, capsule-shaped film-coated tablets that are plain-faced. In addition to the active ingredient, ENTO tablets contain the following inactive ingredients: methanesulfonic acid, hydroxypropyl methylcellulose (hypromellose), mannitol, microcrystalline cellulose, crospovidone, poloxamer 188, silicon dioxide, magnesium stearate, polyethylene glycol, polyvinyl alcohol, talc, titanium dioxide, and FD&C blue #2 aluminum lake.

GS-9973 SDD (ENTO) tablets, 200 mg strength, are also available as beige, capsule-shaped film-coated tablets debossed with “GSI” on one side and “9973” on the other side. In addition to the active ingredient, ENTO tablets contain the following inactive ingredients: methanesulfonic acid, hydroxypropyl methylcellulose (hypromellose), mannitol, microcrystalline cellulose, crospovidone, poloxamer 188, silicon dioxide, magnesium stearate, polyethylene glycol, polyvinyl alcohol, talc, titanium dioxide, ferrosoferric oxide/black iron oxide, iron oxide red, and iron oxide yellow.

5.2.2. Source

GS-9973 and GS-9973 SDD will be supplied free of charge by Gilead Sciences. Any questions or concerns regarding study drug supply should be referred to the Gilead Sciences clinical project manager.

5.2.3. Packaging and Labeling

Sixty (60) GS-9973/GS-9973 SDD tablets are packaged in white, high-density polyethylene bottles with silica gel desiccant, and polyester packing material. Each bottle is capped with a child-resistant polypropylene screw cap fitted with an induction-sealed, aluminum-faced liner.

All study drug labels will meet all applicable requirements of the protocol and the regulatory authorities.

5.2.4. Storage and Handling

GS-9973 tablets should be stored at a controlled room temperature of 25 °C (77 °F); excursions are permitted from 15 °C to 30 °C (59 °F to 86 °F).

GS-9973 SDD tablets should be stored at a controlled room temperature of 25 °C (77 °F); excursions are permitted from 15 °C to 30 °C (59 °F to 86 °F).

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.

5.2.5. Study Drug Accountability

The investigator or designee (eg, pharmacist) is responsible for ensuring adequate accountability of all used and unused study drug bottles during the study. This includes acknowledgement of receipt of each shipment of study drug (quantity and condition) and tracking of bottles assigned/utilized for subject dosing. All unused study drug bottles must be returned to the site by the subjects.

Investigational Drug Accountability records will be provided to each study site to:

- Record the date of receipt and quantity of study drug.
- Record the date of dispensation, subject identifier, and study drug bottle number(s) dispensed.
- Record the date of return and quantity of used and unused study drug bottle(s).

Dispensing records will include the initials of the person dispensing the study drug or supplies.

5.3. Treatment Plan

5.3.1. Premedication

No specific premedications or supporting medications are required in conjunction with GS-9973/GS-9973 SDD administration, although institution of antibiotic prophylaxis for *Pneumocystis (carinii) jiroveci* may be considered in all subjects (see Section 5.5.3).

5.3.2. Administration Instructions

GS-9973/GS-9973 SDD should be taken under fasted conditions (as defined in Section 5.5.10). Subjects should be instructed not to bite or chew the tablets. In case of breakage of the tablets in the oral cavity, additional water should be taken as a rinse.

5.3.3. Dosing Schedule

GS-9973/GS-9973 SDD should be taken at approximately the same times each day. Ideally, doses should be taken at approximately 12-hour intervals, while in a fasted state. While it is realized that variations in the dosing schedule may occur, the prescribed regimen should be followed as closely as possible. Compliance with the protocol dosing schedule will be documented in the subject's chart and the electronic data capture (EDC) at each scheduled visit. Counseling regarding subject compliance may be required.

5.3.4. Dose Schedule Interruptions and Vomited Doses

Subjects who have a delay in administration of a dose of GS-9973 or GS-9973 SDD 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 GS-9973 or GS-9973 SDD of ≥ 6 hours, the dose should not be taken. GS-9973 or GS-9973 SDD administration may continue but the missed dose should not be made up and the planned timing of subsequent GS-9973 or GS-9973 SDD dosing should not be altered.

Vomited doses should be retaken, but only if the tablets are visible in the vomitus.

5.3.5. Transition of GS-9973 MM formulation to GS-9973 SDD formulation

As of protocol amendment 8, subjects receiving GS-9973 MM formulation will be transitioned to the GS-9973 SDD formulation. A comparison of the GS-9973 steady-state AUC_{tau} in healthy subjects following GS-9973 MM formulation and GS-9973 SDD formulation is provided in Figure 5-1 (data from studies GS-US-245-0101, GS-US-245-1222, GS-US-339-0111, GS-US-339-1627 and GS-US-339-1914), and the new dose levels for GS-9973 SDD formulation are provided in Table 5-1. The GS-9973 SDD dose levels in Table 5-1 are expected to provide similar GS-9973 systemic exposure as the indicated dose of GS-9973 MM formulation (Figure 5-1).

Figure 5-1. GS-9973 AUC_{tau} following GS-9973 MM and GS-9973 SDD formulations

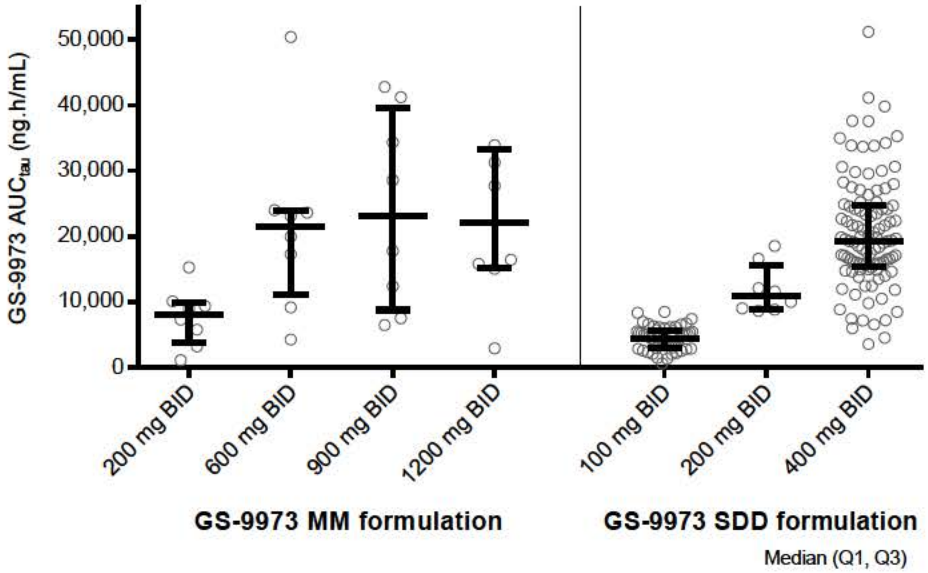


Table 5-1. Transition of GS-9973 MM formulation to GS-9973 SDD formulation

Current dose level GS-9973 MM Dose (mg BID fasting)	Current enrollment at this dose level (N) as of March2017	New dose level GS-9973 SDD Dose (mg BID fasting)
800	11	400
600	2	400
400	1	200
200	0	200

a All cohorts that received GS-9973 MM formulation are closed to further enrollment.

5.3.6. Management of Dose Limiting Toxicities

Adverse events and laboratory abnormalities will be graded using the CTCAE, Version 4.03. Dose modification of GS-9973/GS-9973 SDD should be performed for the following dose limiting AEs:

- Grade 4 hematological toxicities persisting for ≥ 14 days
- Grade ≥ 3 toxicities of other types

Of note, the occurrence of asymptomatic lymphocytosis will not be considered a toxicity requiring dose modification. Dose reduction will not be required for untreated vomiting, diarrhea, or constipation; interruption of dosing until these symptoms are adequately treated is permitted.

Table 5-2. GS-9973 MM Dose Levels

Dose Level	GS-9973 MM Dose (mg BID fasting)
0	800
-1	600
-2	400
-3	200

Table 5-3. GS-9973 SDD Dose Levels

Dose Level	GS-9973 SDD Dose (mg BID fasting)
CLL Prior BTK inhibitor Exposure, CLL Prior PI3K inhibitor Exposure or CLL Dose Ranging randomized to 400mg BID or Dose level 0	400
CLL Dose Ranging randomized to 200mg BID or Dose level -1	200
CLL Dose Ranging randomized to 100mg BID or Dose level -2	100

If a subject experiences an AE or laboratory abnormality that is suspected to be related to GS-9973/GS-9973 SDD, and requires a dose reduction, GS-9973/GS-9973 SDD administration should be interrupted, as necessary, until the AE or laboratory abnormality resolves or stabilizes to an acceptable degree (generally to Grade 1 or the pretreatment severity grade, whichever is higher). More frequent monitoring (eg, once per week) may be warranted until adverse events or laboratory abnormalities are clearly improving. When treatment is reinstituted, the dose of GS-9973/GS-9973 SDD should be reduced by 1 dose level (see Table 5-2 and Table 5-3).

Successive adjustments to progressively lower dose levels can be made. If the subject cannot tolerate GS-9973/GS-9973 SDD at the lowest dose level then the subject should discontinue GS-9973/GS-9973 SDD therapy.

After a dose is reduced, the dose need not be re-escalated, even if there is minimal or no toxicity with the reduced dose. However, if the subject tolerates a reduced dose of GS-9973/GS-9973 SDD for ≥ 4 weeks then the GS-9973/GS-9973 SDD dose may be increased to the next higher dose level, at the discretion of the investigator. Such re-escalation should strongly be considered if further evaluation reveals that the AE that led to the dose reduction was not GS-9973/GS-9973

SDD-related. Successive adjustments to progressively higher dose levels can be made at 4-week intervals up to the highest dose level. Dose escalations above the highest dose level are not allowed. Any study drug dose re-escalation must be discussed between the investigator and the Gilead Sciences Medical Monitor or designee prior to implementation.

Whenever the study drug dose is de-escalated or re-escalated, the appropriate clinic staff should dispense the study drug for the new dose level and instruct the subject/caregiver about the change in dose level.

Note: Dose modifications and clinical management for subjects who enter the study with pre-existing Grade 3 or 4 abnormalities due to their underlying malignancy will be discussed with the study Medical Monitor or designee prior to the initiation of treatment.

5.3.6.1. Guidelines for Dose Modifications

Recommendations for dose modifications based on the type and severity of adverse events or laboratory abnormalities are provided in Table 5-4. The dose adjustment recommendations are based on the 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 study medical monitor should be contacted.

The dose modification instructions focus on the types of events most commonly attributed to GS-9973/GS-9973 SDD or other drugs that target B-cell receptor signaling pathways. The recommendations provided in Table 5-4 comprise only guidelines; variations from these recommendations may be warranted based on an investigator's individual judgment in considering potential risks, benefits, and therapeutic alternatives available to each subject.

Table 5-4. Dose Modification Guidelines

Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4
Neutropenia	Maintain current dose level and schedule.			Consider G CSF support and continue dosing at same or lower dose level at investigator discretion.
Thrombocytopenia	Maintain current dose level and schedule.			Withhold for bruising or bleeding until Grade ≤ 3. May resume dosing at initial or lower dose level at investigator discretion
Dermatological	Maintain current dose level and schedule.		Withhold dosing until ≤ Grade 1. Resume dosing at current dose level. If re-challenge at current dose level results in recurrence, may resume dosing at same or lower dose level at investigator discretion.	Withhold dosing until Grade ≤1. May resume at lower dose level or discontinue dosing at investigator discretion.

Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4
Gastrointestinal Inflammation-Diarrhea	Provide anti-diarrheal (e.g., loperamide) and maintain current dose level and schedule	Provide anti-diarrheal (e.g., loperamide). Withhold dosing until Grade ≤1. Resume dosing at current dose level. If re-challenge results in recurrence, may resume at initial or lower dose level at investigator discretion. Consider addition of anti-inflammatory (e.g., sulfasalazine, budesonide).	Provide anti-diarrheal (e.g., loperamide). Withhold dosing until Grade ≤1. Resume at lower dose level. Consider addition of anti-inflammatory (e.g., sulfasalazine, budesonide).	Provide anti-diarrheal (e.g., loperamide). Withhold dosing until Grade ≤1. May resume at lower dose level or discontinue dosing at investigator discretion. Consider addition of anti-inflammatory (e.g., sulfasalazine, budesonide).
Hepatic (elevations in ALT, AST, or bilirubin)	(ALT/AST≤3xULN) (Direct Bilirubin ≤1.5xULN)	(ALT/AST>3-5xULN) (Direct Bilirubin >1.5-≤3xULN)	(ALT/AST>5-20xULN) (Direct Bilirubin >3-10xULN)	(ALT/AST>20xULN) (Direct Bilirubin >10xULN)
	Maintain current dose level and schedule.	Maintain current dose level and schedule. Monitor ALT, AST, ALP, and direct bilirubin at least 1x per week.	Withhold dosing. Monitor ALT, AST, ALP, and direct bilirubin at least 1x per week until all abnormalities are Grade ≤1. If direct bilirubin was Grade <3, resume dosing at same dose level. If direct bilirubin was Grade ≥3, resume at lower dose level.	Withhold dosing. Monitor ALT, AST, ALP, and direct bilirubin at least 1x per week until all abnormalities are Grade ≤1. If direct bilirubin was Grade <4, resume dosing at lower dose level. If direct bilirubin was Grade 4, discontinue dosing.
Pneumonitis (dyspnea, cough, hypoxia and/or diffuse interstitial pattern or ground-glass opacities on chest CT and no obvious infectious cause)	Maintain current dose level and schedule. Consider Pneumocystis therapy	Withhold dosing until Grade ≤1. Consider systemic corticosteroids and Pneumocystis treatment. May resume at initial or lower dose level at investigator discretion.	Withhold dosing until Grade ≤1. Consider systemic corticosteroids and consider Pneumocystis treatment. May resume at lower dose level or discontinue dosing at investigator discretion.	
Other Study Drug Related, Non-hematological Adverse Events	Maintain current dose level and schedule		Withhold dosing until Grade ≤1. May resume dosing at initial or lower dose level or discontinue dosing at investigator discretion.	

5.3.7. Management of Low Grade Chronic Toxicities

Since subjects will be receiving the study drugs daily, low grade chronic side effects, such as nausea, fatigue and diarrhea, while not meeting the above definition for dose limiting toxicities, may not be tolerable when experienced for long periods of time. Following discussion with the Gilead Sciences Medical Monitor, dose reduction may be permitted if low grade chronic side effects cannot be managed effectively with supportive care.

5.3.8. Specific Considerations for Managing Hyperbilirubinemia

5.3.8.1. Unconjugated (Indirect) Bilirubin Elevations

GS-9973 is an inhibitor of UGT1A1 and reversible increases in unconjugated (indirect) bilirubin values occurred in healthy subjects receiving GS-9973/GS-9973 SDD. In the absence of symptoms or other hepatic laboratory abnormalities, GS-9973/GS-9973 SDD dose modification is not required for elevated indirect bilirubin levels.

5.3.9. Duration of Therapy

Subjects may continue receiving GS-9973/GS-9973 SDD until the occurrence of any events requiring treatment discontinuation as defined in Section 5.6.

