CLINICAL STUDY PROTOCOL

Study Title:	A Phase 3, Double-Blind Extension Study Evaluating the Efficacy and Safety of Two Different Dose Levels of Single-Agent GS-1101 (CAL-101) as Therapy for Patients with Previously Treated Chronic Lymphocytic Leukemia *A Companion Trial to Study GS-US-312-0116: A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Efficacy and Safety of GS-1101 (CAL-101) in Combination with Rituximab as Therapy for Patients with Previously Treated Chronic Lymphocytic Leukemia*	
Sponsor:	Gilead Sciences, Inc. 199 East Blaine Street Seattle, WA 98102 USA	
IND Number:	101254	
EudraCT Number:	2011-006293-72	
Indication:	Chronic Lymphocytic Leukemia	
Protocol ID:	GS-US-312-0117	
Gilead Sciences Study Director:	Name: Office Telephone: Office Fax: Mobile Telephone: E-mail:	PPD PPD PPD PPD PPD PPD
Gilead Sciences Medical Monitor:	Name: Office Telephone: Office Fax: Mobile Telephone: E-mail:	PPD PPD PPD PPD PPD PPD
Protocol Version/Date:	Original	23 January 2012

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PROTOCOL SYNOPSIS
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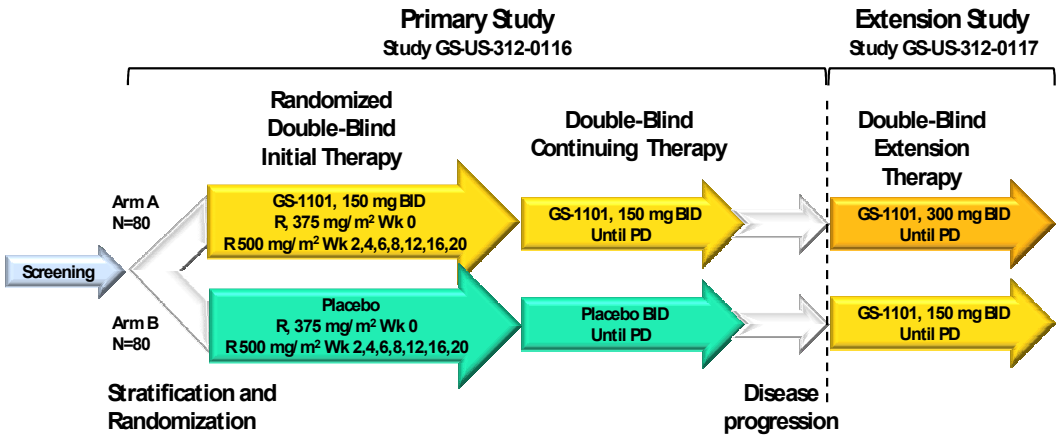
Study Title:	A Phase 3, Double-Blind Extension Study Evaluating the Efficacy and Safety of Two Different Dose Levels of Single-Agent GS-1101 (CAL-101) as Therapy for Patients with Previously Treated Chronic Lymphocytic Leukemia *A Companion Study to Study GS-US-312-0116: A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Efficacy and Safety of GS-1101 (CAL-101) in Combination with Rituximab as Therapy for Patients with Previously Treated Chronic Lymphocytic Leukemia*
Study Centers Planned:	Approximately 70 centers in the United States and in Europe
IND Number:	101254
EudraCT Number:	2011-006293-72
Objectives:	• To determine the effect of GS-1101 on the onset, magnitude, and duration of tumor control • To compare tumor control in subjects receiving rituximab alone in Study GS-US-312-0116 to that observed in the same subjects when receiving the standard dose of GS-1101 alone in Study GS-US-312-0117 • To assess the effect of GS-1101 on measures of subject well-being, including overall survival (OS), health-related quality of life (HRQL), and performance status • To assess the effects of GS-1101 on disease-associated biomarkers and to evaluate potential mechanisms of resistance to GS-1101 • To characterize exposure to GS-1101 as determined by treatment administration and evaluation of GS-1101 plasma concentrations over time • To describe the safety profile observed with GS-1101 • To estimate health resource utilization associated with administration of GS-1101

Study Design: This study is being conducted as part of an overall clinical program evaluating the efficacy and safety of GS-1101 in the therapy of patients with previously treated chronic lymphocytic leukemia (CLL).

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

This clinical trial (Study GS-US-312-0117) is a separate, multicenter, 2-arm, double-blind, parallel-group extension study that is a companion trial to Study GS-US-312-0116; in this trial, compliant subjects from GS-US-312-0116 who are tolerating primary study therapy but experience definitive CLL progression are eligible to receive active blinded GS-1101 therapy at the standard dose or a higher dose, with allocation based on the original primary study randomization.

Study Schema:



Treatment Groups

- Arm A: GS-1101 + rituximab (Study GS-US-312-0116)
  ⇒high-dose GS-1101 (300 mg BID) (Study GS-US-312-0117)
- Arm B: Placebo + rituximab (Study GS-US-312-0116)
  ⇒standard-dose GS-1101 (150 mg BID) (Study GS-US-312-0117)

Treatment Assignment

- Assignment to Arm A or Arm B with allocation based on the original primary study randomization
- Implementation through an interactive web response system (IWRS)

Stratification

Not applicable for Study GS-US-312-0117

Number of Subjects Planned:	Total of up to ~160 subjects (up to ~80 subjects per treatment arm)
Target Population	Subjects in the primary Phase 3 study (Study GS-US-312-0116) who are compliant, are tolerating primary study therapy, and have definitive progression of CLL while receiving primary study drug therapy (GS-1101/placebo).
Diagnosis and Main Eligibility Criteria:	Inclusion Criteria Subjects must meet all of the following conditions to be eligible for enrollment into the study: 1) Participation in Study GS-US-312-0116. 2) Occurrence of confirmed, definitive CLL progression while receiving study drug therapy (GS-1101/placebo) in Study GS-US-312-0116. ***Note: Definitive disease progression is CLL progression based on standard criteria and occurring for any reason (ie, increasing lymphadenopathy, organomegaly, or bone marrow involvement; decreasing platelet count, hemoglobin, or neutrophil count; or worsening of disease-related symptoms) other than lymphocytosis***. ***Subjects must have confirmation by the sponsor working in collaboration with an independent review committee (IRC) that the disease has progressed on the primary clinical trial (Study GS-US-312-0116) before receiving secondary GS-1101 therapy on this extension trial (Study GS-US-312-0117).*** 3) Presence of measurable lymphadenopathy (defined as the presence of ≥1 nodal lesion that measures ≥2.0 cm in the longest dimension [LD] and ≥1.0 cm in the longest perpendicular dimension [LPD] as assessed by computed tomography [CT] or magnetic resonance imaging [MRI]). 4) Permanent cessation of Study GS-US-312-0116 treatment (rituximab and/or GS-1101/placebo) and no intervening or continuing therapy (including radiotherapy, chemotherapy, immunotherapy, systemic corticosteroids, or investigational therapy) for the treatment of CLL. 5) The time from permanent cessation of Study GS-US-312-0116 treatment (rituximab and/or GS-1101/placebo) and the initiation of Study GS-US-312-0117 therapy is ≤12 weeks. ***Note: Study procedures performed as part of Study GS-US-312-0116 need not be repeated and can be used as screening procedures for Study GS-US-312-0117 if performed within 4 weeks prior to initiation of study drug therapy on Study GS-US-312-0117.*** 6) Karnofsky performance score of ≥40.

7) Required baseline laboratory data (within 4 weeks prior to initiation of study treatment) as shown in the table below. ***Note: Confirmation should be considered for out-of-range values to determine if the abnormality is real or artifactual. Values should be obtained within the screening period and should generally be the most recent measurement obtained. Subjects with any degree of neutropenia, thrombocytopenia, or anemia due to CLL or prior therapy may enroll.***

Required Screening Laboratory Values

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

[a] As calculated by the Cockcroft-Gault formula

[b] For women of child-bearing potential only; serum β-HCG must be negative during screening and serum β-HCG or urine dipstick pregnancy test must be negative at randomization (Visit 2)

Abbreviations: β-HCG=beta human chorionic gonadotropin, ALT=alanine aminotransferase, AST=aspartate aminotransferase, eC_{Cr}=estimated creatinine clearance, ULN=upper limit of normal

8) For female subjects of childbearing potential, willingness to abstain from heterosexual intercourse or use a protocol-recommended method of contraception from the screening visit (Visit 1) throughout the study treatment period and for 30 days following the last dose of study drug. ***Note: A female subject is considered to be of childbearing potential unless she has had a hysterectomy, bilateral tubal ligation, or bilateral oophorectomy; has medically documented ovarian failure (with serum estradiol and follicle-stimulating hormone [FSH] levels within the institutional postmenopausal range and a negative serum or urine βHCG), or is menopausal (age ≥55 years with amenorrhea for ≥6 months).***

9) 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 therapy (Visit 2) throughout the study treatment period and for 90 days following the last dose of study drug and to refrain from sperm donation from the start of study treatment (Visit 2) throughout the study treatment period and for 90 days following the last dose of study drug. ***Note: A male subject is considered able to father a child unless he has had a bilateral vasectomy with documented aspermia or a bilateral orchiectomy, or has ongoing testicular suppression with a depot luteinizing hormone-releasing hormone (LH-RH) agonist (eg, goserelin acetate [Zoladex®]), leuprolide acetate [Lupron®]), or triptorelin pamoate [Trelstar®]).***

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

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

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

Exclusion Criteria

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

1) Known histological transformation from CLL to an aggressive lymphoma (ie, Richter transformation).

2) Evidence of ongoing systemic bacterial, fungal, or viral infection at the time of the start of study treatment (Visit 2). ***Note: Subjects with localized fungal infections of skin or nails are eligible. Subjects may be receiving prophylactic antiviral or antibacterial therapies at the discretion of the investigator; anti-pneumocystis prophylaxis is encouraged.***

3) Pregnancy or breastfeeding.

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

5) Concurrent participation in another therapeutic clinical trial.

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

Study Procedures/ Frequency:	Subjects participating in the extension study will be assigned to 1 of the 2 treatment arms, with allocation based on the original randomization in the primary study. In the extension study, blinded GS-1101 high-dose or standard-dose therapy will be taken orally, twice per day (BID), continuously. Clinic/laboratory visits will occur every 2 weeks for the first 12 weeks, every 4 weeks between Weeks 12 and 24, and every 6 weeks between Weeks 24 and 48. Subjects continuing on study treatment past Week 48 will have clinic visits every 12 weeks. Subjects will be assessed for safety at each visit. Subjects will be assessed for CLL disease status by physical and laboratory examinations at each visit and by CT or MRI at Weeks 8, 16, 24, 36, and 48 and every 12 weeks thereafter through Week 96. For follow-up visits after Week 96, CT or MRI is only required at the End-of-Treatment visit.
Test Therapy, Dose, and Mode of Administration:	• Arm A: GS-1101, 300 mg/dose BID starting on Day 1 and administered continuously thereafter; the study drug will be provided as 2 tablets of active GS-1101 for oral administration • Arm B: GS-1101, 150 mg/dose BID starting on Day 1 and administered continuously thereafter; the study drug will be provided as 1 tablet of active GS-1101 and 1 tablet of placebo for oral administration
Reference Therapy, Dose, and Mode of Administration:	Not applicable
Duration of Treatment:	Study drug will be taken continuously until the earliest of subject withdrawal from study, definitive progression of CLL, intolerable study drug-related toxicity, pregnancy, substantial noncompliance with study procedures, or study discontinuation.

Criteria for Evaluation:

Tumor Control

- Progression-free survival (PFS) – defined as the interval from the start of study therapy to the earlier of the first documentation of definitive disease progression or death from any cause; definitive disease progression is CLL progression based on standard criteria and occurring for any reason (ie, increasing lymphadenopathy, organomegaly or bone marrow involvement; decreasing platelet count, hemoglobin, or neutrophil count; or worsening of disease-related symptoms) other than lymphocytosis alone
- Overall response rate (ORR) – defined as the proportion of subjects who achieve a complete response (CR) or partial response (PR)
- Time to response (TTR) – defined as the interval from start of study therapy to the first documentation of CR or PR
- Duration of response (DOR) – defined as the interval from the first documentation of CR or PR to the earlier of the first documentation of definitive disease progression or death from any cause
- Time to treatment failure (TTF) – defined as the interval from start of study therapy to the earliest of the first documentation of definitive disease progression, the permanent cessation of study drug due to an adverse event, or death from any cause
- Percent change in lymph node area – defined as the percent change from baseline in the sum of the products of the greatest perpendicular diameters (SPD) of index lymph nodes
- Lymph node response rate – defined as the proportion of subjects who achieve a ≥50% decrease from baseline in the SPD of index lymph nodes
- Splenomegaly response rate – defined as the proportion of subjects with baseline splenomegaly who achieve an on-study normalization or a decrease by ≥50% from baseline in the pretreatment enlargement of the splenic longest vertical dimension (LVD) (by imaging) or in the pretreatment enlargement of the splenic LVD below the left costal margin (by palpation)
- Hepatomegaly response rate – defined as the proportion of subjects with baseline hepatomegaly who achieve an on-study normalization or a decrease by ≥50% from baseline in the pretreatment enlargement of the hepatic LVD (by imaging) or in the pretreatment enlargement of the hepatic LVD at the right midclavicular line (by percussion)