5.4. Study Drug Disposal

At the start of the study, the study monitor will evaluate each study center's study drug disposal procedures and provide appropriate instruction for return or destruction of unused study drug supplies. If the site has a process instruction (eg, Standard Operating Procedures [SOPs]) for on-site drug destruction which is reviewed by the study monitor, then the site should destroy used (empty bottles) and unused study drug supplies performed in accordance with the site's (hospital/pharmacy) procedure. The destruction process should include records noting the identification and quantity of each unit destroyed the method of destruction, and person who disposed of the drug. A copy of the site's SOP/process document will be obtained for central files at the pre-study or otherwise applicable monitoring visit. Upon study completion, a copy of the relevant Investigational Drug Accountability records must be filed at the site and provided for the sponsor files. If the site does not have acceptable procedures in place for drug destruction, arrangements will be made between the site and Gilead Sciences (or Gilead Sciences' representative) for return of unused study drug supplies.

5.5. Concomitant and Supportive Therapy

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

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

All concomitant medications and over the counter medications must be approved by the Gilead Sciences Medical Monitor or designee prior to study enrollment.

Should subjects have a need to initiate treatment with any excluded concomitant medication, the Gilead Sciences Medical Monitor or designee must be consulted prior to initiation of the new medication. In instances where an excluded medication is initiated prior to discussion with the Gilead Sciences Medical Monitor or designee, the Investigator must notify Gilead Sciences as soon as he/she is aware of the use of the medication.

5.5.1. Excluded Medication

During the course of the clinical trial, study subjects are anticipated to continue the use of prescribed medications identified during the screening procedures, consistent with study inclusion and exclusion criteria.

The following therapies are not permitted at any point during the trial beginning with the first dose of study drug.

- Any non-study anti-cancer chemotherapy or non-study immunotherapy (approved or investigational)
- Co-administration of strong CYP3A and CYP2C9 inducers or moderate CYP2C9 inducers are prohibited in this study. Administration of these medications should be avoided for 2 weeks prior to study drug administration. Examples of these medicines are provided in Table 5-5.
- Caution should be exercised when co-administering drugs that are moderate or strong inhibitors of CYP2C9 (eg fluconazole, voriconazole or amiodarone) as they may increase GS-9973 exposure. These agents are not prohibited.
- Proton pump inhibitors are prohibited in combination with GS-9973. Use of a proton pump inhibitor should be avoided for 1 week prior to study drug administration.

Table 5-5. Examples of Contraindicated Medications in this Study that require prior Gilead Medical Monitor discussion and approval

	Strong	Moderate
CYP3A Inducer	carbamazepine, phenytoin, rifampin, St. John's Wort, enzalutamide, rifabutin, phenobarbital, mitotane, avasimibe	Not prohibited
CYP2C9 Inducer		carbamazepine, rifampin, ritonavir, enzalutamide
Proton Pump Inhibitors	omeprazole, esomeprazole, pantoprazole, lansoprazole, rabeprazole, dexlansoprazole	

- Caution should be exercised when co-administering medications that are transported by OATP1B1, OATP1B3, MATE1, P-gp and BCRP or metabolized by UGT1A1; dose adjustment or switching to an alternative medication may be necessary if clinically indicated.

- The following restrictions apply to the use of HMG-CoA reductase inhibitors with GS-9973:

Concomitant Medication	Restriction
Atorvastatin	Maximum dose 20 mg QD
Rosuvastatin	Maximum dose 10 mg QD
Pravastatin	Maximum dose 40 mg QD
Simvastatin	Maximum dose 20 mg QD
Lovastatin	Maximum dose 20 mg QD
Fluvastatin	Maximum dose 20 mg BID or 40 mg QD
Pitavastatin	Maximum dose 1 mg QD

5.5.2. Anticancer or Experimental Therapies Other than Investigational Treatments

No other anticancer therapies (including chemotherapy, radiation, antibody therapy, immunotherapy, or other experimental therapies) of any kind are permitted while the subject is receiving study treatment. Subjects are not allowed to participate concurrently in any other investigational drug trial with therapeutic intent.

5.5.3. Antibiotics

Except in a subject who has a contraindication, investigators should consider initiation of antibiotic prophylaxis against *pneumocystis* infection (eg, with trimethoprim-sulfamethoxazole, dapsone, aerosolized pentamidine, or atovaquone) beginning prior to GS-9973 administration. Such support may also offer the benefit of reducing the risk for other bacterial infections {Green 2007}. Investigator discretion and local practices or guidelines should be followed.

For subjects who develop an infection, appropriate medical therapy (with antibiotics, antifungals, or antiviral) or other interventions should be instituted. Whenever appropriate, subjects may continue with GS-9973/GS-9973 SDD during treatment for the infection.

5.5.4. Antiemetics and Antidiarrheals

Subjects who experience nausea or vomiting while on study therapy may receive antiemetics based on the judgment of the treating physician and local institutional practices. If possible, systemic corticosteroids should be avoided (see Section 5.5.6).

As needed, subjects may be prescribed supportive medications to control diarrheal symptoms.

5.5.5. Contraception

Please see Section 7.11 for contraception guidelines.

The Gilead Sciences Medical Monitor or designee should be consulted regarding any questions relating to childbearing status or contraception.

5.5.6. Corticosteroids

Subjects may not receive systemic corticosteroids as part of their cancer treatment while in this study. Subjects may receive topical, inhaled, or enteric corticosteroids for non-malignant conditions while on study. The use of systemic corticosteroids is discouraged because their potential antineoplastic activity in subjects with a hematologic malignancy may confound interpretation of antitumor effects mediated by GS-9973/GS-9973 SDD treatment. 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.

5.5.7. Colony-Stimulating Factors and Erythropoietin

Colony stimulating factors, preferably G-CSF preparations, may be administered in response to Grade 4 neutropenia or neutropenic complications; use should be considered particularly if providing hematopoietic support might help to maintain study drug treatment.

Erythropoietic agents may be administered for Grade ≥ 3 anemia.

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

5.5.8. Immunization

Because of their actions to inhibit SYK-dependent B-cell function, GS-9973 could, in theory, impair primary or secondary responses to immunization although the clinical relevance is unknown. However, for subjects who are at substantial risk of an infection (eg, influenza, herpes zoster) that might be prevented by immunization, consideration should be given to providing the vaccine prior to initiation of study therapy.

Of note, the safety of immunization with live viral vaccines following GS-9973/GS-9973 SDD therapy has not been studied and vaccination with live virus vaccines during study treatment is not recommended.

5.5.9. Surgery

The effects of GS-9973 on coagulation or wound healing in humans are not known. Pending receipt of additional information, GS-9973 should be discontinued in the peri-procedural period in subjects who require surgery or invasive procedures. Cases in which this is not in the best interest of the subject should be discussed with the Gilead Sciences Medical Monitor or designee.

Given the half-life of GS-9973 (~10 hours), drug levels should be minimal 48 hours after the last dose of GS-9973/GS-9973 SDD, although the biological effects on SYK and possibly other targets may persist longer than this.

5.5.10. Diet

GS-9973/GS-9973 SDD must be taken under fasted conditions. Fasting is defined as no food or liquids other than water for 2 hours pre- and 1 hour post- dose.

5.6. Discontinuation of Study Drug

Study participants may receive GS-9973/GS-9973 SDD indefinitely, with the following exceptions:

- Any subject has the right to withdraw from the study at any time.
- Any subject who has objective evidence of definitive cancer progression despite optimal therapy should be withdrawn from the study treatment (see Section 6.6).
- Any subject who cannot tolerate GS-9973/GS-9973 SDD at the lowest dose level (see Table 5-2 and Table 5-3) should be withdrawn from study drug.
- Any subject whose medical condition substantially changes after entering the study should be carefully evaluated by the investigator in consultation with the Gilead Sciences Medical Monitor or designee. Such subjects should be withdrawn from study drug if continuing would place them at risk.
- Any subject who becomes pregnant or begins breastfeeding should be withdrawn from study drug.
- Any subject who becomes significantly noncompliant with study drug administration, study procedures, or study requirements should be withdrawn from study drug in circumstances that increase risk or substantially compromise the interpretation of study results.
- The investigator, in consultation with the Gilead Sciences Medical Monitor or designee, may withdraw any subject from the study drug, if, in the investigator's opinion, it is not in the subject's best interest to continue.
- Gilead Sciences, relevant regulatory agencies, or IRB/IECs may request discontinuation of the study at any time.
- If allowed by local regulations, Gilead Sciences may transition subjects from study drug to commercial drug supply when GS-9973/GS-9973 SDD becomes commercially available in the country where the subject is living.

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 in the following text.

Any deviation from protocol procedures should be noted in the source documents and the Sponsor should be notified.

The study center will not be released to initiate dosing until:

- The Research Ethics Board (REB)/Institutional Review Board (IRB)/Independent Ethics Committee (IEC) has reviewed and approved the study and the informed consent document;
- All requested regulatory documents are submitted to and approved by Gilead Sciences;
- A Master Services Agreement and/or Study Agreement is executed;
- The study initiation meeting is conducted by the Gilead Sciences clinical monitor (or designee).

The initiation meeting will include a review of the protocol, the Investigator's Brochure, and Investigator responsibilities.

Documentation of the personally signed and dated informed consent of each subject, using the study-specific informed consent form (ICF), is required before initiating the Screening process. Generic Screening consent forms should not be used in lieu of the study-specific ICF.

6.1. Subject Enrollment and Treatment Assignment

It is the responsibility of the Investigator to ensure that subjects are eligible to participate in the study prior to enrollment and throughout the study. Once consent is obtained, all screening tests and procedures are assessed, and study eligibility is confirmed, subjects will be enrolled to receive GS-9973 as described in Section 5.1 of the protocol.

6.2. Pretreatment Assessments

6.2.1. Screening Visits

Subjects will be screened within 35 days before enrollment (Cycle 1, Day 1) to determine eligibility for participation in the study.

The following procedures will be performed and documented at screening:

- Obtain written informed consent
- Medical history
- Review prior/concomitant medication

- Complete physical examination including height and weight
- Vital signs including blood pressure, respiratory rate, pulse, oxygen saturation by pulse oximetry, temperature
- 12-lead ECG
- Karnofsky performance status (see Section 6.9.3)
- Obtain blood samples for:
  - Chemistry (see Section 6.9.8)
  - Hematology (see Section 6.9.8)
  - Coagulation (see Section 6.9.8)
  - HBV, HCV, and HIV virology
  - Serum pregnancy test (for females of childbearing potential)
- Urinalysis
- CT or MRI of neck, chest, abdomen, and pelvis (scans taken as part of standard medical practice up to 35 days prior to Day 1 of Cycle 1 visit are acceptable). Subjects with LPL/WM who previously failed screening for this study, due to an absence of lymphadenopathy on CT or MRI scans, do not need to be re-scanned if the scans were performed within 16 weeks of first study drug administration to meet eligibility criteria.
- If the subject has DLBCL, subtyping is required. Submission of 15 unstained slides is required for subtyping if the subtype is not already known.
- Subjects with LPL/WM only; evaluation of serum monoclonal IgM by both SPEP and IFE (immunofixation electrophoresis). LPL/WM enrollment limited to those sites which have cryoglobulin analysis capabilities.
- Record any AEs occurring after signing of the consent form
- Complete subject/visit information in IxRS

6.3. Cycle-Based Assessments

Although dosing with study drug will be given twice daily without scheduled breaks, for the purpose of describing protocol-required assessments, a cycle will be considered to be 28 days.

6.3.1. Day 1 of each 28-Day Cycle (± 2 days after Cycle 1)

Subjects who have met all eligibility criteria will come to the clinic on Day 1 to perform study required procedures prior to dosing at Cycle 1 Day 1.

The following procedures will be conducted on Day 1:

- Modified physical examination capturing changes from prior exams and weight will be performed
- Vital signs including blood pressure, respiratory rate, pulse, oxygen saturation by pulse oximetry, temperature
- Karnofsky performance status (see Section 6.9.3)
- Concomitant Medication Review
- Obtain blood samples for:
  - Chemistry (see Section 6.9.8)
  - Hematology (see Section 6.9.8)
  - Coagulation (see Section 6.9.8)
  - GS-9973 plasma concentration pre-dose (Cycles 2-6 only); GS-9973 SDD plasma concentration pre-dose and at 1.5 hours post-dose (± 10 minutes) for CLL dose ranging, CLL prior BTK inhibitor exposure, or CLL prior PI3K inhibitor exposure cohorts only

  ONLY For subjects with SLL, CLL or MCL

  - Cytokines and chemokines (see Section 6.13.1) on Cycle 2, Day 1 and Cycle 12 Day 1 ONLY
  - CTC RNA Pre-dose Cycle 12, Day 1 ONLY
- Urinalysis
- Record the approximate number of hours between the last 2 doses of GS-9973/GS-9973 SDD and the time the blood samples for plasma concentration were obtained
- Urine pregnancy test (for females of childbearing potential)
- Collect used/unused study drug and assess study drug compliance (Cycle 2 onwards)
- Dispense study drug
- Record any AEs

- Complete subject/visit information in IxRS
- Archive tumor tissue specimen as applicable. Efforts to acquire tissue sample should begin on Day 1 of Cycle 1.

Day 1 of Cycle 1 ONLY:

- Administration of study drug at site under fasted conditions (defined in Section 5.5.10) as per Section 5.3.2.
- Obtain blood samples for GS-9973/GS-9973 SDD plasma concentration pre-dose, 1.5 hours post-dose (± 10 minutes) and at 4 hours post-dose (± 10 minutes)
- For subjects with SLL, CLL or MCL: Obtain pre-dose blood samples for Chemokines and Cytokines, CTC RNA, and CTC Molecular Characterization
- Record any AEs prior to discharge
- Genomic testing for CLL dose ranging, CLL prior BTK inhibitor exposure, or CLL prior PI3K inhibitor exposure cohorts only: PBMC samples will be isolated from blood samples, sorted by cell surface marker (CD3) and stored separately (see Section 6.15).
- Buccal Swab for CLL dose ranging, CLL prior BTK inhibitor exposure, or CLL prior PI3K inhibitor exposure cohorts only (germline DNA)
- [redacted]
- Obtain blood samples for BAT Assay pre-dose, 1.5 hours post-dose and at 4 hours post-dose for CLL dose ranging, CLL prior BTK inhibitor exposure, or CLL prior PI3K inhibitor exposure cohorts only

Day 1 of Cycle 2 ONLY:

- Obtain blood samples for **GS-9973/GS-9973 SDD** plasma concentration 12 hours post- last dose (± 4 hours). If necessary the dose may be held until this blood sample has been drawn.
- For subjects with SLL, CLL or MCL: Obtain blood samples for Chemokines and Cytokines

6.3.2. Safety Monitoring Visits (± 2 days): Days 8, 15 and 22 of Cycle 1 and Day 15 of Cycle 2

The following procedures will be conducted on the designated days during Cycles 1 and 2. Please see Study Procedures Table in Appendix 2.

- Modified physical examination capturing changes from prior exams and weight will be performed

- Vital signs including blood pressure, respiratory rate, pulse, oxygen saturation by pulse oximetry, temperature
- Karnofsky performance status (see Section 6.9.3)
- Concomitant Medication Review
- Obtain blood samples for:
  - Chemistry (see Section 6.9.8)
  - Hematology (see Section 6.9.8)
  - Coagulation (see Section 6.9.8)
  - GS-9973 SDD plasma concentration pre-dose, 1.5 hours post-dose (± 10 minutes) and at 4 hours post-dose (± 10 minutes) for CLL dose ranging, CLL prior BTK inhibitor exposure, or CLL prior PI3K inhibitor exposure cohorts only on Cycle 1, Day 8
  - BAT Assay pre-dose and at 4 hours post-dose for CLL dose ranging, CLL prior BTK inhibitor exposure, or CLL prior PI3K inhibitor exposure cohorts only on Cycle 1, Day 8 for BAT Assay pre-dose for CLL dose ranging, CLL prior BTK inhibitor exposure, or CLL prior PI3K inhibitor exposure cohorts only on Cycle 1, Day 15
  - GS-9973 SDD plasma concentration pre-dose and at 1.5 hours post-dose (± 10 minutes) for CLL dose ranging, CLL prior BTK inhibitor exposure, or CLL prior PI3K inhibitor exposure cohorts only on Cycle 1, Day 15, Cycle 1, Day 22 and Cycle 2, Day 15

  ONLY for subjects with SLL, CLL or MCL

  - Cytokines and chemokines on **Cycle 1, Day 8**
  - CTC Molecular Characterization on Cycle 2, Day 15
  - Genomic testing for CLL dose ranging, CLL prior BTK inhibitor exposure, or CLL prior PI3K inhibitor exposure cohorts only on **Cycle 2, Day 15**
- Record the approximate number of hours between the last 2 doses of GS-9973 SDD and the time the blood samples for plasma concentration were obtained
- Urine pregnancy test (for females of childbearing potential) only on Day 15 of Cycles 1 and 2
- 12-lead ECG
- Record any AEs

6.4. Unscheduled Safety Visits

Unscheduled safety visits will be conducted as needed during the study. Some or all of the following procedures can be obtained as clinically indicated:

- Modified physical examination capturing changes from prior exams and weight will be performed
- Vital signs including blood pressure, respiratory rate, pulse, oxygen saturation by pulse oximetry, temperature
- Karnofsky performance status (see Section 6.9.3)
- Concomitant Medication Review
- Obtain blood samples for:
  - Chemistry (see Section 6.9.8)
  - Hematology (see Section 6.9.8)
  - Coagulation (see Section 6.9.8)
- 12-lead ECG
- Record any AEs

6.5. Assessment of Tumor Response

The procedures to assess tumor response will be conducted every 8 weeks during the first 24 weeks on study and then every 12 weeks up to 72 weeks, regardless of cycle number and regardless of any dose interruptions (ie, Weeks 8, 16, 24, 36, 48, 60, 72, etc). Tumor assessments must be done any time during the specified week (+/-3 days around the week). Therefore there is a 13-day window to conduct tumor assessments that begins 3 days prior to the start of the last week of the corresponding 28-day cycle and ends 3 days after the last day of that same corresponding cycle. The description of the assessments to be conducted are detailed in Section 6.12 and outlined in the Study Procedures Table in Appendix 2.

A bone marrow biopsy and aspirate will be collected for all subjects who achieve a CR for confirmatory purpose. For LPL/WM without adenopathy and CLL subjects a bone marrow biopsy/aspirate will be collected to confirm a PD if based only upon declines in the platelet count and/or hemoglobin for CLL subjects or rise in Serum monoclonal IgM in LPL/WM. For all LPL/WM patients who achieve CR or PD and are not evaluable by radiological criteria require confirmation by bone marrow evaluation. If the subject does not otherwise meet criteria for CR or if the nature of PD does not require bone marrow confirmations, it is not necessary to obtain a bone marrow biopsy/aspirate (See Sections 6.20 and 6.21).

ONLY for subjects with LPL/WM, an evaluation of serum monoclonal IgM by both SPEP and IFE will be conducted including cryoglobulin testing (LPL/WM enrollment limited to those sites which have cryoglobulin analysis capabilities). Serum monoclonal IgM as assessed by SPEP will only be considered if baseline total serum IgM quantitation by nephelometry is not available.

This procedure should be conducted on the Day 1 visit occurring during the week window allotted for tumor response assessments. LPL/WM subjects who do not have lymphadenopathy on their screening CT/MRI evaluations are not required to have repeated scans for tumor assessment unless clinically indicated, but all subjects in this subset will require BM evaluations for suspected PD or CR assessments.

Subjects who stop study drug for reasons other than progression of disease (eg, experience unacceptable toxicity) should be continued on the study and followed every 6 months or according to institutional standard of care (if more frequent) until progression is documented or another anti-tumor regimen is initiated. An end of study visit need only to be conducted per Section 6.7 if the subject comes off of study and is no longer to be followed.

6.5.1. Clinical Evaluation after 72 weeks (18 months)

After 72 weeks on study, the subject will be followed for disease status at a minimum of every 6 months or according to institutional standard of care (if more frequent). At each study visit the subject's disease status will be assessed and information will be collected to determine response to treatment. If no change in disease status is identified and the subject is dispensed additional GS-9973/GS-9973 SDD, the most recent prior response documented for the study will be recorded.

All subjects with CLL should have the following laboratory test results recorded at each visit: ALC, PLT, Hgb, ANC. All subjects with WM should have the following laboratory test results recorded at each evaluation visit: IgM, serum M protein.

All subjects will have a CT scan at least once every 6 months and at time of clinical change in response (PR or CR after SD, or CR after PR) or progression. In addition, for initial CR a bone marrow evaluation is required.

6.6. At Disease Progression

All subjects will be followed until initiation of next treatment. If the subject was not receiving study drug at the time tumor progression was documented, or was at a dose level below the maximum and could potentially tolerate a higher dose, after discussion with the Gilead Sciences Medical Monitor, the subject may continue on study and study drug may be re-started or escalated using the algorithm defined in Section 5.3.5 if the investigator feels it is in the subject's best interests to do so.

If the investigator feels the subject is having progressive disease, tumor imaging as described in Section 6.12 should be carried out unless the most recent imaging had documented progressive disease. The images and any other material needed to document progression are to be transferred to the IRC as soon as possible. While waiting for confirmation of progressive disease from the IRC, the subject should continue to receive study drug unless his/her medical condition warrants immediate treatment with different therapy. When progression is confirmed, the following procedures should be carried out while the subject is still receiving study drug.

- Complete physical examination including weight
- Vital signs including blood pressure, respiratory rate, pulse, oxygen saturation by pulse oximetry, temperature
- Karnofsky performance status (see Section 6.9.3)
- Concomitant Medication Review
- Obtain blood samples for:
  - Chemistry (see Section 6.9.8)
  - Hematology (see Section 6.9.8)
  - Coagulation (see Section 6.9.8)
  - GS-9973/GS-9973 SDD plasma concentration (excluding subjects off study drug at time of progression)

  For subjects with SLL, CLL or MCL

  - CTC Molecular characterization (see Section 6.14)
  - Cytokines and chemokines (see Section 6.13.1)
  - CTC RNA pre-dose (see Section 6.13.2)

CCI [redacted]

- Record the approximate number of hours between the last 2 doses of study drug and the time the blood samples for plasma concentration were obtained (excluding subjects off study drug at time of progression)
- Urine pregnancy test (females of childbearing potential)

- For CLL subjects a bone marrow biopsy/aspirate will be collected to confirm a PD. If the nature of PD does not require bone marrow confirmations, it is not necessary to obtain a bone marrow biopsy/aspirate (See Section 6.20).

- Collect used/unused study drug and assess study drug compliance by pill counts (excluding subjects off study drug at time of progression)

- Record any AEs

- Complete subject/visit information in IxRS

6.7. End of Study

The following procedures will be conducted when a subject goes off study and prior to initiating a new anti-tumor regimen. If a subject stops study drug for a reason other than progressive disease, they will be followed as per the scheduled imaging in Section 6.5 with additional CBC (hematology) at time of assessments. If the subject chooses not to continue participation on the study once study drug has been stopped or it is not consistent with good medical practice then the end of study procedures listed below are to be conducted within 30 days of the last dose of study drug or prior to initiating a new anti-tumor regimen. Please see Study Procedures Table in Appendix 2.

The end of study visit and disease progression visit Section 6.6 can occur simultaneously; however, if the end of study visit was not performed at the same time as disease progression, perform the following:

- Complete physical examination including weight

- Vital signs including blood pressure, respiratory rate, pulse, oxygen saturation by pulse oximetry, temperature

- Karnofsky performance status (see Section 6.9.3)

- Concomitant Medication Review

- Obtain blood samples for:

  — Chemistry (see Section 6.9.8)

  — Hematology (see Section 6.9.8)

  — Coagulation (see Section 6.9.8)

  — GS-9973/GS-9973 SDD plasma concentration

For subjects with SLL, CLL or MCL

— CTC Molecular characterization (see Section 6.14)

— Cytokines and chemokines(see Section 6.13.1)

— CTC RNA pre-dose (see Section 6.13.2)

- Record the approximate number of hours between the last 2 doses of GS-9973/GS-9973 SDD and the time the blood samples for plasma concentration were obtained
- Urine pregnancy test (females of childbearing potential)
- Collect used/unused study drug and assess study drug compliance by pill counts
- Tumor response assessment (according to Section 6.5), if not conducted within the last 4 weeks
- Record any AEs
- Complete subject/visit information in IxRS

6.8. Immediate Post-Treatment Safety Follow-up

After the last dose of study drug, subjects should be followed for any drug-related AEs and/or ongoing serious adverse events (SAEs) until those events have resolved or become stable, whichever occurs later. The site will contact the study subject regardless of AE/SAE status or initiation of new anti-tumor regimen 30 (± 7) days following completion of the subject's last dose of study drug to assess for AEs. Subjects will specifically be asked about the development of any adverse events since stopping the study. Contact the subject by phone (or in person, if necessary) to assess the subject's condition and record any adverse events reported during the follow-up contact. Document the phone call or visit.

6.9. Description of Study Procedures

6.9.1. Medical History

A complete medical history will be obtained by the Investigator or designee. Medical history will include information on the subject's prior anti-tumor therapies, significant past medical events (including prior hospitalizations or surgeries), and any concurrent medical illness.

6.9.2. Physical Examination

The Investigator or qualified designee will perform a physical examination at screening and time points outlined in the Study Procedures Table (Appendix 2). Screening abnormal findings will be reported on the medical history page of the eCRF. Any changes from the Screening (baseline) physical examination which represent a clinically significant deterioration will be documented on the AE page of the eCRF.

Height measurement (in centimeters) will be obtained at Screening. Weight measurements (in kilograms) will be obtained at Screening and time points outlined in the Study Procedures Table (Appendix 2).

6.9.3. Karnofsky Performance Status

Karnofsky Performance Status will be assessed using the following scale:

Karnofsky Performance Status	Description
100	Normal. No complaints
90	Able to carry on normal activity. Minor signs or symptoms of disease.
80	Normal activity with effort. Some signs or symptoms of disease.
70	Able to care for self. Unable to carry on normal activity or to do active work.
60	Requires occasional assistance, but is able to care for most needs.
50	Requires considerable assistance and frequent medical care.
40	Disabled. Requires special care and assistance.
30	Severely disabled. Hospitalization is indicated although death not imminent.
20	Hospitalization necessary, very sick, active supportive treatment necessary
10	Moribund. Fatal processes progressing rapidly.
0	Dead

Source: {Schag 1984}

6.9.4. Vital Signs

Vital signs, including oxygen saturation by pulse oximetry, blood pressure, respiratory rate, pulse, and temperature will be measured at the time points listed in the Study Procedures Table in Appendix 2. All measurements will be recorded on the appropriate eCRF page with appropriate source documentation. Any abnormal measurements may be repeated and reported as AEs, if appropriate. All measures of blood pressure will be performed using standard sphygmomanometry. Vital signs should be taken after the subject has been sitting for at least 5 minutes.

6.9.5. Electrocardiogram

Twelve (12)-lead ECGs reporting ventricular rate, PR, QRS, QT, and QTc intervals will be obtained at screening, safety monitoring visits and, if clinically indicated, during the course of the study.

The Investigator or qualified designee will review all ECGs. The ECG tracings will be maintained in the source documentation of each subject and the appropriate data reported on the eCRF.

6.9.6. Adverse Events

Subjects will be assessed for AEs per guidelines in the CTCAE (version 4.03) during each outpatient visit as outlined in the Study Procedures Table (Appendix 2). Any AEs reported throughout the study will be recorded in the eCRF with appropriate source documentation. The site will contact the study subject by phone (or in person, if necessary) 30 (± 7) days following completion of the subject's last dose of study drug to assess for AEs.

6.9.7. Prior/Concomitant Medications

At screening all medication taken up to 30 days prior to the screening visit will be recorded on the eCRF. At each study visit, the site will capture any and all medications taken by the subject since the last visit or during the visit (as applicable). Concomitant medications include prescription, non-prescription medications, vitamins, and minerals.

6.9.8. Laboratory Safety Tests

Blood will be collected for laboratory safety tests according to the Study Procedures Table in Appendix 2. The date and time of blood collection will be recorded in the subject's source documentation. The tests will be analyzed using standard procedures. White blood cell differentials will be reported as absolute counts. All laboratory tests must be reviewed by the Investigator or qualified designee.

The following analytes will be tested (see Table 6-1):

Table 6-1. Blood Samples Collected During the Course of the Study

<table>
<tr><th>Serum Chemistry</th><th>Hematology</th><th>Other</th></tr>
<tr><td rowspan="15">Sodium
Potassium
Chloride
Glucose
BUN
Creatinine
ALT
AST
Alkaline phosphatase
Total bilirubin
Direct bilirubin
Total protein
Albumin
Calcium
Magnesium
Phosphate
Total CPK</td><td>White Blood Cell (WBC) Count
Hemoglobin
Hematocrit
Reticulocyte counts
Platelet Count
Differential</td><td rowspan="15">Pharmacodynamic measurements

GS-9973 plasma concentration

Pharmacogenomics assessment</td></tr>
<tr><td>Coagulation</td></tr>
<tr><td>PT/INR
aPTT</td></tr>
<tr><td>Pregnancy Testing</td><td>Virology</td></tr>
<tr><td>Serum Qualitative β-HCG (females of childbearing potential)[a]
Urine[b] Pregnancy (females of childbearing potential)</td><td>Hep B
Hep C
HIV</td></tr>
</table>

a Serum pregnancy will be conducted at Screening.
b Urine pregnancy will be conducted pre-dose on Days 1 and 15 of Cycles 1 & 2, Disease Progression and at EOS

6.10. Blood Collection

Computations of blood drawing requirements for this study are shown in Table 6-2. The maximum amount of blood to be drawn at a visit is 86.3 mL and the maximum amount of blood to be drawn over the initial 52-week study period (including the 5-week screening period and through Week 47 of the study) is ~419.1 mL. For a 45-kg person (the smallest participant expected to enroll in the study) this equates to maximum blood volume per body weight per visit of ~2.03 mL/kg and a total blood volume per body weight per average 6-week period of ~1.07 mL/kg. These quantities of blood are within accepted limits of 3.0 mL/kg of body weight for a single blood draw and 7.0 mL/kg of body weight for a 6-week period. {U.S. Department of Health and Human Services 2010}

Table 6-2. Blood Drawing Requirements

Test		Sample Type	Blood Per Tube (mL)	Tubes (n)		Blood Volume (mL)	
				Maximum Per Visit	Maximum in Study[a]	Maximum Per Visit	Maximum in Study[a]
Serum virology	Hep B surface antigen, Hep C antibody	Serum	2.5	1	1	2.5	2.5
	HIV1/HIV2 antibody	Serum	3.5	1	1	3.5	3.5
Coagulation		Plasma	1.8	1	17	1.8	30.6
Hematology		Whole Blood	2	1	17	2	34
Serum chemistry (including β-HCG)		Serum	2.5	1	17	2.5	42.5
CTC* SLL/ CLL / MCL Molecular Characterization	Flow Cytometry	Whole Blood	8	1	3	8	15
	Cytogenetics	Whole Blood	8	1	3	8	15
	Molecular Pathology	Whole Blood	8	1	3	8	15
	RNA	Whole Blood	2.5	2	13	5	65
CLL	Basophil Activation Assay	Whole Blood	2	3	6	6	12
	PBMC for genomics	Whole Blood	10	3	9	30	90
Chemokines / Cytokines		Serum	5	2	18	10	90
GS-9973 Drug Levels		Plasma	4	1	1	4	4
Total						91.3	419.1

a Computed for the initial 52-week period (considering 5 weeks for screening and 47 weeks on study with the maximum number of samples for a specific test)

* The CTC samples will be collected only for SLL, CLL, and MCL subjects

CTC=Circulating Tumor Cells, β-HCG=beta human chorionic gonadotropin, RNA=ribonucleic acid, PBMC=peripheral blood mononuclear cells

Specific details regarding blood sample collection and processing requirements will be provided separately in the laboratory manual. The above volumes are approximate and may change depending on the need to further assess clinical status of a subject as determined by the Investigator. CCI

[redacted]

6.11. Pregnancy Testing for Females of Childbearing Potential

All female subjects of childbearing potential will have a serum pregnancy test at Screening and urine pregnancy test on Days 1 and 15 of each cycle, Disease Progression and at the End of Study visit. The results must be confirmed as negative prior to permitting continued participation on the study.