- Platelet response rate – defined as the proportion of subjects with baseline thrombocytopenia (platelet count <100 x 1^{09}/L) who achieve an on-study platelet count ≥100 x 1^{09}/L or demonstrate a ≥50% increase in platelet count from baseline
- Hemoglobin response rate – defined as the proportion of subjects with baseline anemia (hemoglobin <110 g/L [11.0 g/dL]) who achieve an on-study hemoglobin ≥110 g/L (11.0 g/dL) or demonstrate a ≥50% increase in hemoglobin from baseline
- Neutrophil response rate – defined as the proportion of subjects with baseline neutropenia (absolute neutrophil count [ANC] <1 x 10^9/L) who achieve an ANC ≥1 x 10^9/L or demonstrate a ≥50% increase in ANC from baseline

Patient Well-Being

- Overall survival (OS) – defined as the interval from start of study therapy to death from any cause
- Change in HRQL domain and symptom scores based on the Functional Assessment of Cancer Therapy: Leukemia (FACT-Leu) – defined as the change from baseline and the time to definitive increments or decrements of 10%, 20%, and 40% from baseline; time to definitive increment (better than baseline by the specified amount) is the interval from start of study therapy to the first timepoint when the HRQL measure is consistently better than at baseline (including that timepoint as well as all the subsequent timepoints) in a subject whose last HRQL score is better than at baseline; and time to definitive HRQL decrement (worse than baseline by the specified amount) is the interval from start of study therapy to the earliest of death or the first timepoint when the HRQL measure is consistently worse than at baseline (including that timepoint as well as all the subsequent timepoints) in a subject whose last performance status score is worse than at baseline
- Changes in Karnofsky performance status – defined as the change from baseline in the performance status and the time to definitive performance status improvement or worsening; time to definitive performance status improvement (better than baseline) is the interval from start of study therapy to the first timepoint when the performance status is consistently better than at baseline (including that timepoint as well as all the subsequent timepoints) in a subject whose last performance status score is better than at baseline; and time to definitive performance status worsening (worse than baseline) is the interval from study therapy until the earliest of death or the first timepoint when the performance status is consistently worse than at baseline (including that timepoint as well as all the subsequent

timepoints) in a subject whose last performance status score is worse than at baseline

Pharmacodynamic Markers of Drug Activity and Resistance

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

Exposure

- Study drug administration as assessed by prescribing records and compliance as assessed by quantification of used and unused drug
- Trough (pre-dose) and peak (1.5-hour samples) of GS-1101 plasma concentrations as assessed by a validated bioanalytical method

Safety

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

Pharmacoeconomics

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

Statistical Methods:

Analysis Methods

Appropriate data analysis sets will be defined. The full-analysis set will include data from all subjects who receive ≥1 dose of any study therapy on this study; in this data set, study drug assignment (high-dose or standard-dose GS-1101) will be designated according to the planned allocation to this study. A safety analysis set will comprise data from subjects in the full-analysis set with treatment assignments designated according to the actual study drug (high-dose or standard-dose GS-1101) received. Other data sets (responding, evaluable, and pharmacodynamic/pharmacokinetic data sets) will be defined and will include data from subjects who have the necessary baseline and on-study measurements to provide interpretable results for specific parameters of interest.

Subject characteristics and study results will be described and summarized by treatment arm and assessment for the relevant analysis sets. Descriptive summaries will be prepared to show sample size, mean, standard deviation, 95% confidence intervals (CIs) on the mean, median, minimum, and maximum for continuous variables and counts, percentages, and 95% CIs on the percentage for categorical variables.

For endpoints relating to tumor control, patient well-being, and biomarkers, analyses will be done based on the full-analysis, responding, evaluable, or pharmacodynamic data sets, as appropriate. Time-to-event analyses will be performed with reference to the date of first treatment on this study (Study GS-US-312-0117). Similarly, evaluations of on-therapy changes will reference the baseline values obtained prior to treatment in this study. Analyses will focus on evaluation of outcomes within each treatment arm and will be largely descriptive in nature; formal comparisons of outcomes in Arm A vs Arm B are not planned. Time-to-event endpoints will be summarized using Kaplan-Meier methods; medians, ranges, and the corresponding 95% CI will be presented. Continuous and categorical variables will also be summarized as appropriate. Changes from baseline in categorical variables and changes from baseline in continuous endpoints will be analyzed using appropriate methods.

Efficacy outcomes among subjects receiving rituximab alone in Study GS-US-312-0116 will be evaluated relative to those same outcomes among the same subjects receiving standard-dose GS-1101 alone in Study GS-US-312-0117. More specifically, time-to-event endpoints will be compared using the paired Prentice-Wilcoxon test; continuous endpoints will be compared using the paired t-test; and categorical or non-normal data will be compared using the Wilcoxon signed-rank test.

Based on the safety analysis set, information regarding study treatment administration, study drug compliance, safety variables, and post-study therapies will be described and summarized. Using data from the pharmacokinetic analysis set, GS-1101 plasma concentrations will also be described and summarized.

Sample Size Calculation

The sample size for this extension study is not based upon a formal statistical hypothesis. The upper bound of the sample size in this study is determined by the sample size of the preceding primary clinical trial (Study GS-US-312-0116) in which ~160 subjects (~80 per arm) are expected to be enrolled. Assuming a ~10% dropout rate during Study GS-US-312-0116 and a further ~10% dropout rate in the transition from the primary study to the extension study, ~130 subjects are expected to be enrolled into Study GS-US-312-0117.

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

GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

β-HCG	Beta human chorionic gonadotropin
ABCG2	adenosine triphosphate-binding cassette sub-family G member 2 (see also BCRP)
AKT	AKT (a serine/threonine protein kinase)
ALC	absolute lymphocyte count
ALL	acute lymphocytic leukemia
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
ATC	Anatomical-Therapeutic-Chemical classification system for drugs
BCRP	breast cancer resistance protein (see also ABCG2)
BID	twice per day
BTK	Bruton tyrosine kinase
CAL-101	Former name for GS-1101
CCL	chemokine (C-C motif) ligand
CFR	Code of Federal Regulations
CI	confidence interval
CIRS	Cumulative Illness Rating Scale
CLL	chronic lymphocytic leukemia
cGMP	current Good Manufacturing Practice
C_{max}	maximum concentration
CMV	cytomegalovirus
CR	complete response
CRO	contract research organization
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
C_{trough}	trough concentration
CXCL	chemokine (C-X-C motif) ligand
CYP	cytochrome P450 enzyme
DLCO	diffusing capacity of the lung for carbon monoxide
DMC	data monitoring committee
DNA	deoxyribonucleic acid
DOR	duration of response
DSPH	Gilead Sciences Department of Safety and Public Health
ECG	electrocardiogram
eC_{Cr}	estimated creatinine clearance
eCRF	electronic case report form
EDC	electronic data capture
ELISA	enzyme-linked immunosorbent assay
EQ-5D	EuroQoL Five-Dimension utility measure

GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS (CONTINUED)

FACT-Leu	Functional Assessment of Cancer Therapy: Leukemia questionnaire
FCεRI	high-affinity IgE receptor
FDA	United States Food and Drug Administration
FDAMA	Food and Drug Modernization Act
FDG	fluorodeoxyglucose (18F)
FISH	fluorescence in-situ hybridization,
FSH	follicle-stimulating hormone
G-CSF	granulocyte colony-stimulating factor
GGT	gamma-glutamyltransferase
GLP	Good Laboratory Practice
GM-CSF	granulocyte-macrophage colony-stimulating factor
HBc antibody	anti-hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
hERG	human ether-à-go-go-related gene
HL	Hodgkin lymphoma
HIV	human immunodeficiency virus
HRQL	health-related quality of life
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IEC	independent ethics committee
Ig	immunoglobulin (including subtypes A, E, G, and M)
IgHV	immunoglobulin heavy chain variable region
IND	Investigational New Drug (application)
iNHL	indolent non-Hodgkin lymphoma
INR	international normalized ratio
IRB	institutional review board
IRC	independent review committee
ITT	intention to treat
IUD	intrauterine device
IWCLL	International Workshop on CLL
IWRS	interactive web response system
JAK	Janus kinase
K_2-EDTA	potassium-ethylenediaminetetraacetic acid
LD	longest diameter
LDH	lactate dehydrogenase
LH-RH	luteinizing hormone-releasing hormone
LLN	lower limit of normal
LPD	longest perpendicular diameter
LVD	longest vertical dimension
MTD	maximum tolerated dose
MCL	mantle cell lymphoma
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging

GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS (CONTINUED)

mTOR	mammalian target of rapamycin
ND	no disease
NHL	non-Hodgkin lymphoma
NOAEL	no-observed-adverse effect level
NOEL	no-observed-effect level
OCT	organic cation transporter
ORR	overall response rate
OS	overall survival
pAKT	phosphorylated AKT
PD	progressive disease
PET	positron-emission tomography
PI3K	phosphatidylinositol 3-kinase
PI3Kδ	phosphatidylinositol 3-kinase p110δ isoform
PFS	progression-free survival
PML	progressive multifocal leukoencephalopathy
PPD	product of the perpendicular diameters
PRO	patient-reported outcome
PR	partial response
PT	prothrombin time
PVA	polyvinyl alcohol
PVC/PCTFE	polyvinyl chloride/polychlorotrifluoroethylene
QD	once per day
QT (interval)	measure of time between start of Q wave and end of T wave in electrical cycle of heart
RNA	ribonucleic acid
SADR	serious adverse drug reaction
SD	stable disease
SPD	sum of the products of the perpendicular diameters of measured lymph nodes
SSC	study steering committee
SUSAR	suspected, unexpected, serious adverse reaction
SYK	spleen tyrosine kinase
$t_{1/2}$	half-life
T_{max}	time of maximum concentration
TTF	time to treatment failure
TTR	time to response
UGT	uridine 5'-diphospho-glucuronosyltransferase
ULN	upper limit of normal
WHODRUG	World Health Organization Drug Dictionary
ZAP=70	zeta-associated protein 70

1. INTRODUCTION

1.1. Chronic Lymphocytic Leukemia

Chronic lymphocytic leukemia (CLL) is a neoplasia resulting from the progressive accumulation of functionally incompetent monoclonal B lymphocytes in blood, bone marrow, lymph nodes, spleen, and liver [Dighiero 2008]. CLL constitutes the most commonly occurring leukemia in Europe and the United States [Sant 2010, SEER 2011]. While some patients never require treatment, many will need therapy for disfiguring or obstructing lymphadenopathy, debilitating constitutional B symptoms (fevers, night sweats, fatigue, weight loss) [Redaelli 2004], or recurrent cytopenias and infections [Perkins 2002, Keating 2002a]. 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 [SEER 2011].

In younger and relatively healthy patients with CLL, chemoimmunotherapy regimens that include the anti-CD20 monoclonal antibody, rituximab, are commonly employed to control disease manifestations [Gribben 2011]. Such combination therapies are effective in providing durable remissions [Byrd 2005, Hallek 2010, Robak 2010, Fischer 2011, and Iannitto 2011]. However, while rituximab is usually well tolerated [Gentile 2010], the chemotherapeutic agents (typically fludarabine, cyclophosphamide, or bendamustine) in such regimens are acutely cytotoxic, induce permanent bone marrow compromise, and can cause secondary malignancies [Kyasa 2004, Tam 2008, Carney 2010]. Furthermore, in elderly patients or in those with comorbid conditions, such regimens are associated with less efficacy and greater toxicity [Tam 2008, Eichhorst 2009b, Goede 2011].

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

Health constraints in older or compromised patients have prompted noncytotoxic approaches to therapy. Alternative immunotherapeutics, such as the monoclonal antibodies, alemtuzumab [Keating 2002b] or ofatumumab [Wierda 2010], have been developed. However the therapeutic utility of these drugs is modest; median progression-free survival (PFS) values in patients with recurrent CLL have been 4.7 months and 5.8 months, respectively. Moreover, these treatments can have clinical liabilities. Alemtuzumab causes extreme immunosuppression that leads to frequent opportunistic infection. Administration of

the large amounts of protein recommended in ofatumumab product labeling results in frequent infusion reactions and cumbersome infusion schedules.

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

1.2. Phosphatidylinositol 3-Kinase in Lymphoid Malignancies

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

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

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

1.3. GS-1101

1.3.1. Discovery and Efficacy Pharmacology

Gilead Sciences, Inc has developed novel drugs that can suppress tumor growth through targeting of PI3Kδ activity. High-throughput screening was the basis for the discovery of novel agents that selectively inhibit PI3Kδ function but spare other PI3K isoforms and other kinases. Chemical optimization, pharmacological characterization, and toxicological evaluation have led to identification of GS-1101 (also known as CAL-101), a 415-dalton,

orally bioavailable, new chemical entity with potential clinical utility in the treatment of cancers [Gilead Sciences 2011].

In primary tumor samples and in cell lines derived from patients with CLL, indolent non-Hodgkin lymphoma (iNHL), mantle cell lymphoma (MCL), B-cell acute lymphocytic leukemia (ALL), or Hodgkin lymphoma (HL), GS-1101 induces dose-dependent reductions in AKT phosphorylation [Herman 2010, Meadows 2010, Lannutti 2011]. In addition, GS-1101 disrupts the PI3Kδ activation and supportive intercellular signaling observed when CLL or HL cells are cocultured with stromal cells [Meadows 2010, Hoellenriegel 2011]. These effects have therapeutic consequences. In multiple lymphoid primary tumors and malignant cell lines, GS-1101 enhances apoptosis and concentration-dependent cell killing when applied as a single agent and increases the therapeutic efficacy of other antineoplastic agents when given in combination [Hoellenriegel 2011, Meadows 2011]. In preclinical systems, coadministration of GS-1101 with rituximab has not impaired rituximab-mediated activity [Herman 2010].