6.12. Tumor Imaging (CT or MRI)

CT or MRI scans will be obtained to document sites of disease, identify target lesions as described in Section 6.20.4 and 6.21.4 and to assess response and disease progression. 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 iodine-containing or gadolinium contrast material may be omitted in subjects for whom use of a contrast agent would be medically contraindicated. Imaging of the neck, chest, abdomen and pelvis by CT scan (with contrast) or MRI will be performed as part of the Screening Procedures (or within 5 weeks before Dosing Day 1 if the scan was performed as part of standard medical practice). Imaging will then occur every 8 weeks from Cycle 1 Day 1 date during the first 24 weeks of the study and then every 12 weeks thereafter until week 72 regardless of any dose interruptions. After week 72 scans will occur at least every 6 months (± 4 weeks). At all timepoints after Screening, imaging of the chest, abdomen, and pelvis will be required. Imaging of the neck is required at each follow-up time point if the neck scan was positive at baseline or if palpable neck lymphadenopathy appears during the course of the study.

The imaging procedure and specification (eg, the same contrast agent, slice thickness, etc.) used to define measurable target and non-target lesions must be used throughout the study for each subject. Any subject with symptoms suggestive of disease progression should be evaluated for tumor response at the time the symptoms occur. Tumor burden will be characterized at baseline and subsequent response assessments will be carried out according to Section 3. Scans need to be of high quality and digitalized in the Digital Imaging and Communication in Medicine (DICOM) format to be collected and to allow for reading by the IRC (see Section 9.4).

6.13. Pharmacodynamic Assessments

To evaluate the biological effects of GS-9973, samples for pharmacodynamic assessments of drug activity, such as CD63 modulation on basophils, will be obtained on CLL subjects only prior to starting treatment, 1.5 hours and 4 hours after the first dose, predose and 4 hours on Day 8 of Cycle 1 and predose on Day 15 of Cycle 1. **The collection of some or all of these samples may not be feasible at the site due to shipment logistics depending on their geographic location. In addition, sampling timepoints may be eliminated based upon emerging data.**

Because this is a rapidly evolving area of investigation, it is not possible to precisely specify which tests will eventually be done on the specimens provided. ***The testing outlined below is based upon the current state of knowledge and may be modified to drop tests no longer indicated or to add new tests based upon the knowledge base at the time.***

6.13.1. Serum Cytokines and Chemokines

Samples will be analyzed for disease related systemic cytokines and chemokines, which will include at a minimum, but will not be limited to, CCL3, CCL4, CXCL12, CXCL13, and tumor necrosis factor-α.

6.13.2. Circulating Tumor Cells (CTC) – RNA Analysis

For SLL, CLL, and MCL subjects only, RNA sample assessments will include at a minimum, but will not be limited to, expression of c-myc, PTEN, p53, ZAP-70, beta-2 microglobulin levels and bcl-2.

6.14. SLL/CLL/MCL Molecular Characterization

Peripheral blood will be collected from SLL, CLL, and MCL subjects on Day 1 of Cycle 1, Day 15 of Cycle 2, and at disease progression to assess molecular markers for disease progression, response to treatment, and overall prognosis. The baseline status as well as any changes in these molecular markers will be correlated with response to GS-9973.

For consenting subjects in the CLL dose ranging, CLL prior BTK inhibitor exposure, or CLL prior PI3K inhibitor exposure cohorts only, cells will also be extracted from lymph node aspirates at Cycle 1 Day 1 and time of progression for DNA and RNA analysis.

Because this is a rapidly evolving area of investigation, it is not possible to precisely specify which tests will eventually be done on the specimens provided. ***The testing outlined below is based upon the current state of knowledge and may be modified to drop tests no longer indicated or to add new tests based upon the knowledge base at the time.***

6.14.1. Flow Cytometry

6.14.1.1. SLL and CLL

- Differential cell count
- Lymphoid panel – CD2, CD3, CD4, CD5, CD7, CD8, CD10, CD11c, CD19, CD 20, CD38, CD45, CD56, CD57, Kappa, Lambda
- ZAP-70 panel: CD3, CD5, CD19, ZAP-70, CD45

6.14.1.2. MCL

- Differential cell count
- Lymphoid panel – CD2, CD3, CD4, CD5, CD7, CD8, CD10, CD11c, CD19, CD 20, CD38, CD45, CD56, CD57, Kappa, Lambda

6.14.2. Cytogenetics

6.14.2.1. SLL and CLL

- CTG-banding followed by FISH - specific probes: 11q22,3 (ATM)/17p13 (TP53); CEP12/13q14 (D13S319)/13q34; CEP6/6q23 (c-MYB); t(11;14)(CCND1/IGH); c-MYC Break-apart

6.14.2.2. MCL

- CTG-banding followed by FISH - specific probes: t(11;14)(CCND1/IGH); c-MYC Break-apart

6.14.3. Molecular Pathology

6.14.3.1. SLL and CLL

- Molecular Diagnostic tests:
  - IGHV mutation analysis with specific IGHV family and mutation frequency; beta-2 microglobulin levels
  - NOTCH1 mutation analysis;
  - TP53 mutation analysis;
  - MatBA CLL/SLL Array CGH - microarray-based comparative genomic hybridization to simultaneously detect the gain and loss of multiple loci in specimen DNA, includes Loss of 8p, loss of 11q (ATM), loss of 13q (MIR15A/16-1), loss of 13q (RB1), loss of 17p (TP53), gain of 2p, gain of 3q, gain of 8q, gain of 12.

6.14.3.2. MCL

- Molecular Diagnostic tests:
  - B-cell clonality (IGH)
  - NOTCH1 mutation analysis
  - TP53 mutation analysis
  - MatBA MCL

6.15. Samples for Molecular/Pharmacogenomic Testing

A separate blood specimen will be collected on Cycle 1 Day 1, Cycle 2 Day 15, and time of disease progression to isolate PBMC for CLL. The PBMC samples will be sorted for B cell enrichment and stored separately. Matched buccal swab samples will be collected at Cycle 1 Day 1 for DNA extraction and analysis to serve as germline control. CCI [redacted] This specimen will be used to study genetic and genomic mechanisms involved in B-cell malignancy pathogenesis, progression, resistance and outcome. CCI [redacted]

CCI [redacted]

[redacted]

6.16. Archival Tumor Tissue

Fifteen (15) recently prepared (not more than 2 weeks prior to submission) unstained slides from archival tumor tissue will be requested for all subjects who have tissue available. Immunohistochemical staining and/or mass spectrophotometric analysis of proteins harvested from these tumor samples will be conducted to assess known disease prognostic markers, as well as expression of SYK and other proteins, including kinases and various growth factors within the tumor, and other measures related to the underlying malignancy. Genetic basis for disease may also be explored in these samples.

If the subject has DLBCL, subtyping is required. Submission of 15 unstained slides is required for subtyping. Given the possibility that not all DLBCL subjects will respond to therapy, we will investigate tumor characteristics that may be associated with clinical responses, such as CD79b mutations. Protein markers such B cell receptor signaling phosphoproteins, gene expression and DNA will be evaluated from tumor tissue to inform mechanisms of drug activity.

6.17. Optional Future Biomarker Research

CCI [redacted]

CCI [redacted]

6.19. Biological Sample Storage

CCI [redacted]

6.20. Efficacy Assessments: Non-Hodgkin Lymphoma

6.20.1. Tumor Status Assessments

The determination of NHL response and progression will be based on standardized criteria {Cheson 2007, Rourke 2010} as specifically modified for this study to reflect the biology of the diseases under study and the pharmacology of study drugs and the methods to be used in evaluation. During the course of the study, investigators will periodically assess the status of each subject's NHL. 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 will be based on these assessments. Radiographic tumor assessments will be subject to independent confirmation by the IRC (see Section 9.4). The findings of the IRC will be considered primary for analyses of PFS and other tumor control endpoints.

6.20.2. Method of Assessment

In addition to clinical examination, imaging-based evaluation will be used in this study in all subjects enrolled. CT scan is the preferred method for radiographic tumor assessment. MRI scanning may be used at the investigator's discretion in subjects for whom this may be a preferred alternative to CT scanning. Contrast-enhanced scanning is preferred, but iodine-containing or gadolinium contrast material may be omitted in subjects for whom use of a contrast agent would be medically contraindicated. PET scanning can be performed as appropriate. As appropriate, study drug dosing delays, bone marrow aspirate/biopsy information (eg, for confirmation of CR) and biopsy information (eg, for documentation of disease transformation to an aggressive histology) will also be considered. For LPL/WM, quantitative monoclonal IgM protein as assessed by SPEP and IFE will be considered. Clinical palpation, 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 treatment and follow-up. Furthermore, the use of IV contrast should be consistent across timepoints. In the event that the screening/baseline CT scan of the neck, chest, abdomen and pelvis is performed without IV contrast, the follow-up time points should also be performed without IV contrast. CT or MRI of the neck, chest, abdomen, and pelvis should be performed with cuts of ≤ 1.0 cm (ideally ≤ 0.5 cm) in slice thickness contiguously. At Screening CT or MRI of neck, chest, abdomen, and pelvis is required. At all timepoints after Screening imaging of the chest, abdomen, and pelvis will be required. Imaging of the neck is required at each follow-up time point if the neck scan was positive at baseline or if palpable neck lymphadenopathy appears during the course of the study.

All relevant clinical and radiographic information required to make each tumor status assessment must be made available for source verification and for submission to the IRC (see Section 9.4).

For subjects with WM, serum monoclonal IgM as assessed by SPEP will only be considered if baseline total serum IgM quantitation by nephelometry is not available. The same laboratory method for IgM assessment within a given subject should be used throughout the study.

6.20.3. Timing of Assessments

During screening, clinical and imaging-based tumor assessments should be performed within 5 weeks prior to the start of study drug. Clinical tumor assessments should be performed at each clinic visit. On-study CT/MRI tumor assessments should be performed at ~8- to 12-week intervals. An End of Study 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 NHL progression, investigators should continue further follow-up at ~8 or ~12-week intervals until NHL progression is documented.

6.20.4. Identification of Index and Non-Index Tumor Lesions

At baseline, tumor lesions will be categorized as index lesions or non-index lesions as described below.

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

Index lesions will be measured and recorded at baseline and at the stipulated intervals during treatment. The cross-sectional dimensions (the largest cross-sectional diameter, ie, the longest diameter [LD] × the longest perpendicular diameter [LPD]) will be recorded (in cm) for each index lesion. The product of the perpendicular diameters (PPD) will be calculated. The PPDs and 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 treatment. All PPD and SPD measurements will be reported in centimeters squared.

6.20.4.1. Index Lesions

6.20.4.1.1. 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 that is > 1.0 cm and is considered measurable if it has 2 perpendicular diameters that can be accurately measured in cross section with the LD being ≥ 1.0 cm and the LPD also being ≥ 1.0 cm.

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

- Large nodal lesions have a LD that is > 1.5 cm and a 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.

6.20.4.1.2. 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 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.

6.20.4.2. 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 nodal lesions or 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, or lesions with artifacts may be considered as non-index disease.

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

6.20.5. Follow-up of Index and Non-Index Tumor Lesions

6.20.5.1. Nodal Lesions

At follow-up time points, the LDs for individual nodal lesions and the SPD of all nodal index lesions will be considered. Because nodal index lesions that have one or both diameters > 0 cm and < 1.0 cm cannot be reliably measured, a default value of 1.0 cm will be assigned for each diameter that meets these criteria and the resulting PPD will be used in SPD calculations. Based on this convention, a CR may be achieved even if an SPD value is > 0 cm^2.

New or enlarging nodal lesions that are still ≤ 1.0 cm by ≤ 1.0 cm will not be considered to represent recurrent or progressive disease. 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 progressive disease.

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

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

6.20.5.2. Extra-nodal Lesions

At follow-up time points, the LD of each single extra-nodal lesion and the SPD of all extra-nodal index lesions will be considered. Because extra-nodal index lesions that have one or both diameters < 1.0 cm and > 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 progressive disease. A new unequivocal extra-nodal lesion of any size that appears at a site that was not previously involved with lymphoma and is discernable to the radiologist by CT/MRI scan will be considered progressive disease.

6.20.5.3. Definition of Diffuse Disease in the Liver and Spleen

The radiologist will make a qualitative assessment of change in the size of the liver and spleen, and will not perform quantitative measurements of these organs.

Liver and spleen size should be reported as normal, enlarged not due to lymphoma, enlarged due to lymphoma (nodules must be present for this to be reported), unequivocal increase not due to lymphoma, or unequivocal progression (nodules must be present for this to be reported).

6.20.5.4. 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 NHL 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 NHL. In a subject who has a baseline bone marrow biopsy showing no evidence of NHL, declaration of an on-study CR does not require bone marrow examination as long as other criteria for CR are met.

6.20.5.5. Biopsy

Biopsy is not required in the determination of subject eligibility. However, subjects with evidence of transformed aggressive lymphoma on biopsy are ineligible for study participation.

During study participation, a subject who has a biopsy indicating 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 will be considered the date of NHL progression.

6.20.5.6. Serum Monoclonal IgM Protein (LPL/WM Only)

Assessment of circulating monoclonal IgM by quantitative SPEP and IFE should be performed for subjects with LPL/WM.

6.20.6. Date of Time Point Response and Progression

For subjects who have imaging examinations on various dates that are nevertheless assigned to the same time point, the following rules apply for the calculation of the endpoint date:

- The response date will be the last date associated with that particular imaging time point.
- The progression date will be the first date associated with that particular imaging time point.

6.20.7. Definitions of Tumor Response and Progression

6.20.7.1. Best Overall Response

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

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

- A radiological best overall response of CR, PR, SD, PD, NE and ND is allowed.
- Neither a PR nor an SD designation may follow a CR. Once a CR is observed, the subject will continue to be considered to have CR status until the criteria for PD are met.
- An SD designation may not follow a PR designation. In cases where a subject has an apparent worsening of lesions following a PR, the subject will continue to be considered to have PR status until the criteria for PD are met.

- Subjects will be defined NE if there is no adequate on-treatment radiological response assessment. NOTE**:** These subjects will be counted as failures in the primary analysis of tumor response data.
- For subjects with LPL/WM, a minor response and very good partial response is allowed based on a reduction of monoclonal IgM concentrations.

6.20.7.2. Complete Response

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

- No evidence of new disease
- Regression of all index nodal masses to normal size (ie, ≤ 1.5 cm in the LD for nodes that were considered large at baseline and ≤ 1.0 cm in the LD for nodes that were considered small at baseline) (see Section 6.20.4.1.1 for definitions of large and small nodes)
- Regression to normal of all nodal non-index disease and 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 organ 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
- If PET performed (eg, for DLBCL), no evidence of residual disease
- If the subject has WM, disappearance of serum monoclonal protein by IFE and normal serum IgM level

6.20.7.3. Very Good Partial Response (LPL/WM) only

To satisfy criteria for VGPR, both of the following criteria must be met:

- A >90% decrease from baseline in monoclonal IgM concentration by SPEP or total serum IgM quantitation by nephelometry
- Other criteria for CR are met (see Section 6.20.7.2)

6.20.7.4. Partial Response

To satisfy criteria for a PR, all of the following criteria must be met except for subjects with WM as noted below:

- No evidence of new disease
- A ≥ 50% decrease from baseline in the SPD of the index nodal and extra-nodal lesions (eg, splenic or hepatic nodules)

- No increase in the size of non-index nodes or non-measurable disease
- No increase in the size of the liver or spleen and no new organ enlargement
- Persistence of bone marrow involvement in a subject who meets other criteria for CR based on the disappearance all nodal and extra-nodal masses
- If PET performed (eg, for DLBCL):
  - Typically FDG-avid lymphoma: if no pretreatment MRI
  - scan or if the PET scan was positive before therapy, the on-treatment PET is positive in ≥ 1 previously involved site
  - 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 treatment. If the PET scan was positive before therapy, the on-treatment PET is positive in ≥ 1 previously involved site.
- For subjects with LPL/WM:
  - A ≥50% decrease from baseline in monoclonal IgM concentration by SPEP or total serum IgM quantitation by nephelometry
  - Any decrease from baseline in the SPD of the index nodal and extral-nodal lesions (eg, splenic or hepatic nodules)

6.20.7.5. Minor Response (LPL/WM only)

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

A ≥25% but <50% decrease from baseline in monoclonal IgM concentration by SPEP or total serum IgM quantitation by nephelometry

- No increase from baseline in the SPD of the index nodal and extra-nodal lesions (eg, splenic or hepatic nodules)
- No increase in the size of non-index nodes or non-measurable disease
- No increase in the size of the liver or spleen and no new organ enlargements

6.20.7.6. 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 from nadir to qualify for PD

- If the subject has LPL/WM, neither a sufficient decrease from baseline in either monoclonal IgM concentration or total serum IgM quantitation by nephelometry to qualify for MR or PR nor a sufficient increase from nadir in either monoclonal IgM concentration by SPEP or total serum quantitation by nephelometry to qualify for PD

6.20.7.7. Progressive Disease

The occurrence of any of the following events indicates PD:

- Evidence of any new disease that was not present as baseline:
  - A new node that measures > 1.5 cm in any diameter
  - 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.
- 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 if an individual node or extra-nodal mass that now has an LD > 1.5 cm and an LPD of > 1.0 cm.
- Unequivocal increase in the size of non-index lesions or non-measurable disease (eg, pleural effusions or bone lesions)
- An unequivocal increase in the size of the liver, spleen, or other organ
- If PET performed (eg, DLBCL):
  - 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

- Pseudo-progression characterized by a paradoxical rise in serum IgM followed by a delayed response has been recognized early in the course of treatment of subjects with WM/LPL treated with chemotherapy and immunotherapy. The time to responses following pseudo-progression may be delayed for >4 months in some cases. Expert opinion specifically cautions against premature disease response assessment in LPL/Waldenström's therefore unless there is compelling clinical and objective data of progression all subjects should have at least 4 months of treatment before an assessment of PD is made. When assessing for progression a bone marrow biopsy and/or CT scan should be used in conjunction with serum IgM levels to assess disease burden. Criteria for progression based on serum IgM include, a ≥ 25% increase from the nadir in either monoclonal IgM concentration by SPEP or total serum IgM quantitation by nephelometry (with confirmation by a repeat measurement) at least 6 weeks apart.

- An absolute increase of at least 0.5 gram/dL is required to define progression with confirmation at least 6 weeks apart.

Note: If there is uncertainty regarding whether there is true progression, the subject may continue study treatment and remain under close observation (eg, evaluated at 4-week intervals). If subsequent evaluations suggest that the subject is experiencing progression, then the date of progression should be the timepoint at which progression was first identified. A single PD determination followed by a determination that indicates either no change or improvement in disease prior to the single PD observation will not be considered PD.

6.20.7.8. Non-Evaluable

In a subject who does not have evidence of PD, no images or inadequate or missing images indicates a response status of NE. In a subject with LPL/WM, missing on-study monoclonal IgM concentration by SPEP or total serum IgM quantitation by nephelometry will result in response status of NE. If the baseline IgM value is missing, IgM will not be considered for the on-study disease assessments.

6.20.7.9. No Disease

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

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

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

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

- In a subject with LPL/WM, the additional requirement that serum monoclonal IgM protein as assessed by SPEP is absent at both baseline and on-study.

6.21. Efficacy Assessments: Chronic Lymphocytic Leukemia

6.21.1. Tumor Status Assessments

The determination of CLL response and progression will be based on standardized IWCLL criteria {Hallek 2008}, as specifically modified for this study considering the pharmacology of GS-9973 and the methods to be used in evaluation. During the course of this study, investigators will periodically assess the status of each subject's CLL. If CLL progression is suspected, the IRC will be notified and radiographic and pertinent clinical data provided in order to provide expert interpretation (see Section 9.4). The findings of the IRC will be considered primary for analyses of PFS and other tumor control endpoints.

6.21.2. Method of Assessment

In addition to clinical examination, imaging-based evaluation will be used in this study in all subjects enrolled. CT scan is the preferred method for radiographic tumor assessment. MRI scanning may be used at the investigator's discretion in subjects for whom this may be a preferred alternative to CT scanning; however, if MRI is performed, a non-contrast CT of the chest should be performed. Contrast-enhanced scanning is preferred, but iodine-containing or gadolinium contrast material may be omitted in subjects for whom use of a contrast agent would be medically contraindicated. Chest x-ray, ultrasound, endoscopy, laparoscopy, radionuclide scans, or tumor markers will not be considered for response assessment.

At Screening CT or MRI of neck, chest, abdomen, and pelvis is required. At all timepoints after Screening imaging of the chest, abdomen, and pelvis will be required. Imaging of the neck is required at each follow-up time point if the neck scan was positive at baseline or if palpable neck lymphadenopathy appears during the course of the study.

For radiographic evaluations, the same method of assessment and the same technique (eg, scan type, scanner, subject position, dose of contrast, injection/scan interval) should be used to characterize each identified and reported lesion at baseline and during study treatment and follow-up. However, if a subject is imaged without contrast at baseline, subsequent assessments should be performed with contrast, unless the subject cannot tolerate the contrast. All relevant clinical and radiographic information required to make each tumor status assessment must be made available for source verification and for submission to the IRC (see Section 9.4).

6.21.3. Timing of Assessments

During screening, clinical and imaging-based tumor assessments should be performed within 5 weeks prior to the start of study drug. Clinical tumor assessments should be performed at each clinic visit. On-study CT/MRI tumor assessments should be performed at ~8- to 12-week intervals. An End of Study CT/MRI tumor assessment should be performed unless the subject already has radiographic confirmation of disease progression ≤ 4 weeks prior to study drug discontinuation. If a subject permanently discontinues study drug prior to objective documentation of CLL progression, investigators should continue further follow-up at ~8 or ~12-week intervals until CLL progression is documented.

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

6.21.4.1. Index Lesions

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

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

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

At follow-up time points, the LDs for individual lesions and the SPD of all nodal index lesions will be considered. Because nodal index lesions that have one or both diameters > 0 cm and < 1.0 cm cannot be reliably measured, a default value of 1.0 cm will be assigned for each diameter that meets these criteria and the resulting PPD will be used in SPD calculations. Based on this convention, a CR may be achieved even if an SPD value is > 0 cm^2, (ie, if all lymph nodes measure < 1.0 cm^2).

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

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

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

6.21.4.2. Spleen and Liver

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

6.21.4.2.1. Spleen

By imaging, the spleen will be considered enlarged if it is >12 cm in LVD {Bezerra 2005}, with the LVD being obtained by multiplying the number of sections on which the spleen is visualized by the thickness of the sections (eg, if the spleen is seen in 14 contiguous cross-sectional images with 0.5-cm thickness, the LVD is recorded as 7 cm).

For subjects with splenomegaly at baseline or at the splenic LVD nadir, respective response and progression evaluations of the spleen will consider only changes relative to the enlargement of the spleen (ie, the portion of the LVD that is >12 cm by imaging) at baseline or nadir, not changes relative to the total splenic LVD.

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

6.21.4.2.2. Liver

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

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

6.21.4.3. Non-Index Lesions

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

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

6.21.4.4. Biopsy

Biopsy is not required in the determination of subject eligibility. However, subjects with evidence of Richter's transformation to an aggressive lymphoma on biopsy are ineligible for study participation.

During study participation, a subject who has a biopsy indicating Richter's 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 will be considered the date of CLL progression.

6.21.5. Definitions of Tumor Response and Progression

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

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

6.21.5.1. Complete Response

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

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

— Hemoglobin ≥ 110 g/L (11.0 g/dL) without red blood cell transfusions or need for exogenous growth factors (eg, erythropoietin)

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

6.21.5.2. Partial Response

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

- No evidence of new disease
- Change in disease status meeting ≥ 2 of the following criteria, with 2 exceptions in which only 1 criterion is needed: (1) Only lymphadenopathy is present at baseline; (2) Only lymphadenopathy and lymphocytosis are present at baseline. In these 2 cases, only lymphadenopathy must improve to the extent specified below):
  - In a subject with baseline lymphocytosis (ALC ≥ 4 x 10^9/L), a decrease in peripheral blood ALC by ≥ 50% from baseline or a decrease to < 4 x 10^9/L
  - A decrease by ≥ 50% from the baseline in the SPD of the index nodal lesions
  - In a subject with enlargement of the spleen at baseline, a splenomegaly response as defined in Section 6.21.4.2.1
  - In a subject with enlargement of the liver at baseline, a hepatomegaly response as defined in Section 6.21.4.2.2
  - A decrease by ≥ 50% from baseline in the CLL marrow infiltrate or in B-lymphoid nodules
- No index, splenic, liver, or non-index disease with worsening that meets the criteria for definitive PD
- Peripheral blood counts meeting ≥ 1 of the following criteria:
  - ANC > 1.5 x 10^9/L or ≥ 50% increase over baseline without need for exogenous growth factors (eg, G-CSF)
  - Platelet count ≥100 x 10^9/L or ≥ 50% increase over baseline without need for exogenous growth factors
  - Hemoglobin ≥ 110 g/L (11.0 g/dL) or ≥ 50% increase over baseline without red blood cell transfusions or need for exogenous growth factors (eg, erythropoietin)

6.21.5.3. Stable Disease

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

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

6.21.5.4. Definitive Progressive Disease

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

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

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

- Evidence of worsening of index lesions, spleen or liver, or non-index disease:
  - Increase from the nadir by ≥ 50% in the SPD of index lesions
  - Increase from the nadir by ≥50% in the LD if an individual node or extra-nodal mass that now has an LD of >1.5 cm and an LPD of > 1.0 cm
  - Splenic progression, defined as an increase in splenic enlargement by ≥50% from nadir (with a minimum 2 cm increase and a minimum LVD of 12 cm)
  - Hepatic progression, defined as an increase in hepatic enlargement by ≥50% from nadir (with a minimum 2 cm increase and minimum LVD of 18 cm)

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

— Transformation to a more aggressive histology (eg, Richter syndrome) as established by biopsy (with the date of the biopsy being considered the date of CLL progression if the subject has no earlier objective documentation of CLL progression).

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

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

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

Note: If there is uncertainty regarding whether there is true progression, the subject should continue study treatment and remain under close observation (eg, evaluated at 4-week intervals) pending confirmation of progression status by the IRC. In particular, worsening of constitutional symptoms in the absence of objective evidence of worsening CLL will not be considered definitive disease progression. In such subjects, both CLL-related and non-CLL-related causes for the constitutional symptoms should be considered. Worsening of disease during temporary interruption of study treatment (eg, for intercurrent illness) is not necessarily indicative of resistance to study treatment. In these instances, CT/MRI or other relevant evaluations should be considered in order to document whether definitive disease progression has occurred. If subsequent evaluations suggest that the subject has experienced persistent definitive CLL progression, then the date of progression should be the timepoint at which progression was first objectively documented.

6.21.5.5. Non-Evaluable

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

- There are no images or inadequate or missing images.

- Images of the liver and spleen are missing at that time point (with the exception that absence of splenic images will not result in an NE designation in a subject known to have undergone splenectomy).

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

6.21.5.6. No Disease

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

- Index disease absent at both baseline and on-treatment.
- Non-index disease absent at both baseline and on-treatment.
- Enlargement of the liver and spleen absent at both baseline and on-treatment
- Abnormalities of peripheral blood counts (elevated ALC and abnormally low ANC, platelet count, and hemoglobin) and evidence of CLL in bone marrow (if available) absent at both baseline and on treatment

6.21.6. Lymphocytosis During Therapy

GS-9973 will probably mobilize CLL cells from tissues into the peripheral blood. This characteristic pharmacological action can be prominent early in therapy but can persist over time and should not be confused with disease progression in subjects who have persistent control of other CLL-related signs and symptoms. ***In the absence of other objective evidence of disease progression, the occurrence of lymphocytosis will not preclude subjects from meeting the criteria for a PR if other criteria for PR are met and will not be considered evidence of CLL progression if occurring in isolation.*** Subjects with lymphocytosis should be continued on study therapy until the occurrence of definitive disease progression (ie, disease progression that is manifest by worsening CLL-related signs other than lymphocytosis alone), or the occurrence of another reason to discontinue study therapy {Cheson 2012}.