1.3.2. Safety Pharmacology

In vitro and in vivo safety pharmacology studies with GS-1101 have demonstrated a favorable non-clinical safety profile [Gilead Sciences 2011]. These studies indicate that the drug may minimally slow bone marrow progenitor proliferation and differentiation and that it has expected inhibitory effects on B-cell response to antigen challenge. However, the data indicate that GS-1101 is unlikely to cause serious off-target effects or adverse effects on critical organ systems. GS-1101 has no meaningful effect on the human ether-à-go-go-related gene (hERG) channel, indicating that GS-1101 would not be expected to induce clinical QT prolongation.

The drug has also proved well tolerated in standard in vivo Good Laboratory Practice (GLP) studies of pharmacological safety. A functional observation battery in rats revealed no adverse effects on behavior or on autonomic, neuromuscular, or sensorimotor function. In a cardiopulmonary function study in awake, telemeterized male beagle dogs, single doses of GS-1101 induced no meaningful abnormalities in pulmonary, cardiovascular, arterial blood gas, or electrocardiographic (ECG) (including QT interval) parameters. In an assessment of bacterial challenge in rats, GS-1101 enhanced, rather than impaired, the phagocytic host clearance of staphylococcal bacteria.

1.3.3. Nonclinical Pharmacology and Metabolism

In rats and dogs, plasma-concentration time profiles of GS-1101 are available following single oral and intravenous administration as well as following repeated oral administration as part of toxicology studies [Gilead Sciences 2011]. The metabolism of GS-1101 has been studied in vitro and in vivo; the major metabolite has been identified and characterized in rats, dogs, and humans. No human-specific metabolites have been identified.

Drug disposition data document GS-1101 oral bioavailability in test species, characterize similar plasma protein binding across species, and demonstrate that GS-1101 metabolism is dependent upon both hepatic oxidation catalyzed in part by cytochrome P450 (CYP) 3A4 and on glucuronidation mediated by uridine 5'-diphospho-glucuronosyltransferase (UGT) 1A4. Nonclinical findings show that biliary excretion and hepatic metabolism to renal excretion

products are important in GS-1101 elimination. Nonclinical drug-drug interaction data show that GS-1101 is unlikely to alter CYP-dependent metabolism of other drugs but could alter absorption or disposition of agents that are substrates for P-glycoprotein, the organic cation transporter-2 (OCT2), or the adenosine triphosphate-binding cassette sub-family G member 2 (ABCG2) transporter (also known as the breast cancer resistance protein [BCRP]).

1.3.4. Toxicology

In support of clinical development in patients with lymphoid cancers, GS-1101 has undergone toxicological evaluation in conformance with the International Conference on Harmonisation (ICH) S9 guidance on nonclinical evaluation for anticancer pharmaceuticals [FDA 2010].

1.3.4.1. General Toxicology

Completed GLP toxicology studies have included 28-day evaluations in both rats and dogs and a study evaluating the hematological effects of co-administration of GS-1101 and cyclophosphamide [Gilead Sciences 2011]. These studies have shown GS-1101 to be tolerated at exposure levels greater than those expected to provide therapeutic activity and have identified signals to be monitored in the clinic. Reversible lymphoid depletion in rats and dogs was consistent with GS-1101-mediated inhibition of PI3Kδ. In rats, partially reversible inflammation of the tongue was noted in GS-1101-treated animals; this may have represented an exaggeration of background effects related to gavage-mediated irritation. Mild congestion or hemorrhage in the large intestine has been seen in dogs receiving high doses of GS-1101. Rats also showed cardiac and hepatic chronic inflammatory infiltrates, although attribution to GS-1101 was uncertain because background infiltrates of a similar nature were observed in control recovery animals. In dogs, evidence of hepatocellular injury and chronic inflammation was accompanied by elevations of serum transaminase values (serum alanine aminotransferase [ALT] and serum aspartate aminotransferase [AST]). These hepatic effects appeared dose-related, reversible, and monitorable using standard serum chemistry laboratory parameters. In both rats and dogs, persistent minimal to mild degeneration of the seminiferous tubules and decreased spermatozoa were present in male animals receiving GS-1101. When co-administered with cyclophosphamide in rats, GS-1101 did not worsen cyclophosphamide-mediated changes in hematological parameters.

Data from 13-week GLP toxicology studies in rats and dogs are available. These data confirm the 28-day toxicology findings. GS-1101 was well tolerated with no notable clinical observation or changes in body weight at exposure levels approximating or exceeding those observed in subjects at the planned clinical starting dose of 150 mg/dose administered twice per day (BID). In both species, dose-dependent lymphoid depletion was observed that was consistent with PI3Kδ inhibition by GS-1101. In dogs, expected transient low-level elevations of serum ALT in 2 animals receiving the highest GS-1101 dose were observed at Day 29 of the study; of note, animals showed spontaneous recovery during continued GS-1101 dosing, with no elevations at Day 60 or Day 90. Microscopic review of dog tissues indicated no evidence of persistent or residual liver pathology at the conclusion of the study. Consistent with previous studies, findings of persistent hypospermatogenesis and decreased testicular weight were observed in both species.

In an investigative study, a further characterization of the pattern of serum transaminase changes associated with administration of high-dose of GS-1101 to dogs confirmed hepatic adaptation to the effect. In this study, mean serum ALT/AST values peaked at approximately Day 24 to Day 27 and resolved spontaneously as the dogs continued on GS-1101 through the end of the study on Day 44.

1.3.4.2. Genotoxicity

GS-1101 was not genotoxic in a standard battery of assays [Gilead Sciences 2011]. In the Ames assay, GS-1101 did not cause mutagenic effects. In human peripheral blood lymphocytes, the compound induced no chromosomal aberrations. In a rat micronucleus study, GS-1101 did not show evidence of clastogenicity.

1.3.4.3. Reproductive Toxicology

Data from a non-GLP embryo-fetal developmental toxicity study in rats suggested no evidence of maternal toxicity at GS-1101 doses of 25, 50, 75, and 100 mg/kg/day. No GS-1101-related findings were observed based on external examination of the fetus at any dose level although lower fetal body weights were evident at 100 mg/kg/day and were considered related to treatment with GS-1101. Thus, the no-observed-effect level (NOEL) for maternal toxicity was 100 mg/kg/day and the NOEL for fetal developmental toxicity was 75 mg/kg/day. Definitive GLP reproductive toxicology studies in rats and rabbits are planned.

As noted in Section 1.3.4.1, 28-day and 13-week general toxicology studies in rats and dogs indicated dose-dependent reductions in testicular weights, with persistent minimal to mild degeneration of the seminiferous tubules and decreased spermatozoa in rats and hypospermatogenesis in dogs. The no-observed-adverse effect level (NOAEL) was 50 mg/kg/day for rats and 5 mg/kg/day for dogs. The impact of these testicular changes on fertility, if any, has not been assessed.

1.3.5. GS-1101 Clinical Studies

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

Three studies in healthy subjects (Studies 101-01, 101-04, and 101-05) have provided information regarding drug safety, pharmacokinetics, food effects, and the potential for drug interactions with CYP3A4 inhibitors [Webb 2010, Gilead Sciences 2011]. One of these trials also included a preliminary evaluation of absorption, metabolism and excretion in healthy volunteers; in this trial, unlabeled GS-1101 was co-administered with a trace amount of [^{14}C]GS-1101 given either orally or intravenously and biological samples were assessed by accelerator mass spectrometry.

Safety results from these studies indicated that GS-1101 was well tolerated when administered to healthy subjects at single doses through 400 mg (the highest dose level tested) and was also generally well tolerated when administered to healthy subjects over 7 days at dose levels through 200 mg/dose BID (the highest dose level tested). Dosing with 200 mg/dose BID for 7 days resulted in a skin rash in 3 out of 6 subjects; histological findings were consistent with a delayed-type hypersensitivity maculopapular exanthema. Rashes have sometimes occurred in patients with hematological malignancies receiving GS-1101, but have not typically proved dose- or treatment-limiting. In placebo-controlled

single-dose and multiple-dose trials, repeated ECG evaluations performed in tandem with pharmacokinetic monitoring showed no evidence of drug-, dose-, or exposure-dependent effects on cardiac rhythm or cardiac intervals (eg, QT interval).

Pharmacokinetic results indicated that increases in plasma GS-1101 maximum concentration (C_{max}) and area under the concentration-time curve (AUC) values were dose-proportional with increasing single-dose administration but less-than-dose-proportional with increasing multiple-dose administration. There was only modest accumulation with BID dosing over 7 days. Consistent with mean half-life ($t_{1/2}$) values in the range of 6 to 10 hours, steady state was achieved within 7 days of repeated dosing. Mean plasma GS-1101 trough concentrations (C_{trough}) exceeded target values known to be associated with pharmacological activity based on nonclinical testing.

Ingestion of a high-fat, high-calorie meal just prior to administration of GS-1101 moderately delayed absorption, increasing the drug's median time of maximum concentration (T_{max}) from 0.75 hours to 3 hours without altering mean C_{max}. The aggregate effect was an increase of 1.4-fold in mean AUC. While the data indicate a food effect, the changes in GS-1101 pharmacokinetics were modest; thus, GS-1101 may be given with or without food.

When GS-1101 was administered following 4 days of daily dosing with ketoconazole (a potent inhibitor of CYP3A4), increases in mean GS-1101 C_{max} and AUC values were 1.3- and 1.8-fold, respectively. The data indicate that some alterations in GS-1101 pharmacokinetics occur but that GS-1101 is not a sensitive substrate for CYP3A4. Thus, co-administration of CYP3A4 inhibitors and GS-1101 is not contraindicated and does not require special monitoring.

The ^{14}C-labeled GS-1101 results showed that the drug has an oral bioavailability of 56%. Hepatic metabolism and biliary excretion appeared to be particularly important in GS-1101 elimination. Consistent with the metabolism data from animal studies, an oxidation product was observed in human plasma and a hydrolyzed product was observed in urine and feces. [^{14}C]-GS-1101-derived materials were primarily excreted in feces (>65% of total dose) with lesser elimination via urine (<15% of total dose).

Pharmacodynamic results showed that a GS-1101 dose of 200 mg inhibited ex vivo basophil activation via the PI3Kδ-specific, high-affinity immunoglobulin (Ig)E receptor (anti-FCεR1) in basophils collected from healthy volunteers. The findings were confirmed when the drug was assessed over 7 days in a Phase 1b study in subjects with allergic rhinitis. In this study, GS-1101 at a dose level of 100 mg/dose BID showed clinical and pharmacodynamic activity (attenuating adverse responses to allergenic challenge and decreasing markers of inflammation) and was well tolerated.

1.3.5.2. Phase 1 Studies in Patients with Hematological Malignancies

1.3.5.2.1. Phase 1 Monotherapy Study in Patients with Hematological Malignancies

A Phase 1 dose-ranging study (Study 101-02) of single-agent GS-1101 extended safety and pharmacokinetic observations; documented the clinical and pharmacodynamic activity of GS-1101 in subjects with iNHL, MCL, and CLL; and provided dosing information in support of further development [Brown 2011, Coutre 2011, Gilead 2011, Kahl 2011]. In this study, GS-1101 was administered in cohorts of subjects across a range of dose levels from

50 mg/dose BID to 350 mg/dose BID. GS-1101 administration was continued as long as individual subjects were safely benefitting from therapy. Subjects were evaluated in 4-week cycles; response and progression assessments were based on standard criteria [Hallek 2008].

Altogether, 192 subjects were enrolled to the study, including 55 subjects with CLL. As expected given the demographics of these diseases, subjects were predominantly male and were often elderly, ranging in age to 82 years for the subjects with CLL. The majority (82%) of the subjects with CLL had bulky tumors (≥1 lymph node ≥5 cm in diameter) and 31% had the adverse prognostic factor of a 17p chromosomal deletion (which commonly confers a p53 mutation in the tumors of these subjects). Subjects were heavily pretreated with chemoimmunotherapy; the median number of prior therapies by disease was 5 among subjects with CLL, but ranged up to 15 prior treatments. Among those with CLL, prior rituximab, alkylator, and fludarabine use were nearly universal and 33% had received prior alemtuzumab. Considering only rituximab use after initial therapy, 35% had received single-agent rituximab at least once (some patients up to 3 times) and a total of 51/54 (94%) had received rituximab given alone or in combination with other agents. In the estimation of the investigators, a substantial proportion (72%) of these subjects had disease that was refractory to the last prior therapy. In these subjects, therapy was administered for a median of 9 cycles, ranging up to 24 cycles (ie, 96 weeks).

In this single-agent experience, GS-1101 was generally well tolerated at dose levels through 350 mg BID (the highest dose tested). No maximum tolerated dose (MTD) was apparent within the tested dose range. Furthermore, subjects typically found the drug tolerable over periods extending to >2 years; there was no profile suggestive of bothersome chronic events such as headache, nausea, diarrhea, or fatigue. No subject had tumor lysis syndrome. No overt pattern of myelosuppression was associated with GS-1101 treatment. The data also did not suggest drug-related reductions in circulating CD4+ cells or serum Igs.

Among Grade 3-4 nonhematological adverse events, pneumonia/pneumonitis was observed most frequently, occurring in 24% of subjects with CLL. In most instances, these cases were considered bacterial in origin, based either on culture results or on response to conventional antibiotics. Subjects with CLL have occasionally been diagnosed with *Pneumocystis (carinii) jiroveci* pneumonia; the specific causal role of GS-1101 has been difficult to elucidate because infection was sometimes present before starting GS-1101 or the subjects had other pre-existing risk factors. Such subjects were not receiving pneumocystis prophylaxis. The rate of pneumonia over time (0.045 events/subject/month) with GS-1101 was not worse than the expected rate (0.06 events/patient/month) reported historically in comparable patients with recurrent CLL [Perkins 2002].

Monitorable, reversible elevations of hepatic transaminases were observed in some subjects; ~5% of subjects with previously treated CLL had Grade 3-4 increases in serum ALT or AST. The onset of changes was time-dependent; among those with serum ALT/AST abnormalities, onset typically occurred 2 to 8 weeks after GS-1101 initiation. In subjects with Grade 1-2 events, serum ALT/AST elevations resolved despite continued GS-1101 dosing. In subjects with Grade 3-4 events, GS-1101 was temporarily interrupted. Upon resolution of serum ALT/AST abnormalities, resumption of GS-1101 at a reduced dose did not result in recurrence of serum transaminase increases in the majority (>70%) of subjects who were rechallenged. This pattern suggests an adaptation to the effect similar to that observed in

dogs receiving GS-1101. Such an adaptive response is commonly observed with other drugs that induce transaminase elevations [Tujios 2011].

GS-1101 proved highly active in subjects with CLL, iNHL, and MCL. Among subjects with CLL, GS-1101 reduced lymphadenopathy in all 51 (100%) of those with ≥1 post-treatment tumor assessment. In subjects with CLL tumors having a known 17p chromosomal deletion, substantial antitumor activity was observed, although PFS appeared shorter in these subjects relative to other trial participants without such a deletion or in whom the 17p chromosomal deletion status was unknown.

The pattern of changes in CLL was particular notable. Rapid and substantial reductions in lymph node size were observed in subjects with CLL with >80% of subjects showing a lymph node response (≥50% reductions in index nodal lesions). Among subjects who entered the trial with baseline thrombocytopenia or anemia, GS-1101 induced sustained increases in mean platelet counts and hemoglobin levels. In study participants who entered the study with enlarged spleens due to CLL, >70% showed a resolution in splenomegaly. The median PFS was 14 months, with some subjects having tumor controlling for durations exceeding 2 years. Antitumor activity and tumor control were longest in subjects starting GS-1101 at doses of ≥150 mg/dose BID.

A characteristic finding in the single-agent experience was that the majority of subjects had an initial increase in peripheral absolute lymphocyte count (ALC) from baseline. The increase was maximal during the first 2 cycles and generally decreased thereafter but could be persistent in some subjects or could be seen repeatedly in subjects who had interruption and resumption of drug therapy (eg, due to intercurrent illness). The characteristics of this lymphocytosis indicated a mobilization of CLL cells from tissues rather than a proliferative event or a disease flair. The effect was evident within 4 hours of initiating treatment, was asymptomatic, and was associated with quiescence of CLL cells as indicated by reductions in AKT phosphorylation and decreases in circulating levels of disease-associated chemokines, CCL3 and CCL4, and the stroma-derived chemokine, CXCL13. The lymphocyte mobilization phenomenon is consistent with in vitro data showing that GS-1101 depresses chemokine-mediated signaling between CLL cells and stromal cells [Hoellenriegel 2011]. These preclinical data support the concept that drug-mediated PI3Kδ inhibition releases CLL cells from sanctuary sites in lymph nodes and bone marrow. This action is not unique to GS-1101 alone. Drugs that inhibit spleen tyrosine kinase (SYK) [Friedberg 2010], Bruton tyrosine kinase (BTK) [Burger 2010a], or mTOR [Zent 2010] cause a CLL cell redistribution from tissue sites to the peripheral blood. Because of the occurrence of this type of pattern, investigators working with GS-1101 or inhibitors of these other pathways now rely upon measures of disease control other than peripheral blood lymphocyte count in determining whether a patient's disease has progressed.

An analysis of steady-state GS-1101 plasma concentrations (Day 28 C_{max}, $AUC_{0\text{-}6h}$, or C_{trough}) relative to dose in subjects with both NHL and CLL showed increases in these parameters through the dose level of 150 mg/dose BID. At higher doses, flattening of the mean dose-plasma exposure curve was observed, resulting in smaller incremental increases in exposure. Considering all safety, efficacy, and pharmacokinetic findings together, the data supported 150 mg/dose BID as an appropriate GS-1101 monotherapy starting dose for future studies in patients with CLL and other lymphoid malignancies.

1.3.5.2.2. Phase 1 Combination Study in Patients with Hematological Malignancies

A separate Phase 1 trial (Study 101-07) has evaluated the safety and preliminary activity of GS-1101 given in combination with rituximab to subjects with recurrent iNHL or CLL [Brown 2011, Leonard 2011].

In this study, rituximab was administered at a standard dose of 375 mg/m^2 per infusion weekly for 8 weeks in all subjects. GS-1101 was started simultaneously with the rituximab, first at a dose level of 100 mg/dose BID (n=13) and then at a dose level of 150 mg/dose BID (n=12) and was administered continuously to both subjects with CLL (n=13) and subjects with iNHL (n=12) for as long as individual subjects were safely benefiting from therapy. Subjects were evaluated in 4-week cycles; response and progression assessments were based on standard criteria [Hallek 2008].

Among the subjects with CLL, the median age was 63 and ranged to 85 years. Bulky tumors (≥1 lymph node ≥5 cm in diameter) were present in 63% of the subjects. The median number of prior therapies by disease was 2 and ranged up to 8 prior treatments. All had received prior rituximab and the majority had received prior fludarabine or alkylating agents. Approximately one-third of subjects had CLL that was refractory to the last prior therapy. At the time of data cut-off, therapy had been administered for a median of 5 cycles, ranging up to 12 cycles (ie, 48 weeks).

No GS-1101-related dose-limiting toxicities were observed within the tested subject cohorts. Grade 3-4 adverse events largely comprised background events resulting from pre-existing disease- or treatment-related conditions or from intercurrent illness. Among subjects with CLL, 2 (15%) developed pneumonia. For subjects receiving GS-1101 together with rituximab, Grade 3-4 elevations in ALT/AST were not observed in those with CLL, although 3 subjects (25%) of those with iNHL had such events.

The GS-1101 plus rituximab combination showed a high level of antitumor activity in both subjects with CLL and those with iNHL. Altogether 92% of subjects with CLL receiving the combination of GS-1101 and rituximab had reductions in nodal size and 77% showed a lymph node response (≥50% reduction in index nodal lesions). Although concomitant administration of rituximab did not eliminate the redistribution lymphocytosis that is associated with GS-1101, it blunted the magnitude of the change. As a result, the overall response rate (ORR) was also 77% among subjects participating in this study. At the time of last data analysis, PFS through 48 weeks was 70% and a median PFS had not yet been observed.

Collectively, the emerging data from this study support further evaluation of GS-1101 together with rituximab in subjects with CLL and indicate that co-administration of GS-1101 with rituximab is tolerable when using GS-1101 at full dose, ie, at a starting dose level of 150 mg/dose BID.

1.4. Summary and Justification for the Current Study

Gilead Sciences is conducting this Phase 3 study program to evaluate the efficacy and safety of GS-1101 in patients with previously treated, recurrent CLL. Collectively the data derived from the primary clinical trial (Study GS-US-312-0116) and from this extension trial (Study GS-US-312-0117) address the activity of GS-1101 together with rituximab, the

activity of GS-1101 when given alone, and the potential for dose-dependent restoration of drug activity in subjects who have disease that appears to be drug resistant.

The design and conduct of this clinical trial program is supported by knowledge of the demographics of patients with CLL, the natural history and current therapies for the disease, and the nonclinical and clinical information regarding GS-1101. The collective data support the following conclusions:

- CLL is a serious, disabling, and potentially life-threatening disorder of older patients that requires sequential treatment with agents that provide alternative mechanisms of tumor control. Existing cytotoxic agents have serious acute and chronic toxicities, making them less suitable for frail or unfit patients. Single-agent rituximab can offer disease palliation with good tolerability in some patients with relapsed CLL but tumor control is not lasting, especially in patients with bulky adenopathy. Development of a non-cytotoxic combination therapy of GS-1101 with rituximab or a monotherapy regimen of GS-1101 that can address disease pathogenesis with a new mechanism of action and might offer complementary nodal and peripheral blood activity would address an unmet medical need, particularly when applied in patients with substantial comorbidities or myelosuppression from prior chemotherapies.
- PI3Kδ over-expression plays an important role in CLL biology. Further evaluation of GS-1101 as a potential treatment for CLL has sound scientific rationale founded on knowledge of the actions of the drug to selectively abrogate PI3Kδ activity and to inhibit malignant cell growth and stromal cell signaling in nonclinical models of CLL. These data are supported by clinical documentation of GS-1101 inhibition of PI3Kδ signaling in patients with CLL.
- The potential for clinical efficacy of GS-1101 monotherapy or of GS-1101 plus rituximab in patients with relapsed or refractory CLL is supported by the observed antitumor activity of GS-1101 – given alone or in combination with rituximab – in patients with heavily pretreated CLL and iNHL.
- The safety of advancing development of the GS-1101 monotherapy and of a regimen of GS-1101 plus rituximab in this Phase 3 clinical trial program is well supported by safety pharmacology and toxicology studies and by Phase 1 single-agent and combination safety data obtained in healthy volunteers and in subjects with lymphoid cancers.
- Dose-safety, dose-exposure, and dose-activity relationships identified in Phase 1 studies have established a firm basis for the dosing regimen and dose modification provisions in this study.
- Observations relating to patterns of CLL response among subjects receiving GS-1101 alone or in combination with rituximab in Phase 1 trials provide the foundation for efficacy monitoring in this trial. Of particular note is that GS-1101 mobilizes CLL cells from tissues into the peripheral blood. This characteristic pharmacological action is prominent early in therapy but can persist over time and should not be confused with disease progression in patients who have persistent control of other CLL-related signs and symptoms. For this reason, in this Phase 3 study program, subjects will be continued on therapy until the occurrence of definitive disease progression, ie, disease progression

that is manifest by worsening CLL-related signs or symptoms other than lymphocytosis alone.

- Thorough nonclinical and clinical characterization of the type, severity, manifestations, and expected timing of adverse events establish the safety monitoring plan in this trial program.
- The scientific correlative work performed in prior preclinical and clinical studies provides strong scientific underpinnings for the companion laboratory studies to be performed as a component of this clinical trial program.
- Given the seriousness of previously treated CLL in patients with substantial comorbidity, and the aggregate potential benefits considered in the context of potential risks, further development of GS-1101 in this Phase 3 clinical trial program is justified.

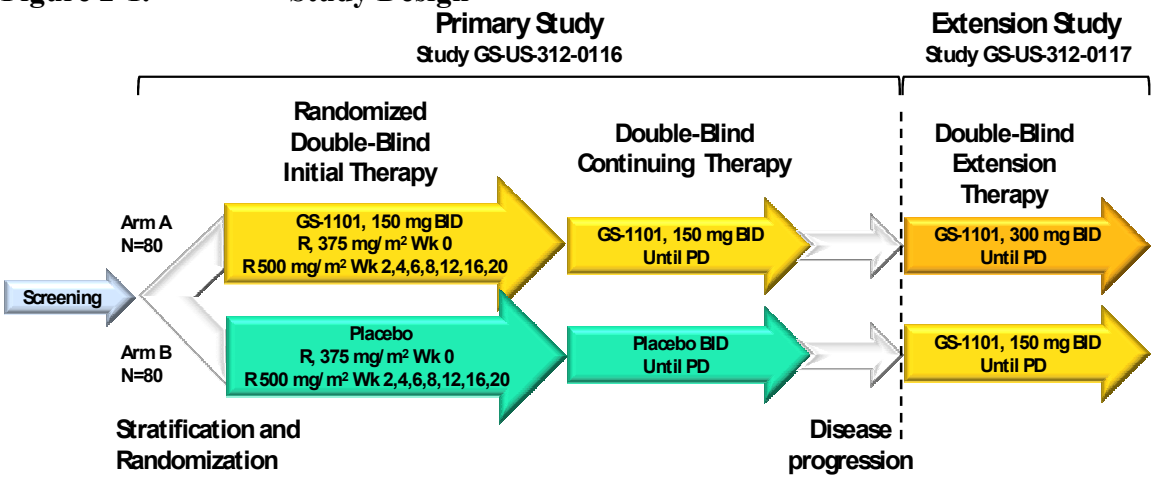
The rationale for specific design features is provided in relevant sections of the protocol, including Section 3.2 (Endpoint Selection Rationale), Section 2.2 (Design Rationale), Section 4.3 (Enrollment Criteria Rationale), Section 5.9 (Study Treatment Rationale), and Section 6.4 (Study Procedure Rationale).

2. STUDY DESIGN

2.1. Design Overview and Study Schema

This study is being conducted as part of an overall-clinical program that is evaluating the efficacy and safety of GS-1101 in the therapy of patients with previously treated CLL (see Figure 2-1). Within this program, the primary clinical trial (Study GS-US-312-0116) is a Phase 3, multicenter, 2-arm, randomized, double-blind, placebo-controlled, parallel-group study. This clinical trial (Study GS-US-312-0117) is a separate, multicenter, 2-arm, double-blind, parallel-group extension study that is a companion study to the primary study.

Figure 2-1. Study Design



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

Primary study subjects will be stratified based on 17p deletion and/or a p53 mutation status (either vs neither), immunoglobulin heavy chain variable region (IgHV) mutation status (unmutated vs mutated), and any prior therapy with an anti-CD20 therapeutic monoclonal antibody (yes vs no) and randomized in a 1:1 ratio to receive 1 of the 2 treatment arms.