6.22. Documentation of Definitive CLL Progression

Of importance, CLL response and progression data will be subjected to IRC review (see Section 9.4). If there is uncertainty regarding whether there is definitive progression, the subject should continue study drug(s) pending confirmation of progression status by the IRC**.**

7. ADVERSE EVENTS AND TOXICITY MANAGEMENT

7.1. Adverse Events

An adverse event (AE) is any untoward medical occurrence in a clinical investigation subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

AEs also include the following:

- All AEs that occur from the signing of the informed consent onwards and throughout the duration of the study, including the 30-day follow-up off-study period.
- Pre- or post-treatment complications that occur as a result of a protocol-mandated procedure (eg, venipuncture or biopsy) during or after screening (before the administration of study investigational medicinal product)
- Any pre-existing condition that increases in severity, or changes in nature during or as a consequence of the study investigational medicinal product phase of this trial, will also be considered an AE
- Complications and termination of pregnancy

An AE does not include the following:

- Medical or surgical procedures (eg, surgery, endoscopy, tooth extraction, transfusion) performed; the condition that led to the procedure may be an AE if applicable
- Pre-existing diseases or 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 7.7)
- Any medical condition or clinically significant laboratory abnormality with an onset date before the consent form is signed. It is considered to be pre-existing and should be documented on the medical history eCRF
- Uncomplicated pregnancy
- An induced elective abortion to terminate a pregnancy without medical reason

7.2. Serious Adverse Events

A **serious adverse event** (SAE) or serious adverse drug reaction (SADR) is defined as follows:

Any adverse drug experience occurring at any dose that results in any of the following outcomes:

- Death
- Life-threatening situation (subject is at **immediate** risk of death)
- In-patient hospitalization or prolongation of existing hospitalization
- Persistent or significant disability/incapacity
- Congenital anomaly/birth defect in the offspring of a subject who received investigational medicinal product
- Other: medically significant events that may not be immediately life-threatening or result in death or hospitalization, but based upon appropriate medical and scientific judgment, may jeopardize the subject or may require medical or surgical intervention to prevent one of the outcomes listed above

Examples of such events are as follows:

- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias or convulsions that do not result in hospitalization
- Development of drug dependency or drug abuse

Clarification regarding Serious Adverse Events

- Death is an outcome of an AE, and not an AE in itself.
- An SAE may occur even if the subject was not on investigational medicinal product at the time of occurrence of the event. Dosing may have been given as treatment cycles or interrupted temporarily before the onset of the SAE.
- "Life-threatening" means that the subject was at immediate risk of death from the event as it occurred. This does not include an event that might have led to death if it had occurred with greater severity.
- Complications that occur during hospitalizations are AEs. If a complication prolongs the hospitalization, it is a SAE.

- "In-patient hospitalization" means the subject is formally admitted to a hospital for medical reasons, for any length of time. This may or may not be overnight. It does not include presentation and care within an emergency department.

- The investigator should attempt to establish a diagnosis of the event on the basis of signs, symptoms and/or other clinical information. In such cases, the diagnosis should be documented as the AE and/or SAE and not the individual signs/symptoms.

Disease Progression and Death Related to Disease Progression:

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 drugs will not be considered SAEs:

- Progression of malignancy being studied

- Death due to malignancy being studied

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

7.3. Describing Adverse Event Relationship to Study Drug and Study Procedures

The relationship of an AE or SAE to investigational medicinal product should be assessed using clinical judgment, describing the event as either unrelated (No) or related (Yes) consistent with the following definitions:

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

- **Yes**: A temporal relationship exists between the AE onset and administration of the investigational medicinal product that cannot be readily explained by the subject's clinical state or concomitant therapies. Furthermore, the AE appears with some degree of certainty to be related, based on the known therapeutic and pharmacologic actions or AE profile of the investigational medicinal product. In case of cessation or reduction of the dose the AE may abate or resolve and it may reappear upon rechallenge.

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

The relationship of an AE or SAE to study procedures (eg, invasive procedures such as venipuncture or biopsy) should be assessed using clinical judgment, describing the event as either unrelated (No) or related (Yes) consistent with the following definitions:

- **No:** Evidence exists that the AE has an etiology other than the study procedure.
- **Yes:** A temporal relationship exists between the AE onset and a protocol-mandated procedure that cannot be readily explained by the subject's clinical state or concomitant therapies. Furthermore, the AE appears with some degree of certainty to be related to the study procedure based on the known potential complications of that procedure.

7.4. Adverse Drug Reactions

An adverse drug reaction (ADR) is defined as an AE that is considered causally related to an investigational medicinal product. A serious ADR (SADR) is an ADR which meets the seriousness criteria.

7.5. Unexpected Adverse Event

An unexpected AE is defined as an event that has a nature or severity, or specificity that is not consistent with the applicable Investigator's Brochure or that is symptomatically and pathophysiologically related to a known toxicity but differs because of greater severity or specificity. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the Investigator's Brochure only referred to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the Investigator's Brochure only listed cerebral vascular accidents. "Unexpected," as used in this definition, refers to an adverse drug experience that has not been previously observed and reported rather than an experience that has not been anticipated based on the pharmacological properties of the study drug.

7.6. Grading of the Severity of an Adverse Event

The severity grading of AEs will be assessed as Grade 1, 2, 3, 4 or 5 using the CTCAE (version 4.03).

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

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 above.

7.7. Special Situation Reports

Special situation reports include pregnancy reports, reports of medication error, abuse, misuse, or overdose, and reports of adverse reactions associated with product complaints.

A pregnancy report is used to report pregnancies following maternal or paternal exposure to the product.

Medication error is any unintentional error in the prescribing, dispensing, or administration of a medicinal product while in the control of the health care provider, subject, or consumer.

Abuse is defined as persistent or sporadic intentional excessive use of a medicinal product by a subject.

Misuse is defined as any intentional or inappropriate use of a medicinal product that is not in accordance with the protocol instructions or the local prescribing information.

An overdose is defined as an accidental or intentional administration of a quantity of a medicinal product given per administration or cumulatively which is above the maximum recommended dose as per protocol or in the product labelling (as it applies to the daily dose of the subject in question).

In cases of a discrepancy in drug accountability, overdose will be established only when it is clear that the subject has taken the excess dose(s) or the investigator has reason to suspect that the subject has taken the additional dose(s).

Product complaint is defined as any written or verbal report arising from potential deviations in the manufacture, packaging or distribution of the product.

Instructions for reporting Special Situation Reports are described in Section 7.8.1

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

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

All AEs, regardless of cause or relationship, that occur from initiation of study medication until 4 weeks after last administration of study IMP must be reported to the CRF/eCRF database as instructed.

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

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

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

- All AEs and SAEs will be recorded in the CRF/eCRF database within the timelines outlined in the CRF/eCRF completion guideline.
- At the time of study start, SAEs will be reported using a paper serious adverse event reporting form. During the study conduct, sites may transition to an electronic SAE (eSAE) system. Gilead will notify sites in writing and provide training and account information prior to implementing an eSAE system.

Serious Adverse Event Paper Reporting Process

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

Electronic Serious Adverse Event (eSAE) Reporting Process

- Site personnel record all SAE data in the eCRF database and from there transmit the SAE information to Gilead DSPH within 24 hours of the investigator’s knowledge of the event. Detailed instructions can be found in the eCRF completion guidelines.
- If for any reason it is not possible to record the SAE information electronically, ie, the eCRF database is not functioning, record the SAE on the paper serious adverse event reporting form and submit within 24 hours 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 CRF/eCRF database within the timelines outlined in the CRF/eCRF completion guideline.
- Site personnel record all SAE data in the eCRF database and from there transmit the SAE information to Gilead DSPH within 24 hours of the investigator’s knowledge of the event. Detailed instructions can be found in the eCRF completion guidelines.

- If for any reason it is not possible to record the SAE information electronically, ie, the eCRF database is not functioning, record the SAE on the paper serious adverse event reporting form and submit within 24 hours 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.
- 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 CRF/eCRF and the event description section of the SAE form.

Site reporting requirements for AEs are summarized in Table 7-1.

Table 7-1. Site Reporting Requirements for Adverse Events

Classification	Reporting Time	Reporting Action
Serious	Within 24 hours	Record and submit all SAE information on appropriate eCRFs and from there transmit the SAE information to Gilead Sciences DSPH. Print out the SAE report in order to submit to the site IRB/IEC, as per local IRB/IEC requirements. Detailed instructions can be found in the eCRF completion guidelines.
	Per eCRF submission procedure	Record and submit information on appropriate eCRFs
Nonserious	Per eCRF submission procedure	Record and submit information on appropriate eCRFs

Contact details for PPD Pharmacovigilance are provided in Table 7-2:

Table 7-2. Contact Information for Reporting Serious Adverse Events

PPD Pharmacovigilance:	Fax: PPD SAE phone: PPD

Report an SAE to PPD Pharmacovigilance if eSAE reporting is unavailable. Also report Special Situations and Pregnancies to PPD Pharmacovigilance per below (Section 7.8.1).

7.8.1. Special Situation Reporting Instructions

Instructions for Reporting Pregnancies:

- The Investigator should report all pregnancies to PPD Pharmacovigilance using the Pregnancy Report form within 24 hours of becoming aware of the pregnancy as outlined in Section 7.12.

Instructions for Reporting Other Special Situations:

- All other Special Situation reports must be reported on the Special Situation Report Form and forwarded to PPD Pharmacovigilance within 24 hours.

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

7.8.2. Gilead Sciences Reporting Requirements for Adverse Events

Depending on relevant 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 Sciences may be required to expedite reports to regulatory authorities for the following types of AEs: SAEs including events related to study procedures; SADRs; and suspected, unexpected, serious adverse reactions (SUSARs). In accordance with the EU Clinical Trials Directive (2001/20/EC), Gilead or a specified designee will notify worldwide regulatory agencies and the relevant IEC in concerned Member States of applicable SUSARs as outlined in current regulations.

Each SAE report received from the investigator will be evaluated by Gilead Sciences DSPH who will assess the seriousness of the event (see Section 7.2), the relationship to participation in the study (Section 7.3), and the expectedness of the event (see Section 7.5). For regulatory reporting purposes, expectedness will be determined by Gilead Sciences DSPH using reference safety information specified in the Investigator's Brochure.

Gilead Sciences or its designee will also provide all investigators and the DMC (if applicable) a safety letter e-mail, fax, or overnight mail notifying them of a SUSAR. Investigators will be requested to provide written notification of the SUSAR to the IRB/IEC as soon as is practical, consistent with local regulatory requirements and local institutional policy.

7.8.3. Post-Study Reporting Requirements

All AEs and SAEs including deaths, regardless of cause or relationship, must be reported for subjects on study through the last study visit and the 30-day follow-up phone call (or in person, if necessary).

Any SAEs and deaths that occur after the End of Study visit but within 30 days of the last dose of investigational medicinal product, regardless of causality, should also be reported.

Investigators are not obligated to actively seek SAEs after the 30 day time period. However, if the investigator learns of any SAEs that occur after study participation and the event is deemed relevant to the use of investigational medicinal products, he/she should promptly document and report the event to Gilead Sciences DSPH.

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

Laboratory abnormalities are usually not recorded as AEs or SAEs. However, laboratory abnormalities (eg, clinical chemistry, hematology, and urinalysis) that require medical or surgical intervention or lead to investigational medicinal product interruption or discontinuation must be recorded as an AE, as well as an SAE, if applicable. In addition, laboratory or other abnormal assessments (eg, electrocardiogram, X-rays, vital signs) that are associated with signs and/or symptoms must be recorded as an AE or SAE if they meet the definition of an AE or SAE as described in Sections 7.1 and 7.3, respectively. If the laboratory abnormality is part of a syndrome, record the syndrome or diagnosis (ie, anemia) not the laboratory result (ie, decreased hemoglobin).

Severity should be recorded and graded according to the CTCAE (version 4.03).

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

7.10. Toxicity Management

Treatment-emergent toxicities will be noted by the Investigator and brought to the attention of the Gilead Sciences Medical Monitor or designee. Whether or not considered treatment-related, all subjects experiencing AEs must be monitored periodically until symptoms subside, any abnormal laboratory values have resolved or returned to baseline levels or they are considered irreversible, or until there is a satisfactory explanation for the changes observed.

Grade 3 or 4 clinically significant laboratory abnormalities should be confirmed by repeat testing as soon as practical to do so, and preferably within 3 calendar days after receipt of the original test results.

Any questions regarding toxicity management should be directed to the Gilead Sciences Medical Monitor or designee.

7.11. Contraception Requirements

7.11.1. Definitions

7.11.1.1. Definition of Childbearing Potential

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

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

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

7.11.1.2. Definition of Male Fertility

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

7.11.2. Contraception Requirements for Female Subjects

7.11.2.1. Study Drug Effects on Pregnancy and Hormonal Contraception

GS-9973 is contraindicated in pregnancy as the risks of treatment with GS-9973 during pregnancy have not been evaluated. GS-9973 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.

7.11.2.2. Contraception Requirements for Female Subjects of Childbearing Potential

The inclusion of female subjects of childbearing potential requires the use of highly effective contraceptive measures. They must also not rely on hormone-containing contraceptives as a form of birth control during the study. They must have a negative serum pregnancy test at Screening. Female subjects must agree to one of the following from Screening until 30 days following the end of relevant systemic exposure.

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

Or

- Consistent and correct use of 1 of the following methods of birth control listed below.
  - — Intrauterine device (IUD) with a failure rate of <1% per year
  - — Tubal sterilization
  - — Essure micro-insert system (provided confirmation of success 3 months after procedure)
  - — Vasectomy in the male partner (provided that the partner is the sole sexual partner and had confirmation of surgical success 3 months after procedure)

Female subjects must also refrain from egg donation and in vitro fertilization during treatment and until at least 30 days after the end of relevant systemic exposure.

7.11.3. Contraception Requirements for Male Subjects

It is theoretically possible that a relevant systemic concentration may be achieved in a female partner from exposure of the male subject's seminal fluid. Therefore, male subjects with female partners of childbearing potential must use condoms during treatment and until 90 days after the end of relevant systemic exposure. Additional contraception recommendations should also be considered if the female partner is not pregnant.

Male subjects must also refrain from sperm donation during treatment and until at least 90 days after the end of relevant systemic exposure.

7.11.4. Unacceptable Birth Control Methods

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

The Gilead Sciences Medical Monitor or designee should be consulted regarding any questions relating to childbearing status or contraception.

7.12. Procedures to be followed in the Event of Pregnancy

Each female subject should be instructed to discontinue further study therapy and inform the investigator **immediately** if she becomes pregnant at any time between the initiation of study drug until 30 days after last receiving study drug.

The investigator must report any pregnancy to PPD Pharmacovigilance within 24 hours of the time the investigator becomes aware of the pregnancy.

The investigator should counsel the subject regarding the possible effects of investigational medicinal product exposure on the fetus and the need to inform the study site of the outcome of the pregnancy.

All pregnancies of study subjects and female partners of male subjects that occur during the study should be reported using the Pregnancy Report eCRF. Monitoring of the pregnancy in both female study subjects and female partner of male study subjects should continue until the conclusion of the pregnancy. The outcome of the pregnancy should be reported on the Pregnancy Outcome Report eCRF within 5 days of the conclusion of the pregnancy. If the end of the pregnancy occurs after the study is completed, the outcome should be reported directly to Gilead Sciences DSPH (facsimile: PPD e-mail: PPD

Neither the pregnancy itself nor an induced elective abortion to terminate the pregnancy without medical reasons is considered an AE; such occurrences should be reported on the appropriate pregnancy report forms. However, if the outcome of the pregnancy meets the criteria for classification as an SAE (ie, spontaneous abortion, induced abortion due to complications, stillbirth, neonatal death, or congenital anomaly [including that in an aborted fetus]), the investigator should follow the procedures for reporting SAEs, ie, report the event by submission of the appropriate AE and/or SAE eCRFs (see Section 7.8.1).

Pregnancy outcomes that are classified as SAEs include:

- Any spontaneous abortion, including miscarriage and missed abortion.
- An induced therapeutic abortion to terminate any pregnancy due to complications or other medical reasons. The underlying medical reason for this procedure should be recorded as the AE term.
- All neonatal deaths that occur within 1 month of birth, regardless of causality. In addition, any infant death after 1 month that the investigator assesses as possibly related to the *in utero* exposure to the study drug should also be reported as a SAE.

In the case of a live birth, the "normality" of the newborn can be assessed at time of birth (ie, there is no required minimum follow-up of a presumably normal infant before the Pregnancy Outcome Report eCRF can be completed).