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

GS-1101 or placebo will be taken orally, twice per day continuously while on study treatment. GS-1101 or placebo treatment will persist until the earliest of subject withdrawal from study, definitive progression of CLL, intolerable study drug-related toxicity, pregnancy, substantial noncompliance with study procedures, or study discontinuation. Subjects will be

encouraged to continue with protocol-specified therapy for each of the therapeutic agents (GS-1101/placebo or rituximab) that continues to be tolerated, even if the other agent needs to be discontinued due to drug-specific toxicity.

Compliant subjects who are tolerating therapy but who develop definitive disease progression in the primary clinical trial (Study GS-US-312-0116) can consider enrollment in this separate companion extension trial (Study GS-US-312-0117). In the extension trial, subjects will take active blinded GS-1101 therapy, either at a higher starting dose or at the standard starting dose, with allocation based on the original primary study randomization.

The primary objective of Study GS-US-312-0116 will be to evaluate the effect of the addition of GS-1101 to rituximab on PFS. Secondary objectives will focus on determining the effect of the addition of GS-1101 to rituximab on the onset, magnitude, and duration of tumor control; overall survival (OS); health-related quality of life (HRQL); changes in subject performance status; disease-associated biomarkers and potential mechanisms of resistance; treatment administration; safety; and health resource utilization. In Study GS-US-312-0117, the same endpoints will be assessed as in Study GS-US-312-0116; the focus of the analysis will be largely descriptive except for the within-subject assessment of treatment effects among subjects receiving first rituximab alone and then GS-1101 alone on Arm B of each trial. No formal comparisons of outcomes in Arm A vs Arm B are planned within Study GS-US-312-0117.

2.2. Design Rationale

The randomized, add-on design for the primary trial (Study GS-US-312-0116) is customary in the comparative evaluation of new therapies for cancer. While this design provides GS-1101 efficacy and safety information only in the context of administration of a companion antineoplastic agent, it is appropriate because it documents the incremental benefit and toxicity of the investigational therapy in the context of a controlled clinical trial while ensuring that all participants receive potentially active treatment.

This separate extension trial (Study GS-US-312-0117) enhances subject acceptance of randomization in the primary study and provides further information regarding GS-1101 efficacy, resistance, and safety. Among subjects in Arm A, escalation to a higher dose level allows evaluation of dose-dependent resistance and a determination if a higher dose can reestablish disease control. The safety data obtained in these subjects will add to the overall safety database. Among subjects randomized to Arm B in the primary study, evaluation of GS-1101 at a starting dose of 150 mg/dose BID in the extension study may permit a within-subject assessment of the treatment effects with single-agent GS-1101 relative to the effects previously observed with rituximab alone. Of importance, the extension study maintains the partial blinding of the primary study, thus minimizing the bias that might occur if the overall design entailed only a 1-way crossover to open-label GS-1101 among subjects who had received placebo on Arm B of the primary study. To ensure confirmation of disease progression, tumor size data collected from the primary study will be subjected to independent review by an independent review committee (IRC) (see Section 10.4.3); subjects will continue with study therapy pending confirmation of progression status by the sponsor working in collaboration with the IRC. Subjects must have confirmation that the disease has

progressed on the primary study before being permitted to receive secondary GS-1101 therapy on the extension study.

3. OBJECTIVES AND ENDPOINTS

- To determine the effect of GS-1101 on the onset, magnitude, and duration of tumor control
- To compare tumor control in subjects receiving rituximab alone in Study GS-US-312-0116 to that observed in the same subjects when receiving the standard dose of GS-1101 alone in Study GS-US-312-0117
- To assess the effect of GS-1101 on measures of subject well-being, including overall survival (OS), health-related quality of life (HRQL), and performance status
- To assess the effects of GS-1101 on disease-associated biomarkers and to evaluate potential mechanisms of resistance to GS-1101
- To characterize exposure to GS-1101 as determined by treatment administration and evaluation of GS-1101 plasma concentrations over time
- To describe the safety profile observed with GS-1101
- To estimate health resource utilization associated with administration of GS-1101

3.1. Endpoints

3.1.1. Tumor Control

- Progression-free survival (PFS) – defined as the interval from the start of study therapy to the earlier of the first documentation of definitive disease progression or death from any cause; definitive disease progression is CLL progression based on standard criteria and occurring for any reason (ie, increasing lymphadenopathy, organomegaly or bone marrow involvement; decreasing platelet count, hemoglobin, or neutrophil count; or worsening of disease-related symptoms) other than lymphocytosis alone
- Overall response rate (ORR) – defined as the proportion of subjects who achieve a complete response (CR) or partial response (PR)
- Time to response (TTR) – defined as the interval from start of study therapy to the first documentation of CR or PR
- Duration of response (DOR) – defined as the interval from the first documentation of CR or PR to the earlier of the first documentation of definitive disease progression or death from any cause
- Time to treatment failure (TTF) – defined as the interval from start of study therapy to the earliest of the first documentation of definitive disease progression, the permanent cessation of study drug due to an adverse event, or death from any cause
- Percent change in lymph node area – defined as the percent change from baseline in the sum of the products of the greatest perpendicular diameters (SPD) of index lymph nodes
- Lymph node response rate – defined as the proportion of subjects who achieve a ≥50% decrease from baseline in the SPD of index lymph nodes

- Splenomegaly response rate – defined as the proportion of subjects with baseline splenomegaly who achieve an on-study normalization or a decrease by ≥50% from baseline in the pretreatment enlargement of the splenic longest vertical dimension (LVD) (by imaging) or in the pretreatment enlargement of the splenic LVD below the left costal margin (by palpation)
- Hepatomegaly response rate – defined as the proportion of subjects with baseline hepatomegaly who achieve an on-study normalization or a decrease by ≥50% from baseline in the pretreatment enlargement of the hepatic LVD (by imaging) or in the pretreatment enlargement of the hepatic LVD at the right midclavicular line (by percussion)
- Platelet response rate – defined as the proportion of subjects with baseline thrombocytopenia (platelet count <100 x 10^9/L) who achieve an on-study platelet count ≥100 x 10^9/L or demonstrate a ≥50% increase in platelet count from baseline
- Hemoglobin response rate – defined as the proportion of subjects with baseline anemia (hemoglobin <110 g/L [11.0 g/dL]) who achieve an on-study hemoglobin ≥110 g/L (11.0 g/dL) or demonstrate a ≥50% increase in hemoglobin from baseline
- Neutrophil response rate – defined as the proportion of subjects with baseline neutropenia (absolute neutrophil count [ANC] <1 x 10^9/L) who achieve an ANC ≥1 x 10^9/L or demonstrate a ≥50% increase in ANC from baseline

3.1.2. Patient Well-Being

- Overall survival (OS) – defined as the interval from start of study therapy to death from any cause
- Change in HRQL domain and symptom scores based on the Functional Assessment of Cancer Therapy: Leukemia (FACT-Leu) (see Appendix 2) – defined as the change from baseline and the time to definitive increments or decrements of 10%, 20%, and 40% from baseline; time to definitive increment (better than baseline by the specified amount) is the interval from start of study therapy to the first timepoint when the HRQL measure is consistently better than at baseline (including that timepoint as well as all the subsequent timepoints) in a subject whose last HRQL score is better than at baseline; and time to definitive HRQL decrement (worse than baseline by the specified amount) is the interval from start of study therapy to the earliest of death or the first timepoint when the HRQL measure is consistently worse than at baseline (including that timepoint as well as all the subsequent timepoints) in a subject whose last performance status score is worse than at baseline
- Changes in Karnofsky performance status – defined as the change from baseline in the performance status (see Appendix 3) and the time to definitive performance status improvement or worsening; time to definitive performance status improvement (better than baseline) is the interval from start of study therapy to the first timepoint when the performance status is consistently better than at baseline (including that timepoint as well as all the subsequent timepoints) in a subject whose last performance status score is better than at baseline; and time to definitive performance status worsening (worse than

baseline) is the interval from study therapy until the earliest of death or the first timepoint when the performance status is consistently worse than at baseline (including that timepoint as well as all the subsequent timepoints) in a subject whose last performance status score is worse than at baseline

3.1.3. Pharmacodynamic Markers of Drug Activity and Resistance

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

3.1.4. Exposure

- Study drug administration as assessed by prescribing records and compliance as assessed by quantification of used and unused drug
- Trough (pre-dose) and peak (1.5-hour samples) of GS-1101 plasma concentrations as assessed by a validated bioanalytical method

3.1.5. Safety

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

3.1.6. Pharmacoeconomics

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

3.2. Endpoint Selection Rationale

The proposed endpoints have been chosen based on relevance to the pathophysiology and clinical manifestations of CLL, the known pharmacology of GS-1101, and the goals of the study in documenting GS-1101 benefit-to-risk ratio. These types of endpoints have been employed in prior studies in CLL and can be evaluated with acceptable reliability and accuracy.

3.2.1. Tumor Control Endpoints

Assessments of the magnitude and duration of changes in tumor size are routinely employed in registration-directed oncology clinical studies to determine therapeutic effect. Unlike OS, these endpoints directly assess the ability of the drug to control the malignancy. Such assessments are also integral to treatment decisions; because subjects are being treated until

disease progression, repeated tumor assessment must be performed in order to define the proper duration of treatment for each study participant. Standard response and progression criteria have been established by the International Workshop on CLL (IWCLL) [Hallek 2008]; the assessments of treatment effects in this study will be based on these criteria, taking into account the specific pharmacology of GS-1101.

In CLL, disease-related nodal enlargement is a major cause of patient discomfort and can cause organ dysfunction [Dighiero 2008]. Extensive lymphadenopathy constitutes a reason to treat CLL and controlling the size of pathologically enlarged lymph nodes is an important therapeutic goal for improving patient well-being and relieving obstructive symptoms [Hallek 2008]. Given that the natural history of recurrent CLL is inexorable nodal growth, enhancing tumor shrinkage and prolonging tumor control provides strong evidence of pharmacological activity.

Endpoints of overall tumor control as evaluated in this trial are customarily assessed and reported in studies of new therapies in patients with cancer. PFS offers a well established outcome measure that directly measures treatment effect, conveys important longitudinal information regarding tumor control, can be characterized in all subjects using intention-to-treat (ITT) principles, and is readily analyzed using statistical methods such as Kaplan-Meier techniques. ORR provides an integrated assessment of the magnitude and extent of changes in lymphadenopathy, organomegaly, bone marrow infiltration, and bone marrow function that conveniently categorizes and describes treatment effects. TTR and DOR are important in characterizing the rapidity of achieving tumor shrinkage and the duration of tumor control. TTF offers a further characterization of subject outcome that incorporates the added dimension of drug tolerability; the degree of correspondence between PFS and TTF provides an assessment of how commonly adverse effects are compromising the ability to maintain therapy.

Beyond providing descriptions on overall response assessment using ORR, this protocol will also seek to characterize the individual components of response that are important in assessment of CLL [Hallek 2008]. Thus, changes in lymph node area and in the proportion of subjects having a lymph node response will be analyzed. In addition, among subjects who enter the study with splenomegaly, the proportion achieving substantial (≥50%) reductions in spleen size will be assessed. Similarly, the proportions of subjects who experience improvements in platelets, hemoglobin, and neutrophil counts will be characterized in order to provide specific insight into the degree to which therapy alters these individual parameters.

Because GS-1101 mobilizes CLL cells from tissues into the peripheral blood as part of its pharmacological effect, there is a risk of falsely declaring a subject to have experienced disease progression if lymphocyte count is considered as the sole basis for potential CLL worsening. To account for this potential problem, changes in lymphocyte count will not be considered in determining whether a subject has progressive disease, ie, subjects will only be declared to have progressive CLL if they meet any of the IWCLL criteria for progressive disease other than lymphocytosis alone. Thus, subjects with worsening lymphadenopathy, organomegaly, bone marrow involvement, progressive cytopenias, appearance of new disease, recurrence of B symptoms, or transformation to an aggressive lymphoid malignancy histology (eg, Richter syndrome) will be considered to have progressed. Subjects with lymphocytosis without any of these other events will not be considered to have progressed.

Given that lymphocytosis has no prognostic significance in patients with relapsed/refractory disease [Silverman 2002, Tsimberidou 2007] and is not generally considered a reason to treat in patients with CLL [Hallek 2008, Eichhorst 2010, Zelenetz 2011], this approach does not jeopardize subject safety or subsequent therapy. Furthermore, it will allow complete collection of all response and progression data (both considering lymphocytosis and ignoring lymphocytosis) with the intent of providing complete information for regulatory authority review.

The current IWCLL guidelines indicate that physical examination is generally sufficient to evaluate nodal response and progression in patients with CLL [Hallek 2008] but that radiographic assessments may be appropriate in clinical trials. Computed tomography (CT) is considered the preferred imaging method unless patients have contraindications that require use of magnetic resonance imaging (MRI). Given the low fluorodeoxyglucose (FDG) avidity of CLL, positron- emission tomography (PET) does not have a role in evaluation of this disease. The incremental benefits of using radiographic imaging are limited in patients undergoing long-term follow-up following first-line therapy [Blum 2007, Eichhorst 2011]. However, in the patients with advanced CLL and bulky adenopathy such as those who will be enrolled to this trial, it is known that CT scans commonly detect bulky intra-abdominal lymphadenopathy and splenomegaly that would be missed by palpation alone and that the presence of large-volume, intra-abdominal disease of the nodes and spleen is associated with a poor prognosis [Norin 2010]. Thus, while use of CT confers greater radiation exposure, subjects have the chance to benefit from radiographic imaging because it will offer more accurate information regarding their response to protocol therapy and the appropriate duration of protocol treatment. Having this information is particularly important in this trial because PI3Kδ inhibition precludes use of lymphocyte counts as evidence for disease progression. In addition, the risk is offset by the fact that the trial subjects will primarily be patients who have already received more potent mutagens (eg, purine analogs, alkylating agents), and all of whom have advanced cancer and limited treatment options at study entry. Based on published data [Keating 2002, Wierda 2010], median OS for patients with comparably advanced CLL is <18 months, so the long-term secondary malignancy risk from CT-related radiation exposure is very low. Finally, in the context of a registration-directed pivotal trial of a new drug with a new mechanism of action, radiographic imaging is critically important to provide reassurance regarding subject safety and trial validity. In this regard, CT evaluations of the lung can be used retrospectively to assess for radiographic evidence of drug-induced lung changes [White 2010, Maroto 2011]. Furthermore, CT measurements have greater accuracy and reproducibility than palpation, are subject to independent expert review, and can be audited against electronic case report form (eCRF) information.

The timing of radiographic tumor assessments has been carefully considered. To avoid duplication, the CT scan documenting CLL progression in Study GS-US-312-0116 will serve as the baseline CT scan for Study GS-US-312-0117. Among patients receiving GS-1101 in Phase 1b/2 studies who experienced a nodal response (≥50% regression in tumor area), such responses were observed with the first 16 week of therapy [Coutre 2011, Leonard 2011]; the planned timing of tumor assessments (at Weeks 8, 16, 24, 36, 48 and then every 12 weeks on thereafter through 96 weeks) in this study fits with this known timing of changes in lymph node size during GS-1101 therapy. Scans at 8-week intervals during the first 24 weeks allow initial documentation of response (at Week 8 or 16) and follow-up confirmation of response

8 weeks later (at Week 16 or 24) consistent with current response criteria [Hallek 2008]. During this period, early documentation of disease progression allows subjects who are not benefiting from study therapy to move rapidly to alternative treatments. After 24 weeks on study, the reduction in the frequency of CT scans (to 12-week intervals through 96 weeks) reduces the overall protocol burden for subjects while still allowing characterization of the expected median PFS in this trial. Permitting investigators to omit scans after 96 weeks (ie, after ~2 years) further limits the burden on subjects after this period. As outlined in Section 7.3, iodine-containing or gadolinium contrast material may be omitted in subjects for whom use of a contrast agent would be medically contraindicated.

3.2.2. Measures of Patient Well-Being

3.2.2.1. Overall Survival

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

However, given the life-threatening nature of systemic malignancy, documentation of OS is customary in oncology therapeutic clinical trials, including those evaluating subjects with recurrent CLL [Keating 2002, Wierda 2010]. Evaluation of OS in this study continues the survival assessment from the primary study (Study GS-US-312-0116). The study program as a whole (considering both the primary randomized trial and secondary extension study) offers the potential to better understand OS and causes of death in a frail population of patients with both CLL and comorbidities.

3.2.2.2. Health-Related Quality of Life

Direct patient reporting of outcomes using standardized methods has become an increasingly important component of therapeutic assessment. Evaluation of patient-reported outcomes (PROs) is particularly relevant in patients who cannot be cured of disease [Fairclough 2002]. PRO questionnaires have been previously used in CLL to understand how patients differ from the general population in terms of health concerns [Holzner 2004, Eichhorst 2007, Shanafelt 2007, Else 2008], to understand differences in perceptions of well-being in younger vs older patients [Levin 2007, Else 2008], to determine how treatment affects HRQL [Catovksy 2007, Eichhorst 2007, Efficace 2008], and to assess the pharmacoeconomic cost of improvements in HRQL [Stephens 2005].

Patients with CLL have overtly impaired well-being relative to comparable controls [Holzner 2004, Eichhorst 2007, Shanafelt 2007, Else 2008]. Fatigue is cited as a common complaint, being present in the substantial majority of patients. Impairment of HRQL prior to any treatment is apparent in those with B symptoms or in patients with anemia, supporting the concept of initiating treatment when patients experience symptomatic disease. Factors associated with lower overall HRQL have included older age, greater fatigue, severity of co-morbid health conditions, advanced stage, and ongoing treatment for CLL [Shanafelt 2007]. Younger patients appear to have worse emotional and social well-being but older

patients experience worse physical HRQL [Levin 2007]. In comparative evaluation of chemotherapy-containing regimens, differences in HRQL between therapies (eg, fludarabine vs fludarabine-cyclophosphamide vs chlorambucil) reflected differences in toxicity while improved HRQL was associated with greater efficacy [Catovksy 2007, Eichhorst 2007].

In this study, it is postulated that GS-1101-mediated tumor control will be correlated with greater positive changes in HRQL and that assessments of the drug's safety profile will be supported by HRQL evaluations. The FACT-Leu (Appendix 2) has been selected to evaluate such outcomes for the study. The FACT-Leu comprises a general HRQL measure for patients receiving cancer treatment that yields a total score and subscales for physical, functional, social/family and emotional well-being [Cella 1993] and a diagnosis-specific measure for patients with leukemia [Webster 2002]. The FACT-Leu was developed to assess symptoms (eg, fevers, chills, night sweats, nodal swelling, fatigue) specifically relevant to patients with leukemia. FACT instruments have documented psychometric properties [Cella 1993, Webster 2002, Brucker 2005, Cella 2005, Victorson 2008].

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

3.2.2.3. Changes in Performance Status

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

In this study, it is hypothesized that GS-1101-mediated tumor control will be correlated with changes in performance status and that assessments of the drug's safety profile might be supported by performance status evaluations. The well-established, reliable, and validated Karnofsky performance score [Karnofsky 1949, Yates 1980, Schag 1984] (see Appendix 3) will be employed in the trial for characterization of the subject population and repeated assessment of performance status.

3.2.3. Pharmacodynamic Markers of Drug Activity and Resistance

In CLL, disease-related perturbations in inflammatory status can be clinically overt; patients often develop bothersome B symptoms (fevers, night sweats, and weight loss) that are characteristic of excessive systemic inflammation [Redaelli 2004]. Consistent with such disease manifestations, the PI3Kδ/AKT/mTOR pathway is constitutively overactive in circulating CLL cells [Coutre 2011]. In addition, chemokines and cytokines that are markers of aberrant B-cell trafficking or perturbations in inflammation are overexpressed by CLL tissues or by stromal cells and circulate in plasma [Burger 2010b, Coutre 2011]. In Phase 1 studies of GS-1101 it has been confirmed that GS-1101 largely normalizes AKT

phosphorylation and induces dose-dependent reductions in plasma concentrations of circulating chemokines and cytokines in patients with CLL [Coutre 2011].

In this study, it is hypothesized that incremental changes in these biomarkers provide direct evidence of mechanism-specific GS-1101 effects on PI3Kδ activity or indirectly document drug effects on overall tumor cell volume. In either case, improvements in these pharmacodynamic measures provide corroborative evidence in support of GS-1101 pharmacological activity; conversely, worsening of these biomarkers may indicate acquisition of resistance to GS-1101. In addition, it is possible that disease-or inflammation-related biomarkers may provide corollary information relating to the adverse effects of GS-1101 on the liver; such data might allow better prediction of which subjects might be most susceptible to ALT/AST elevations during GS-1101 treatment. Finally, it can also be postulated that genetic, protein, or metabolic changes in CLL cells could provide signatures that would correlate with drug sensitivity and resistance.

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

Plasma will be collected for assessment of circulating concentrations of relevant chemokines and cytokines with a particular focus on CCL2, CCL3, CCL4, CXCL12, CXCL13, CCL17, CCL19, CCL21, CCL22, sCD40 ligand, tumor necrosis factor-α, and C-reactive protein. In addition serum markers of iron metabolism (eg, hepcidin, iron, ferritin, transferrin) that might provide markers linking disease-related inflammation with perturbations of liver iron and sensitivity to liver injury will be evaluated [Nemeth 2003, Ferrucci 2010]. Clinically validated assays (eg, enzyme-linked immunosorbent assays [ELISAs]) will be used to measure circulating concentrations of chemokines and cytokines at baseline and during the course of GS-1101 therapy.

CLL cell deoxyribonucleic acid (DNA), ribonucleic acid (RNA), and protein will be collected at baseline and at the conclusion of a subject's treatment on study. DNA and RNA samples will be analyzed using gene array technologies to evaluate for changes in DNA mutations or in RNA expression patterns that might be associated with intrinsic or acquired resistance to study treatments. Similarly, protein will be evaluated for state-specific changes in protein phosphorylation to evaluate for differences in pathway activation at baseline or during therapy that might be associated with differences in response or in acquisition of resistance to therapy.

3.2.4. Assessments of Exposure

3.2.4.1. Study Drug Administration and Compliance

Evaluation of study drug administration and compliance provides context for assessments of safety, pharmacokinetics, and pharmacological activity. Evaluations of treatment administration and modifications from planned therapy document the influence of

treatment-emergent adverse events on prescribing practice. Compliance assessment offers a general indication of patients' acceptance of therapy, integrating factors of tolerability, palatability, and convenience.

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

3.2.4.2. Pharmacokinetics

Given the intent of this protocol to assess longer-term dosing, collection of plasma for GS-1101 concentrations is important for evaluating the steady-state maintenance of exposure over time. These data may allow correlations of exposure with measures of efficacy, toxicity, and resistance, will be important part of exploring exploration of 2 different GS-1101 dose levels. Because the GS-1101 pharmacokinetic profile has been well characterized in Phase 1 studies, limited plasma sampling will be performed in this study. Samples will be collected pre-dose and 1.5 hours post-dose relative to the morning administration of GS-1101. This approach will provide information regarding plasma C_{trough} values and will describe drug absorption as characterized by plasma concentrations at the approximate T_{max} after the morning dose. The 1.5-hour timepoint has been assessed in prior Phase 1 studies, allowing across-study correlations of exposure. Based on discussions with investigators, collecting more than 2 samples in the morning is not considered reasonable given the need to minimize time requirements for study participants and to avoid substantial inconvenience for clinic staff.

Evaluation of GS-1101 plasma concentrations will be performed using liquid chromatography with tandem mass spectrometry. The method has been fully validated in the context of prior Phase 1 studies. Plasma samples will be retained for potential later analyses of GS-1101 metabolites.

3.2.5. Evaluations of Safety

In defining the therapeutic relevance of a drug in a particular clinical setting, it is imperative that its safety profile be fully characterized. As is conventional in all clinical studies, proper description of each adverse event or laboratory abnormality requires an understanding of the type, incidence, timing, severity, and relatedness to study drug. While information on all reported adverse events will be collected, listed, and summarized, particular focus will be placed on monitoring and reporting adverse events and laboratory abnormalities that were encountered in the prior toxicology studies and clinical experience with GS-1101. Safety parameters of specific interest in reporting study results will include those relating to infection, pulmonary events (eg, pneumonia/pneumonitis), liver injury, rash, and bone marrow dysfunction. Additional scrutiny will be applied to Grade 3-4 adverse events, to adverse events causing interruption or discontinuation of GS-1101, and to serious adverse events.

In addition, the protocol will evaluate for potential adverse GS-1101 effects on laboratory parameters of immune function; the absolute number of CD4+ and CD8+, CD16/CD56+, CD19+, and CD20+ cells will be assessed by flow cytometry. Serum concentrations of IgA, IgE, IgG, and IgM will be obtained.

For consistency of interpretation, adverse events will be coded using the standard Medical Dictionary for Regulatory Activities (MedDRA) [http://www.meddramsso.com]), and the severity adverse events and laboratory abnormalities will be graded using the well-defined Common Terminology Criteria for Adverse Events (CTCAE), Version 4.03 (*http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf).* Standard definitions for seriousness will be applied (see Section 8.1.2).

3.2.6. Pharmacoeconomic Measures

It is increasingly important to understand the potential cost implications of introducing a new medication into patient care for CLL [Main 2010, Hornberger 2011]. In order to analyze the pharmacoeconomic consequences of GS-1101 administration, data will be collected regarding the health status of subjects and regarding health care resource utilization.

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

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

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

The basic approach will be to combine the resource utilization data from the trial with data on unit prices (collected separately) to estimate total costs. The costs will be described relative to the health care findings as measured by duration of tumor control, the symptom-free survival period, and/or utility outcomes or some other appropriate measure of clinical benefits.

4. SUBJECT POPULATION

4.1. Number of Subjects

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

4.2. Subject Selection Criteria

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

4.2.1. Inclusion Criteria

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

1) Participation in Study GS-US-312-0116.
2) Occurrence of confirmed, definitive CLL progression while receiving study drug therapy (GS-1101/placebo) in Study GS-US-312-0116. ***Note: Definitive disease progression is CLL progression based on standard criteria and occurring for any reason (ie, increasing lymphadenopathy, organomegaly, or bone marrow involvement; decreasing platelet count, hemoglobin, or neutrophil count; or worsening of disease-related symptoms) other than lymphocytosis***. ***Subjects must have confirmation by the sponsor working in collaboration with an independent review committee (IRC) that the disease has progressed on the clinical trial (Study GS-US-312-0116) before receiving secondary GS-1101 therapy on this extension trial (Study GS-US-312-0117).***
3) Presence of radiographically measurable lymphadenopathy (defined as the presence of ≥1 nodal lesion that measures ≥2.0 cm in the longest dimension [LD] and ≥1.0 cm in the longest perpendicular dimension [LPD] as assessed by CT or MRI).
4) Permanent cessation of Study GS-US-312-0116 treatment (rituximab and GS-1101/placebo) and no intervening or continuing therapy (including radiotherapy, chemotherapy, immunotherapy, systemic corticosteroids, or investigational therapy) for the treatment of CLL.
5) The time from permanent cessation of Study GS-US-312-0116 treatment (rituximab and/or GS-1101/placebo) and the initiation of Study GS-US-312-0117 therapy is ≤12 weeks. ***Note: Study procedures performed as part of Study GS-US-312-0116 need not be repeated and can be used as screening procedures for Study GS-US-312-0117 if performed within 4 weeks prior to initiation of study drug therapy on Study GS-US-312-0117.***
6) Karnofsky performance score of ≥40.