The "normality" of an aborted fetus can be assessed by gross visual inspection unless there are pre-abortion laboratory findings suggestive of a congenital anomaly, in which case pathologic examination should be requested.

8. STATISTICAL CONSIDERATIONS

8.1. Objectives

The primary objective of this study is:

- To evaluate the efficacy of GS-9973 in subjects with relapsed or refractory hematologic malignancies

The secondary objectives of this study are:

- To evaluate the safety and tolerability of GS-9973 in subjects with relapsed or refractory hematologic malignancies

- To evaluate GS-9973 plasma exposure in subjects with relapsed or refractory hematologic malignancies

8.2. Endpoints

8.2.1. Primary Endpoint

PFS rate at 16 weeks (CLL after BCR targeted therapy, MCL and DLBCL) or 24 weeks (CLL and iNHL). PFS is defined as the interval from the first dose of GS-9973 to the earlier of the first documentation of definitive disease progression or death from any cause. The findings of the IRC will be considered primary for analyses of PFS rate.

PFS rate of the CLL prior BTK inhibitor exposure and CLL prior PI3K inhibitor exposure cohorts will be estimated separately.

PFS rate of the CLL dose ranging cohort will be estimated by dose levels.

8.2.2. Secondary Endpoints

Safety: abnormal laboratory data and AEs. Safety will be assessed by grading of laboratory values and AEs according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03

Efficacy:

- Objective response rate (ORR). ORR will be determined from the subjects' best response during GS-9973 therapy and will include complete response (CR) or partial response (PR) (or VGPR or MR for subjects with LPL/WM).

- Duration of response (DOR). DOR will be defined as time from the first response (CR or PR [or VGPR or MR for subjects with LPL/WM]) is achieved until the earlier of the first documentation of definitive disease progression or death from any cause.

- Time to response (TTR). TTR will be defined as time from the first dose of GS-9973 to the first time the response (CR or PR [or VGPR or MR for subjects with LPL/WM]) is achieved.

The findings of the IRC will be considered primary for analyses of secondary efficacy endpoints.

8.2.3. Exploratory Endpoints

[redacted]

8.3. Analysis Sets

8.3.1. Full Analysis Set

The full analysis set includes all subjects who receive ≥ 1 dose of GS-9973. This analysis set will be used in the analyses of subject characteristics, study drug treatment administration, safety, and efficacy endpoints including PFS, and ORR. The analyses of TTR and DOR will be based on the subjects in full analysis set who achieve a CR or PR (or VGPR or MR for subjects with LPL/WM).

8.3.2. Pharmacokinetic/Pharmacodynamic Analysis Sets

The Pharmacokinetic/Pharmacodynamic analysis sets include subjects in the full analysis set who have the necessary baseline and on-study measurements to provide interpretable results for specific parameters of interest. These analysis sets will be used in the analyses of GS-9973 drug levels and changes in CD63 expression in peripheral blood basophils. Analysis for GS-9973 SDD and original formulation will be done separately.

8.4. Data Handling Conventions

8.4.1. General Methods

By-subject listings will be created for important variables from each eCRF module. Summary tables for continuous variables will contain the following statistics: N (number in population), n (number with data), mean, standard deviation, 95% confidence intervals (CIs) on the mean, median, minimum, and maximum. Summary tables for categorical variables will include: N, n, percentage, and 95% CIs on the percentage. Unless otherwise indicated, 95% CIs for binary variables will be calculated using the binomial distribution (exact method) and will be 2-sided. Data will be described and summarized for all subjects and by cohort, analysis set, and timepoint. As appropriate, changes from baseline to each subsequent timepoint will be described and summarized. Similarly, as appropriate, the best change from baseline during the study will also be described and summarized. Graphical techniques (eg, waterfall plots, Kaplan-Meier curves, line plots) may be used when such methods are appropriate and informative.

The baseline value used in each analysis will be the last (most recent) pre-treatment value. Data from all sites will be pooled for all analyses. Analyses will be based upon the observed data unless methods for handling missing data are specified. If there is a significant degree of non-normality, analyses may be performed on log-transformed data or nonparametric tests may be applied, as appropriate.

8.4.2. Calculation of Tumor Control Variables

Tumor control assessments will be based on standardized response and progression criteria for NHL {Cheson 2007} and CLL {Hallek 2008}, as specifically modified for this study considering the pharmacology of GS-9973 {Cheson 2012}. The individual and composite endpoints of response and progression (considering changes in lymph node area, liver and spleen size, bone marrow, platelet counts, hemoglobin, neutrophil counts, and peripheral blood lymphocyte counts) will be determined. Tumor control will be documented at each assessment by response category (eg, CR, PR, SD, definitive PD) as defined for each response parameter, SPD value, percentage change in SPD values from baseline or nadir, date that response is first documented, date that response is confirmed, and date of disease progression.

Changes in tumor status as provided by the investigator and changes in tumor status as adjudicated by the IRC (see Section 9.4) will be described and compared. The findings of the IRC will be considered primary for analyses of all tumor control endpoints.

For time-to-event endpoints of PFS and DOR, the following censoring conventions will be applied:

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

8.5. Analysis Plan

8.5.1. Subject Disposition and Baseline Characteristics

A listing of all full-analysis subjects will be generated to describe site, subject number, first screening date, first treatment date, malignancy, duration of study drug treatment, and the reason for discontinuing study treatment. Available information on subjects who were screened or registered but not treated may be listed separately. A table will be created summarizing these categories in terms of number and percent for the full-analysis set.

Subject baseline characteristics will be listed and summarized for the full-analysis set.

8.5.2. Efficacy Analyses

8.5.2.1. Primary Efficacy Endpoint

For the primary analysis of the primary efficacy endpoint, PFS will be described using Kaplan-Meier methods in the full analysis set. Medians, ranges, the proportion of subjects who are progression-free at Week 16 (CLL after BCR targeted therapy, MCL and DLBCL) and 24 (CLL and iNHL) (based on Kaplan-Meier estimates) will be presented. The findings of the IRC will be considered primary for analyses of PFS rate.

As a sensitivity analysis, the aforementioned analysis will be done excluding subjects without adequate drug exposure.

8.5.2.2. Time-to-Event Tumor Control Endpoints

TTR and DOR will be described in the subjects in full analysis set who achieve a CR or PR (or VGPR or MR for LPL/WM) using Kaplan-Meier methods.

8.5.2.3. Categorical Endpoints

ORR, CR, and PR rates, nodal response rate, splenomegaly response rate, hepatomegaly response rate, platelet response rate, hemoglobin response rate, and neutrophil response rate will be described in the full analysis set. In the analyses of ORR, subjects who do not have sufficient baseline or on-study tumor assessment to characterize response will be counted as failures. For all analyses, the corresponding 95% CIs will be presented.

As a sensitivity analysis, the aforementioned analysis will be done excluding subjects without adequate drug exposure.

8.5.2.4. Continuous Endpoints

Changes in lymph node area, CD63 expression, and plasma chemokines/cytokines will be assessed using mixed model for repeated measures (MMRM) with baseline values as covariates and timepoints as factor; in these analyses, means of changes from baseline at each subsequent timepoint will be estimated and plotted over time.

8.5.2.5. Sensitivity Analyses for Efficacy in CLL subjects

Novel targeted agents can cause a rapid reduction in lymph node size and spleen mass concomitant with an increase in lymphocytosis from baseline {Cheson 2012}. A sensitivity analysis is planned by considering PR with lymphocytosis as response.

To satisfy criteria for PR with lymphocytosis, the following criteria must be met:

- No evidence of new disease.
- A decrease by ≥ 50% from the baseline in the SPD of the index nodal lesions.
- Peripheral blood counts meeting ≥ 1 of the following criteria:
  - ANC > 1.5 x 10^9/L or ≥ 50% increase over baseline without need for exogenous growth factors (eg, G-CSF)
  - Platelet count ≥100 x 10^9/L or ≥ 50% increase over baseline without need for exogenous growth factors
  - Hemoglobin ≥ 110 g/L (11.0 g/dL) or ≥ 50% increase over baseline without red blood cell transfusions or need for exogenous growth factors (eg, erythropoietin)

- There is neither sufficient evidence to qualify for CR/PR nor sufficient evidence to qualify for definitive PD

Sensitivity analyses will be carried out for ORR, DOR and TTR:

- Objective response rate (ORR). ORR will be determined from the subjects' best response during GS-9973 therapy and will include CR or PR or PR with lymphocytosis.

- Duration of response (DOR). DOR will be defined as time from the first response (CR or PR or PR with lymphocytosis) is achieved until the earlier of the first documentation of definitive disease progression or death from any cause.

- Time to response (TTR). TTR will be defined as time from the first dose of GS-9973 to the first time the response (CR or PR or PR with lymphocytosis) is achieved.

8.5.3. Exposure and Safety Analyses

8.5.3.1. Treatment Administration and Study Drug Compliance

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

GS-9973 compliance will be described for all subjects and by cohort in terms of the proportion of study drug actually taken based on returned pill count relative to the amount that was dispensed (taking into account physician-prescribed reductions and interruptions).

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

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

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

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

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

8.5.3.3. 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 an AE that occurs or worsens in the period from the first dose of study treatment to 30 days after the last dose of study treatment. Adverse events that occur before the first dose of study treatment or > 30 days after the subject is discontinued from study treatment will be included in data listings.

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

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

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

- Study-drug-related AEs
- AEs that are Grade ≥3 in severity
- AEs leading to study drug interruption and/or dose modification
- AEs leading to study drug discontinuation
- SAEs (with categorization of the primary reason that the AE is considered serious, eg, death, hospitalization, etc)

8.5.3.4. Laboratory Evaluations

All laboratory data will be listed. Summaries of laboratory data will be based on observed data and will be reported using conventional units. 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 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. Laboratory abnormalities that occur before the first dose of study treatment or > 30 days after the subject is discontinued from study treatment will be included in data listings.

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

Hematological, serum biochemistry, and coagulation results and their changes from baseline will be summarized. 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, serum biochemistry, and coagulation will also be presented by showing change in CTCAE severity grade from baseline to each visit. For parameters for which a CTCAE scale does not exist, shift tables will be presented showing change in results from baseline (normal, low and high [or abnormal]) to each visit (normal, low and high [or abnormal]). Tables will be prepared to show frequencies adjusted for baseline values; for this frequency, subjects with the same or worse toxicity grade at baseline are not considered.

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

8.5.4. Exploratory Analyses

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8.6. Continuous Data Review of PFS Endpoint Rate at 16 weeks (CLL after BCR Targeted Therapy, MCL and DLBCL) or 24 weeks (CLL and FL)

For subjects with MCL, DLBCL, CLL (except for the CLL dose ranging cohort), and FL, a Bayesian, continuous data review approach using a Beta-Binomial model ({Thall 1994}) will be used to update the estimates of the PFS rates at 16 weeks (CLL after BCR targeted therapy, MCL and DLBCL) or 24 weeks (CLL and FL) and, therefore, assess efficacy once each subject's primary endpoint becomes available for a malignancy. The Bayesian analysis method will be applied separately to each of the MCL, DLBCL, FL cohorts and the CLL cohorts (except for the CLL dose ranging cohort).

In this model, response is defined as a subject not experiencing progression or death by Week 16 (CLL after BCR targeted therapy, MCL and DLBCL) or week 24 (CLL and FL). Only subjects with known progression/death status at Week 16 (CLL after BCR targeted therapy, MCL and DLBCL) or week 24 (CLL and FL) are included in the analysis. Subjects who withdraw or are lost to follow-up before Week 16 (CLL after BCR targeted therapy, MCL and DLBCL) or week 24 (CLL and FL) will be considered as a non-responder for the analysis. In this Beta-Binomial model, a binomial likelihood for the data and a conjugate Beta (0.5, 1.5) prior distribution for response rate θ are assumed. Statistical inference and decision-making will be based on the posterior distribution of response rate θ, which is a Beta distribution with parameters $x+0.5$ and $n-x+1.5$, where x is the observed number of subjects who achieve the response and n is the total number of subjects who have a response result for a given malignancy. More details about the Bayesian design and analysis model will be provided in the statistical analysis plan (SAP).

The Bayesian model will be fit to the data sequentially as subjects' response status becomes available; decisions based on the estimate of response rate will be made accordingly. The posterior distribution of the response rate θ in each malignancy will be provided on an ongoing basis and at the end of the trial. Let $Pr(\theta<0.2|data)$ denote the probability that the response rate θ is less than 0.2 given the current data. The decision rules and actions to be taken based on the updated posterior distribution of response rate θ given the current data are as follows:

- If $Pr(\theta<0.2|data) > 0.9$ in a cohort, the sponsor will consider terminating enrollment to that cohort, taking into account efficacy, drug exposure, and subtype (for DLBCL), unless there are subjects who remain on treatment and have not yet reached 16 weeks (CLL after BCR targeted therapy, MCL and DLBCL) or 24 weeks (CLL and FL). In that case, enrollment will be suspended until the next on-going subjects' primary endpoint become available and another data review is conducted. If, after review of all available subjects, the futility boundary has still been crossed and the lack of drug exposure or DLBCL subtype does not explain the lack of activity, enrollment to that cohort may be terminated.

- Otherwise, continue recruiting subjects until a total of 40 subjects are enrolled for a cohort (CLL, FL, CLL subjects after BCR targeted therapy without experiencing Richter's transformation, MCL and DLBCL), or a total of 20 subjects are enrolled for CLL subjects after BCR targeted therapy experiencing Richter's transformation.

This monitoring will continue until a maximum of 40 or 20 subjects with a given cohort is reached.

To simplify decision-making, a plot of the a futility boundary($Pr(\theta<0.2|data) > 0.9$) in terms of the total number of subjects and the number of progression-free subjects at Week 16 (CLL after BCR targeted therapy, MCL and DLBCL) or Week 24 (CLL and iNHL) based on the above decision rule will be in Figure 3-2.

The data review for the two cohorts of BCR targeted therapy (CLL prior BTK inhibitor exposure and CLL prior PI3K inhibitor exposure) will be conducted independently for Richter's and non-Richter's.

The continuation data review of futility will not be conducted for the CLL dose ranging cohort.

8.7. Power and Sample Size Calculation

This study comprises of multiple cohorts. The planned sample size for CLL, FL, DLBCL, MCL is from 10 up to 40 each cohort; for the cohort of LPL, SLL and MZL is 45; for the CLL BCR targeted therapy cohort (CLL prior BTK inhibitor exposure and CLL prior PI3K inhibitor exposure, respectively) is from 20 up to 60 (up to 20 for subjects experiencing Richter's transformation and up to 40 for those without experiencing Richter's transformation); for the CLL dose ranging cohort is 60 (20 at each dose level). The total sample size is from 185 up to 385.

Given a Beta(0.5, 1.5) prior and a sample size of 40 subjects per cohort Table 8-1 shows the posterior mean and 95% credible interval for response rate after observing response rate ranging from 0.1 to 0.65.

Given the same prior and a sample size of 20 subjects for the CLL subjects experiencing Richter's transformation after BCR targeted therapy, Table 8-2 shows the posterior mean and 95% credible interval for response rate after observing response rate ranging from 0.1 to 0.65.