7) Required baseline laboratory data (within 4 weeks prior to initiation of study treatment) as shown in the table below. ***Note: Confirmation should be considered for out-of-range values to determine if the abnormality is real or artifactual. Values should be obtained within the screening period and should generally be the most recent measurement obtained. Subjects with any degree of neutropenia, thrombocytopenia, or anemia due to CLL or prior therapy may enroll.***

Table 4-1. Required Screening Laboratory Values

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

a As calculated by the Cockcroft-Gault formula (see Appendix 5)

b For women of child-bearing potential only; serum β-HCG must be negative during screening and serum β-HCG or urine dipstick pregnancy test must be negative at start of study treatment (Visit 2)

Abbreviations: β-HCG= beta human chorionic gonadotropin, ALT=alanine aminotransferase, AST=aspartate aminotransferase, eC_{Cr}=estimated creatinine clearance, ULN=upper limit of normal

8) For female subjects of childbearing potential, willingness to abstain from heterosexual intercourse or use a protocol-recommended method of contraception from the screening visit (Visit 1) throughout the study treatment period and for 30 days following the last dose of study drug. ***Note: A female subject is considered to be of childbearing potential unless she has had a hysterectomy, bilateral tubal ligation, or bilateral oophorectomy; has medically documented ovarian failure (with serum estradiol and follicle-stimulating hormone [FSH] levels within the institutional postmenopausal range and a negative serum or urine βHCG), or is menopausal (age ≥55 years with amenorrhea for ≥6 months).***

9) 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 therapy (Visit 2) throughout the study treatment period and for 90 days following the last dose of study drug and to refrain from sperm donation from the start of study treatment (Visit 2) throughout the study treatment period and for 90 days following the last dose of study drug. ***Note: A male subject is considered able to father a child unless he has had a bilateral vasectomy with documented aspermia or a bilateral orchiectomy, or has ongoing testicular suppression with a depot luteinizing hormone- releasing hormone (LH-RH) agonist (eg, goserelin acetate [Zoladex®]), leuprolide acetate [Lupron®]), or triptorelin pamoate [Trelstar®]).***

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

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

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

4.2.2. Exclusion Criteria

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

1) Known histological transformation from CLL to an aggressive lymphoma (ie, Richter transformation).
2) Evidence of ongoing systemic bacterial, fungal, or viral infection at the time of the start of study treatment (Visit 2). ***Note: Subjects with localized fungal infections of skin or nails are eligible. Subjects may be receiving prophylactic antiviral or antibacterial therapies at the discretion of the investigator; anti-pneumocystis prophylaxis is encouraged.***
3) Pregnancy or breastfeeding.
4) Intentional breaking of the blind in Study GS-US-312-0116 by the investigator or the study subject.
5) Concurrent participation in another therapeutic clinical trial.
6) Prior or ongoing clinically significant illness, medical condition, surgical history, physical finding, electrocardiogram (ECG) finding, or laboratory abnormality that, in the investigator's opinion, could adversely affect the safety of the subject or impair the assessment of study results.

4.3. Enrollment Criteria Rationale

The eligibility criteria are designed to limit enrollment to subjects who participated in the primary clinical trial (Study GS-US-312-0116), are compliant, have been generally able to tolerate study therapy and study procedures, and have experienced definitive CLL progression while receiving study treatment (rituximab and/or GS-1101/placebo) in the primary study.

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

To ensure that subjects are not so acutely ill from life-threatening comorbidities that they require hospitalization and stabilization, subjects with Karnofsky performance scores <40 (ie, those who are bed-bound or hospitalized) will not be enrolled. Baseline laboratory evaluations are designed to limit participation to subjects who have not developed serious organ compromise that would pose a safety risk or confound the interpretation of adverse

effects. Pregnancy testing and restrictions on eligibility relating to reproduction, pregnancy, and nursing are important because GS-1101 is a new chemical entity and it is unknown if it may have adverse effects on conception, on fetal development, or on the health of a breast-feeding child. To minimize missing data and premature discontinuations, subjects should have sufficient psychological and social resources to comply with study procedures and restrictions. Consistent with GCP guidelines, subjects must provide informed consent before initiation of any study procedures.

5. TREATMENT OF SUBJECTS

5.1. Enrollment

5.1.1. Interactive Web Response System

An interactive web response system (IWRS) will be employed to manage the conduct of the trial. The IWRS will be used to maintain a central log documenting enrollment, to manage dose modifications, to assess current inventories of study drug, to initiate any necessary resupply of study drug, and to document discontinuation of study treatment.

5.1.2. Treatment Assignment

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

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

- Arm A: GS-1101 + rituximab (Study GS-US-312-0116)
  ⇒high-dose GS-1101 (300 mg BID) (Study GS-US-312-0117)

- Arm B: Placebo + rituximab (Study GS-US-312-0116)
  ⇒standard-dose GS-1101 (150 mg BID) (Study GS-US-312-0117)

The IWRS will assign blister card numbers and instructions for dispensing of blinded study drug (high-dose or standard-dose GS-1101). It is anticipated that subjects will usually begin study drug immediately at Visit 2 of the study.

5.1.3. Blinding

The identity of the treatments will be concealed by central blinding of study drug assignments. Blinding will be accomplished through use of a placebo that is well-matched to the active drug in appearance, packaging, labeling, and schedule of administration (see Section 5.2.1). During the study, subjects, caregivers, investigational site personnel, Gilead Sciences study team members, and all other study personnel will remain blinded to the identity of the treatment assignments; these assignments will be available only to the IWRS, the data monitoring committee (DMC) for the study, an independent bioanalytical group that is not part of the study team, and drug safety personnel who are not part of the study team. Unblinding during the study will only occur in the case of subject emergencies (see Section 5.5) or as requested by the DMC. Where required by local regulation, expedited reporting of serious adverse events to specific regulatory authorities will include information regarding the study drug treatment assignment (high-dose or standard-dose GS-1101); this will be done in such a way that subjects, investigational site personnel, institutional review board/independent ethics committees (IRB/IEC), and study team members remain blinded as to the treatment assignment for the subject described in the adverse event report.

The final unblinded analysis of the study will only be performed when the database is completed and locked. While bioanalytical assays to determine GS-1101 concentrations may be performed prior to unblinding, pharmacokinetic data that would allow identification of treatment assignments for individual subjects will not be available to the study team until after the blind is broken and the primary analysis has occurred. Except for emergency unblinding, individual subjects, caregivers, and site personnel will not be informed of the treatment assignments until the implications of revealing such data for the overall GS-1101 study program have been determined by the clinical project leader for the GS-1101 development program.

5.2. Investigational Study Drug (GS-1101/Placebo)

5.2.1. Description

Subjects allocated to Arm A of the study will be provided with 2 tablets of active GS-1101 for oral administration at each dose. Each tablet contains 150 mg or 100 mg of active GS-1101. The 150-mg tablets will be used for initial therapy; the 100-mg tablets are provided for use by those subjects who require a dose reduction (see Table 5-1).

Subjects allocated to Arm B of the study will be provided with 1 tablet of active GS-1101 and 1 tablet of placebo for oral administration at each dose. Each active tablet contains 150 mg or 100 mg of active GS-1101. The 150-mg tablets (and matching placebo) will be used for initial therapy; the 100-mg tablets (and matching placebo) are provided for use by those subjects who require a dose reduction.

The 150-mg tablets are pink, film-coated, and include the following inactive excipients: microcrystalline cellulose, hydroxypropyl cellulose, croscarmellose sodium, sodium starch glycolate, magnesium stearate, red iron oxide, polyethylene glycol, talc, polyvinyl alcohol (PVA), and titanium dioxide. The 100-mg tablets are orange, film-coated, and include the following inactive excipients: microcrystalline cellulose, hydroxypropyl cellulose, croscarmellose sodium, sodium starch glycolate, magnesium stearate, yellow iron oxide, polyethylene glycol, talc, PVA, and titanium dioxide.

The placebo tablets match the active GS-1101 formulations in appearance. The placebo tablets matching the 150-mg tablets are pink, film-coated, and include the following inactive ingredients: silicified microcrystalline cellulose, sodium starch glycolate, magnesium stearate, red iron oxide, polyethylene glycol, talc, PVA, and titanium dioxide. The placebo tablets matching the 100-mg tablets are orange, film-coated, and include the following inactive ingredients: silicified microcrystalline cellulose, sodium starch glycolate, magnesium stearate, yellow iron oxide, polyethylene glycol, talc, PVA and titanium dioxide.

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

5.2.2. Source

Both active GS-1101 and placebo will be supplied free of charge by Gilead Sciences.

5.2.3. Packaging and Labeling

Study drug (GS-1101 or GS-1101/placebo) will be provided in blister cards. The blister cards are made of polyvinyl chloride/polychlorotrifluoroethylene (PVC/PCTFE) film and have

aluminum foil lidding materials. Each blister card contains 120 tablets (4-week supply plus a modest overage) of one of the relevant dose strengths. The 100-mg or 150-mg and matching placebo tablets will be combined in order to obtain the daily doses to be used in this study. Thus, in Arm A, the 300-mg GS-1101 dose will be obtained by administering two 150-mg tablets and the 200-mg GS-1101 dose will be obtained by administering two 100-mg tablets. In Arm B, the 150-mg GS-1101 dose will be obtained by administering one 150-mg tablet and one placebo tablet and the 100-mg GS-1101 dose will be obtained by administering one 100-mg tablet and one placebo tablet.

Each blister card will have a unique number. Labeling for blister cards dispensed to subjects in Arm A will appear identical to blister cards dispensed to subjects in Arm B. All labels for study drugs to be distributed to centers in the United States, the EU, and other countries will meet all applicable requirements of the United States Food and Drug Administration (FDA), the EU Annex 13 of Current Good Manufacturing Practice (cGMP) (Manufacture of Investigational Medicinal Products, July 2003), and/or other local regulations as applicable.

5.2.4. Storage and Handling

Blister cards containing tablets of study drug (GS-1101 or GS-1101/placebo) should be stored at controlled room temperature (ie, ~25°C, with a range of 15 to 30°C). While the stability of study drug tablets stored at controlled room temperature has been confirmed, brief excursions to temperatures as low as 5°C or as high as 40°C (eg, during shipping) will not adversely affect the drug. Freezing should be avoided. Updated stability data will be provided to the sites, as appropriate.

5.2.5. Dispensing

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

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

5.2.6. Return

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

5.2.7. Accountability

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

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

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

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

5.2.8. Overdose Precautions

In Phase 1 studies, an MTD for GS-1101 was not reached when the drug was administered continuously at dose levels through 350 mg/dose BID (700 mg per day) [Coutre 2011, Kahl 2011]. However, in this protocol, an overdose is defined as administration of more than the prescribed daily dose (ie, >600 mg in a single day). In a subject who experiences an overdose consideration should be given as to whether GS-1101 administration should be temporarily interrupted. If the overdose ingestion is recent and substantial, and if there are no medical contraindications, use of gastric lavage or induction of emesis may be considered. Observation for any symptomatic side effects should be instituted, and biochemical and hematological parameters should be followed closely (consistent with the protocol or more frequently, as needed). Appropriate supportive management to mitigate adverse effects should be initiated.

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

5.2.9. Inadvertent Exposure and Spill Precautions

Based on available data from nonclinical studies, GS-1101 does not appear to be acutely toxic, genotoxic, or irritative at levels that are likely to result from inadvertent exposure to the contents of broken tablets. However, personnel handling the drug should use reasonable precautions to avoid eye contact, skin contact, inhalation, or ingestion of the study drug product. For further information regarding inadvertent exposure and spill precautions, please consult the GS-1101 investigator brochure.

5.3. Study Drug Administration

5.3.1. Premedication

No specific premedications or supporting medications are required in conjunction with study drug administration, although institution of antibiotic prophylaxis for *Pneumocystis (carinii) jiroveci* should be considered in all subjects (see Section 5.6.2).

5.3.2. Administration Instructions

The prescribed dose of study drug (GS-1101/placebo) should be taken orally. At each dose administration, the tablet number corresponding to the appropriate dose of study drug is to be swallowed whole with 100 to 200 mL (~ 4 to 8 ounces) of water. In case of breakage of the tablets in the oral cavity, additional water should be taken as a rinse.

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

5.3.3. Dosing Schedule

Study drug should be taken on a BID schedule at approximately the same times each day. Ideally, doses should be taken at ~12-hour intervals (eg, at ~7 AM and at ~7 PM). While it is realized that variations in dosing schedule may occur in the outpatient setting, the prescribed regimen should be followed as closely as possible, especially in the clinic.

At specified clinic visits, the study drug will be administered in the clinic with dosing appropriately timed relative to blood sampling for GS-1101 pharmacokinetics. As detailed in Section 6.2, clinic staff should record GS-1101 administration information, including the exact clock time of each dose, for doses of study drug administered in the clinic or hospital. Thereafter, subjects will be given an adequate supply of tablets to take at home.