Table 8-1. Estimated Posterior Mean and 95% Credible Interval of Response Rate with Sample Size = 40

Observed Response Rate	Posterior Mean	95% Credible Interval
0.10	0.107	(0.034, 0.215)
0.20	0.202	(0.097, 0.335)
0.30	0.297	(0.171, 0.442)
0.40	0.393	(0.253, 0.543)
0.50	0.488	(0.340, 0.637)
0.60	0.583	(0.433, 0.726)
0.65	0.631	(0.482, 0.769)

Table 8-2. Estimated Posterior Mean and 95% Credible Interval of Response Rate with Sample Size = 20

Observed Response Rate	Posterior Mean	95% Credible Interval
0.10	0.114	(0.020, 0.272)
0.20	0.205	(0.068, 0.392)
0.30	0.295	(0.129, 0.497)
0.40	0.386	(0.199, 0.593)
0.50	0.477	(0.277, 0.681)
0.60	0.568	(0.362, 0.763)
0.65	0.614	(0.407, 0.801)

With the decision rule employed in this study and assuming enrollment is terminated once the futility criterion is met, for a given true response rate within a malignancy, Table 8-3 shows the probability of claiming futility and the sample size needed to claim futility for this design, which is based on 10,000 simulations. When the true response rate is low (0.1), this design has a high probability (~84%) of claiming futility and when the true response rate is high (0.5), this design has a low probability (0.15%) of claiming futility.

Table 8-3. Probability and Sample Size of Claiming a Futility by the End of Study Using Futility Criteria Pr(θ<0.2|data) > 0.9

True response rate	Probability of claiming futility	Sample size to claim futility or *		
		25th	Median	75th
0.10	0.8408	10	14	28
0.20	0.3162	21	40	40
0.30	0.0685	40	40	40
0.40	0.0125	40	40	40
0.50	0.0015	40	40	40
0.60	0.0003	40	40	40
0.65	0.0001	40	40	40

* When futility cannot be claimed, the sample size is converted to the maximum size of 40.

8.8. Multiplicity

Since this is an exploratory study with a learning objective, no multiplicity adjustment will be applied.

8.9. Timing of Analysis

The analysis for the primary efficacy endpoint will be initiated after data for at least 10 subjects are available for a given cohort. Due to the Bayesian adaptive nature of this study, analyses will be performed on an ongoing basis. To facilitate timely decision-making, analysis will be conducted immediately to sequentially update knowledge regarding drug efficacy among the 5 investigated hematologic malignancies whenever new data for the primary efficacy endpoint are mature for analysis.

8.10. Final Analysis

Final study reporting is expected to occur after the earliest of all subjects have completed study or 48 weeks after accrual of the final subject.

9. RESPONSIBILITIES

9.1. Investigator Responsibilities

9.1.1. Good Clinical Practice

The investigator will ensure that this study is conducted in accordance with the principles of the "Declaration of Helsinki" (as amended in Edinburgh, Tokyo, Venice, Hong Kong, and South Africa), International Conference on Harmonisation (ICH) guidelines, or with the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the study subject. These standards are consistent with the European Union Clinical Trials Directive 2001/20/EC and Good Clinical Practice Directive 2005/28/EC. The investigator will ensure that the basic principles of "Good Clinical Practice," as outlined in 21 CFR 312, subpart D, "Responsibilities of Sponsors and Investigators," 21 CFR, part 50, 1998, and 21 CFR, part 56, 1998, are adhered to.

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

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

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

This protocol and any accompanying material to be provided to the subject (such as advertisements, subject information sheets, or descriptions of the study used to obtain informed consent) will be submitted by the investigator to an IRB/IEC. Approval from the IRB/IEC must be obtained **before** starting the study and should be documented in a letter to the investigator specifying the protocol number, protocol version, protocol date, documents reviewed, and date on which the committee met and granted the approval.

Any modifications made to the protocol after receipt of IRB/IEC approval must also be submitted to the IRB/IEC for approval before implementation.

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 utilize an IRB- or IEC-approved consent form for documenting written informed consent. Each informed consent will be appropriately signed and dated by the subject or the subject's legally authorized representative and the person obtaining consent.

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, and an identification code (ie, not names) should be recorded on any form or biological sample submitted to the Sponsor, IRB/IEC, or laboratory. *NOTE* The investigator must keep a screening log showing codes, names, and addresses for all subjects screened and for all subjects enrolled in the trial.

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

9.1.5. Study Files and Retention of Records

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

The investigator's study file will contain the protocol/amendments, 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 are listed in the Source Data verification Plan, and should include sequential notes containing at least the following information for each subject:

- subject identification (name, date of birth, gender);
- documentation that subject meets eligibility criteria, ie, history, physical examination, and confirmation of diagnosis (to support inclusion and exclusion criteria);

- participation in trial (including trial number);
- trial discussed and date of informed consent;
- dates of all visits;
- documentation that protocol specific procedures were performed;
- results of efficacy parameters, as required by the protocol;
- start and end date (including dose regimen) of trial medication (preferably drug dispensing and return should be documented as well);
- record of all adverse events and other safety parameters (start and end date, and preferably including causality and intensity);
- concomitant medication (including start and end date, dose if relevant; dose changes should be motivated);
- date of trial completion and reason for early discontinuation, if applicable.

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

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

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

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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 on the day of the subject visit to enable the Sponsor to perform central monitoring of safety data. Subsequent to data entry, a study monitor will perform source data verification within the EDC system. Original entries as well as any changes to data fields will be stored in the audit trail of the system. Prior to database lock (or any interim time points as described in the clinical data management plan), the Investigator will use his/her log in credentials to confirm that the forms have been reviewed, and that the entries accurately reflect the information in the source documents. The eCRF captures 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. Drug Accountability

Gilead recommends that used and unused IMP supplies be returned to the shipping facility from which it came for eventual destruction. The study monitor will provide instructions for return. If return is not possible, the study monitor will evaluate each study center's IMP disposal procedures and provide appropriate instruction for destruction of unused IMP supplies. If the site has an appropriate SOP for drug destruction as determined by Gilead QA, the site may destroy used (empty or partially empty) and unused IMP supplies in accordance with that site's approved SOP. A copy of the site's approved SOP will be obtained for central files.

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

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

9.1.8. Inspections

The investigator should understand that source documents for this trial should be made available to appropriately qualified personnel from Gilead Sciences or its representatives, to IRBs [or] IECs, 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 Sciences. All protocol modifications must be submitted to the IRB [or] IEC in accordance with local requirements. Approval must be obtained before changes can be implemented.

9.2.2. Study Reporting and Publication

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

After conclusion of the study and without prior written approval from Gilead Sciences, 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 Sciences in an abstract, manuscript, or presentation form; or
- the study has been completed at all study sites for at least 2 years.

No such communication, presentation, or publication will include Gilead Sciences' confidential information.

The investigator will submit 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. The investigator will comply with Gilead Sciences' request to delete references to its confidential information (other than the study results) in any paper or presentation 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. Access to Information for Monitoring

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

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

9.3.2. Access to Information for Auditing or Inspections

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

9.3.3. 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 Sciences 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 review of radiographic data and pertinent clinical data in order to provide expert interpretation of changes in tumor status. The IRC will include ≥ 1 independent board-certified radiologist and ≥ 1 independent board-certified hematologist or oncologist, and will be managed by a CRO selected by Gilead Sciences. The review of radiographic and clinical data by the IRC will be performed on an ongoing basis. The specifics of the IRC's processes and reading methods will be described in an independent review charter developed by the contracted central imaging vendor in conjunction with Gilead Sciences.

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11. APPENDICES

Appendix 1. Investigator Signature Page

GILEAD SCIENCES, INC.
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FOSTER CITY, CA 94404

STUDY ACKNOWLEDGEMENT
A Phase 2, Open-Label Study Evaluating the Efficacy, Safety, Tolerability, and Pharmacodynamics of GS-9973 in Subjects with Relapsed or Refractory Hematologic Malignancies

GS-US-339-0102 Protocol Amendment 8: 31 March 2017

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

PPD

Medical Monitor

PPD

Signature

3/31/17

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

Study Phase	Screening	Cycle 1 (28 days)	Subsequent Cycles (28 days)	Safety Monitoring Visits	Tumor Response Assessments	Disease Progression or EOS[c]	30-Day Follow Up
Cycle Day	**Screening**	**1**	**1**	**Varies[a]**	**Q8 or 12 wks or 6 months[b]**	**N/A**	
Window	**-35**		**±2 days**	**±2 days**		**N/A**	
Study Assessments							
Informed Consent	X						
Medical History	X						
Physical Exam[d]	X	X	X	X		X	
Vital Signs[e]	X	X	X	X		X	
12-lead ECG	X			X			
Karnofsky Performance Status	X	X	X	X		X	
Prior/Concomitant Meds	X	X	X	X		X	
AEs[f]	X	X	X	X		X	X
CT or MRI	X[g]				X[h]	X[i]	
Bone Marrow Biopsy and Aspirate					X[j]	X[j]	
DLBCL Subtyping[k]		X					
Collect Archival Tumor Tissue (if available)		X[l]					
Complete Subject/Visit info in IxRS	X	X	X			X	
Sample Collection							
Chemistry	X	X	X[x]	X		X	
Beta-2-microglobulin		X	X			X	
Hematology	X	X	X[x]	X		X	
Coagulation	X	X	X[x]	X		X	
Urinalysis	X	X	X				
HBV, HCV and HIV Virology	X						

Study Phase	Screening	Cycle 1 (28 days)	Subsequent Cycles (28 days)	Safety Monitoring Visits	Tumor Response Assessments	Disease Progression or EOS[c]	30-Day Follow Up
Cycle Day	**Screening**	**1**	**1**	**Varies[a]**	**Q8 or 12 wks or 6 months[b]**	**N/A**	
Window	**-35**		**±2 days**	**±2 days**		**N/A**	
Pregnancy Test[n]	X	X	X	X		X	
GS-9973 Plasma Concentration[o, p, v]		X	X	X		X	
Buccal Swab[u]		X					
CCI							
Serum monoclonal IgM SPEP/IFE and cryoglobulin testing[q]		X			X		
Study Drug Dosing							
GS-9973 up to 800 mg BID Fasting or 100, 200 or 400 mg GS-9973 SDD BID Fasting		X----------					----------X
Dispense Study Drug		X	X				
Study Drug Compliance[r]		X	X			X	
Collect Used/Unused Study Drug[w]			X			X	
For CLL, SLL and MCL subjects only							
Cytokines and Chemokines		X[m]	X[m]	X[m]		X	
CTC Molecular Characterization		X		X[s]		X	
CTC RNA[w]		X[w]	X[w]			X[w]	
CLL ONLY: Pharmacodynamic Measurements (BAT Assay)		X[t]					
CLL ONLY: Pharmacogenomic Testing		X		X[s]		X	

a Days 8, 15, and 22 of Cycle 1 and Day 15 of Cycle 2

b Tumor assessments will be performed every 8 weeks during the first 24 weeks of the study and then every 12 weeks thereafter regardless of cycle number and regardless of dose interruptions. Tumor assessments may be performed at other timepoints during the treatment phase as clinically indicated (to assess tumor progression). After week 72 scans will occur at least every 6 months (± 4 weeks). The same evaluation procedures must be used throughout the study for each subject. Scans should be of high quality and digitalized in the DICOM format to allow for reading at a centralized facility.

c If a subject stops study drug for a reason other than progressive disease and consistent with good medical practice, they will be followed as per the scheduled imaging in Section 6.5 with additional CBC (hematology) at time of assessments.
d Complete physical examination will be performed at Screening and at Disease Progression or EOS. A modified physical examination capturing changes from prior exams will be performed at other visits. Weight should be measured (in kilograms) at each physical examination. Height will be measured (in centimeters) at Screening only.
e Vital signs (including blood pressure, respiratory rate, pulse, oxygen saturation by pulse oximetry and temperature) should be taken after the subject has been sitting for at least 5 minutes.
f Adverse events will be assessed once ICF is signed, pre- and post-dose during applicable clinic visits, and 30 (±7) days following completion of the subject's last dose of study drug. Subjects should be contacted by phone (or in person, if necessary) 30 days (± 7 days) after the subject's last dose of study drug to assess AEs. Subjects should specifically be asked about the development of any adverse events since stopping the study.
g CT or MRI scans of neck, chest, abdomen, and pelvis taken as part of standard medical practice up to 35days prior to Day 1 of Cycle 1 visit are acceptable for use at the Screening. Subjects with LPL/WM who previously failed screening for this study, due to an absence of lymphadenopathy on CT or MRI scans, do not need to be re-scanned if the scans were performed within 16 weeks of first study drug administration to meet eligibility criteria.
h At all timepoints after Screening imaging of the chest, abdomen, and pelvis will be required. Imaging of the neck is required at each follow-up time point if the neck scan was positive at baseline or if palpable neck lymphadenopathy appears during the course of the study.
i Tumor evaluations should be conducted at the End of Study Visit if not conducted in the previous 4 weeks. If a subject permanently discontinues study drug prior to objective documentation of progression, investigators should continue further follow-up at the ~8 or ~12-week intervals until progression is documented.
j A bone marrow biopsy and aspirate will be collected for all subjects who achieve a CR for confirmatory purpose. For CLL subjects a bone marrow biopsy/aspirate will be collected to confirm a PD. If the subject does not otherwise meet criteria for CR or if the nature of PD does not require bone marrow confirmations, it is not necessary to obtain a bone marrow biopsy/aspirate (See Sections 6.18 and 6.20).
k If the subject has DLBCL, subtyping is required. Submission of 15 unstained slides is required for subtyping if the subtype is not already known. Subjects for whom tissue is not available but the subtype is already known may be included if approved by the Medical Monitor following discussion with the investigator.
l Fifteen recently prepared unstained slides from archival tumor tissues will be collected. Efforts to acquire tissue sample should begin on Day 1 of Cycle 1.
m Collect on Cycle 1 Day 1, Cycle 1 Day 8, Cycle 2 Day 1 and Cycle 12, Day 1 only
n For females of childbearing potential, a serum pregnancy test will be performed at Screening and urine pregnancy tests will be performed on Days 1 of each Cycle and Day 15 of Cycles 1 & 2 and at EOS.
o Record the approximate number of hours between the last 2 doses of GS-9973 and the time the blood samples for plasma concentration were obtained
p GS-9973: PK samples will be collected on Day 1 of Cycle 1 pre-dose, 1.5 hours post-dose and 4 hours post-dose; on Day 1 of Cycles 2-6 pre-dose (12 hours post last dose).
GS-9973 SDD: PK samples will be collected on Day 1 of Cycle 1 pre-dose, 1.5 hours post-dose and 4 hours post-dose; on Day 8 of Cycle 1 pre-dose, 1.5 hours post-dose and 4 hours post-dose; on Days 15 and 22 of Cycle 1 pre-dose and 1.5 hours post-dose; and on Day 1 of subsequent cycles pre-dose and 1.5 hours post-dose.
q Subjects with LPL/WM only. This procedure should be conducted on the Day 1 visit occurring during the week window allotted for tumor response assessments.
r Includes date/time of last dose of GS-9973 (excluding Day 1 of Cycle 1)
s Collect on Cycle 2, Day 15 only
t On Day 1 of Cycle 1, samples will be collected pre-dose, 1.5 hours post-dose (± 10 minutes) and 4 hours post-dose ((± 10 minutes); on cycle 1 day 8 (predose and 4 hours post dose) and cycle 1 day 15 (predose)
u For CLL dose ranging, CLL prior BTK inhibitor exposure, or CLL prior PI3K inhibitor exposure cohorts only
v Excluding subjects off study drug at time of progression
w Samples will be collected pre-dose on Cycle 1 Day 1, Cycle 12 Day 1 and at Disease Progression or EOS only
x May be collected up to 2 days prior to the Day 1 visit