5.3.4. Dose Levels

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

Table 5-1. Study Drug Dose Levels

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

Abbreviation: BID=twice per day

5.3.5. Dose Schedule Interruptions and Vomited Doses

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

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

5.3.6. Safety Monitoring and Study Drug Interruption/Dose Modification

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

Based on Phase 1 clinical experience adverse events potentially attributable to GS-1101 in patients with CLL have included infrequent hepatic events (manifest primarily as asymptomatic and isolated elevations in serum ALT/AST), and instances of pneumonitis, gastrointestinal inflammation, or rash. Myelosuppression has not been an overt toxicity of GS-1101 in previous experience but provisions for intervention in subjects experiencing very protracted treatment-emergent neutropenia or thrombocytopenia are provided as a precaution. It is possible that GS-1101 is responsible for other adverse events for which a causal relationship has not yet been established.

If a subject experiences an adverse event that is suspected to be related to study drug and requires a dose modification during the course of study therapy, then study drug administration should be held, as necessary, until the adverse event resolves or stabilizes to an acceptable degree (generally to Grade ≤1). Thereafter, study drug may be reinstituted, but the dose should be reduced to Dose Level -1 (see Table 5-1). If the adverse event occurs again, one further attempt at reinitiation of therapy at Dose Level -1 may be attempted if the investigator feels that a second rechallenge is medically appropriate. If the subject cannot tolerate GS-1101 at Dose Level -1 after 2 rechallenges, then the subject should be discontinued from study drug therapy.

After the study drug dose is reduced, the dose need not be re-escalated, even if there is minimal or no toxicity with the reduced dose. However, if the subject tolerates the lower dose level of study drug for ≥4 weeks then the dose level may be increased to the starting dose level (see Table 5-1) at the discretion of the investigator. Such re-escalation may be particularly warranted if further evaluation reveals that the adverse event that led to the dose reduction was not study-drug-related. The starting dose level should not intentionally be exceeded in this study.

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

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

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

Hepatic Study-Drug-Related Event (Elevation in ALT, AST, or Bilirubin)				
CTCAE Grade	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
ALT/AST	**>ULN-3 x ULN**	**>3-5 x ULN**	**>5-20 ULN**	**>20 x ULN**
Bilirubin	**>ULN-1.5 x ULN**	**>1.5-3 x ULN**	**>3-10 x ULN**	**>10 x ULN**
GS-1101 Dosing Recommendation	Maintain dose level	Maintain dose level. Monitor ALT, AST, ALP, and bilirubin at least 1x per week until all abnormalities are ≤Grade 1	Withhold study drug and confirm abnormalities within 3 days. Monitor ALT, AST, ALP, and bilirubin at least 1x per week until all abnormalities are Grade ≤1. May resume drug at next lower dose level.	

Cutaneous Study-Drug-Related Event				
CTCAE Grade	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
GS-1101 Dosing Recommendation	Withhold study drug until toxicity is Grade 0. Resume study drug at current dose level. If rechallenge at same dose level results in recurrent rash, may resume study drug at next lower dose level.		Withhold study drug until toxicity is Grade 0. May resume study drug at next lower dose level.	

Hematological Study-Drug-Related Event				
CTCAE Grade	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Neutropenia (ANC x 10^9/µL)	**ANC <LLN-1.5**	**ANC <1.5-1.0**	**ANC <1.0-0.5**	**ANC <0.5**
Thrombocytopenia (platelets x 10^9/µL)	**Platelets <LLN-75**	**Platelets <75-50**	**Platelets<50-25**	**Platelets<25**
GS-1101 Dosing Recommendation	Maintain dose level	Maintain dose level	Maintain dose level	For neutropenia of Grade 4 for ≥14 days, consider G-CSF support or may withhold study drug until Grade ≤3. May resume study drug at next lower dose. For Grade 4 thrombocytopenia with bruising or bleeding, withhold study drug until Grade ≤3. May resume study drug at next lower dose level.

Other Study-Drug-Related Event				
CTCAE Grade	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
GS-1101 Dosing Recommendation	Maintain dose level	Maintain dose level	Withhold study drug until toxicity is Grade ≤1. May resume study drug at next lower dose level unless subject has developed a condition requiring discontinuation of therapy (see Section 5.8).	

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

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

5.4.1. Dermatological Events

GS-1101 administration has occasionally been associated with the occurrence of a maculopapular rash affecting the trunk and extremities [Gilead Sciences 2011]. Based on skin biopsy data in several subjects, the findings have been consistent with a delayed-type hypersensitivity reaction. Rechallenge with GS-1101 has resulted in recurrence of rash in some but not all subjects.

In subjects who develop a rash while on study drug, causes related to concomitant medications, environmental exposures, or infection should be considered and eliminated. Depending upon the severity of the initial dermatological event, rechallenge with study drug therapy at the same or a lower dose level (see Table 5-2) should be considered if continued drug administration offers the potential for clinical benefit.

5.4.2. Gastrointestinal Events

Inflammation of the tongue has been noted in rats undergoing repeated gavage administration of GS-1101; this inflammation may have represented a drug-related exacerbation of gavage-mediated irritation. Mild congestion or hemorrhage in the large intestine has been seen in dogs receiving high doses of GS-1101. In patients, isolated cases of gastrointestinal inflammation (eg, stomatitis, colitis, cecitis) have been noted. Cholangitis manifest as hyperbilirubinemia out of proportion to serum transaminase elevations has been observed. While disease-related factors, neutropenia, toxicity from prior therapies, effects of ongoing supportive care, or pre-existing cholelithiasis may have initiated such events, it is possible that GS-1101 played a contributory role due to its immunomodulatory effects [Gilead Sciences 2011].

For study subjects who develop severe abdominal pain, particularly if early during therapy, the possibility of a bowel obstruction or perforation should be considered. Appropriate clinical and radiographic examination should be performed and supportive care and surgical intervention should be considered. Upon recovery, study therapy may be continued if appropriate for the clinical situation.

For subjects who develop persistent diarrhea, causes related to concomitant medications or gastrointestinal infection should be considered and eliminated. Depending upon the clinical circumstances, endoscopy and biopsy may be warranted. In such subjects, rechallenge with GS-1101 at a lower dose level has resulted in recurrence of symptoms in some but not all subjects and has not been associated with other severe adverse events. One patient who developed evidence of inflammatory bowel disease during GS-1101 therapy has been treated with sulfasalazine (Azulfidine®) and antidiarrheals (eg, loperamide) while continuing on GS-1101.

Thus, depending upon the type and severity of the initial gastrointestinal event, rechallenge with study drug at a reduced dose level and with and appropriate support care may be warranted if continued drug administration offers the potential for clinical benefit.

5.4.3. Hepatic Events

Dogs receiving GS-1101 for 28 days were observed to have dose-related hepatic inflammation and cellular necrosis, primarily affecting sinusoids in the centrilobular to midzonal regions of the liver [Gilead Sciences 2011]. The changes were associated with elevations in serum ALT/AST concentrations. In dogs, serum transaminase elevations typically reversed despite continued administration of GS-1101. In some patients with lymphoid malignancies, reversible serum ALT/AST elevations have been observed [Coutre 2011, Kahl 2011]. In these patients, onset has typically occurred within 2 to 8 weeks of starting GS-1101 therapy. Patients with NHL have been affected more commonly than those with CLL, suggesting that disease-related factors may alter the sensitivity to GS-1101-mediated hepatic effects. While conclusive evidence for a dose-response relationship does not exist, higher doses or exposures of GS-1101 may be associated with a greater risk of adverse hepatic events.

Among patients with Grade 1-2 ALT/AST abnormalities, continued dosing has been possible; transaminase values commonly resolve despite continued GS-1101 treatment. For those with Grade 3-4 ALT/AST elevations, drug interruption has resulted in resolution over 2 to 6 weeks. Successful rechallenge at lower dose levels of GS-1101 has been achieved in the majority of patients. Thus, in subjects with uncomplicated hepatic events, the instructions in Table 5-2 should be followed in an attempt to maximize the potential that subjects who appear to be benefiting can continue with study drug treatment.

In selected subjects who experience more complicated hepatic adverse events, further work-up may be warranted, as requested by the Gilead Sciences medical monitor. Such an evaluation may be particularly warranted in subjects who first experience a serum ALT/AST elevation ≥12 weeks from the start of study drug therapy, who have an elevation in serum bilirubin concentration or coagulation parameters, or who have other characteristics that suggest an atypical change in transaminase values. Further workup may include: obtaining a history of recent symptoms/illnesses and of relevant past history (eg, history of hepatitis or of hepatitis A or hepatitis B vaccination); obtaining information regarding concomitant drug use (prescription and nonprescription medications, dietary supplements, alcohol, illicit drugs, special diets); questioning the subject regarding potential exposure to environmental toxins; ruling out viral hepatitis A, B, C, D (if hepatitis B is positive), and E, Epstein-Barr virus, cytomegalovirus, autoimmune hepatitis, alcoholic hepatitis, nonalcoholic steatohepatitis, hypoxic/ischemic hepatopathy, and biliary tract disease; obtaining additional tests to evaluate liver function (eg, prothrombin time [PT], activated partial thromboplastin time [aPTT], international normalized ratio [INR], albumin); and considering gastroenterology or hepatology consultation [FDA 2009].

Of note, HBV reactivation can occur in patients treated with rituximab with a median time to diagnosis of hepatitis among patients with hematologic malignancies of 4 months after the initiation of rituximab but such events can occur months after completion of rituximab therapy. The risk is very low among patients with negative anti-HBc serology [Matsue 2010]. Because subjects with serum anti-HBc antibodies are excluded from the primary study (Study GS-US-312-0116), this complication is not anticipated. However, among subjects with evidence of Grade ≥3 serum ALT/AST abnormalities, evaluation for HBV reactivation (manifest as positivity for serum HBsAg) should be performed as a precautionary measure.

In a subject with active HBV, anti-HBV antiviral agents should be initiated. At the discretion of the investigators, study drug may be continued if HBV infection can be adequately controlled, particularly if the subject is experiencing clinical benefit from study therapy and there are few other options for treating the subject's CLL.

5.4.4. Hematological and Immunological Events

In the Phase 1 experience with GS-1101 in CLL, patients with Grade≥3 neutropenia, anemia, and and/or thrombocytopenia were enrolled to clinical trials. Decreased levels of neutrophil counts, hemoglobin, or platelet counts during therapy were largely due to minor fluctuations in these parameters among patients with pre-existing hematological abnormalities due to disease or prior therapy. Thus, GS-1101 did not appear to induce overt myelosuppression. Obvious patterns of drug-mediated reductions in circulating CD4+ lymphocyte counts or suppression of serum IgG levels were also not observed.

Given that patients with CLL commonly have Grade ≥3 hematological abnormalities due to underlying disease or prior therapy and that GS-1101 is not associated with substantial myelotoxicity or off-target immunosuppression, alterations in study drug dose level for such events should only focus on subjects with protracted or symptomatic neutropenia or thrombocytopenia, unresponsive to G-CSF supportive care. No modification of GS-1101 for changes in circulating CD4+ counts or Ig levels is planned.

5.4.5. Infectious Events

Patients with CLL receiving GS-1101 have developed serious bacterial, fungal, and viral infections during therapy [Gilead Sciences 2011]. Similarly, serious bacterial, fungal, and new or reactivated viral infections have also occurred during and for ~1 year following rituximab-based therapy [Gea-Banacloche 2010]. New or reactivated viral infections in patients receiving rituximab have included cytomegalovirus, herpes simplex virus, parvovirus B19, varicella zoster virus, West Nile virus, HBV (see Section 5.4.3) and HCV. Because patients with lymphoid malignancies (particularly those with CLL) are susceptible to infection due to the underlying disease, neutropenia, and the effects of prior therapy, the specific causal role of GS-1101 or rituximab in any of these types of events is unclear.

Patients with previously treated CLL have developed *Pneumocystis (carinii) jiroveci* pneumonia while receiving GS-1101. While GS-1101 has not specifically been implicated in such cases, patients with lymphoid malignancies (particularly those with CLL) may be susceptible to pneumocystis infections due to the underlying disease and the effects of prior therapy. Pre-existing risk factors of specific concern may include previous pneumocystis pneumonia, underlying disease (eg, CLL), prior therapy (eg, alemtuzumab, progenitor cell transplantation), or immunocompromised status (low CD4+ lymphocyte counts, HIV infection) [Green 2007].

Unless there is a contra-indication in a specific study subject, consideration should be given to initiation of antibiotic prophylaxis against pneumocystis infection (eg, with trimethoprim-sulfamethoxazole, dapsone, aerosolized pentamidine, or atovaquone) beginning prior to study drug administration. Such support may also offer the benefit of reducing the risk for other bacterial infections [Green 2007]. Local practices or guidelines may be followed.

For subjects who develop an infection, appropriate medical therapy (with antibiotics, antifungals, or antiviral) or other interventions should be instituted. Whenever appropriate, subjects should continue with study drug during treatment for the infection.

5.4.6. Progressive Multifocal Leukoencephalopathy

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

The diagnosis of PML should be considered in any subject presenting with new-onset neurologic manifestations. Evaluation of PML may include consultation with a neurologist, brain MRI, and lumbar puncture. In subjects diagnosed with PML, study drug should also be permanently discontinued.

5.4.7. Pulmonary Events

Documented bacterial, fungal, viral, and pneumocystis pneumonias have been observed in patients receiving GS-1101, primarily in patients with CLL. Some patients receiving GS-1101 alone or in combination have developed evidence of pneumonitis without documented lung infection. The specific role of GS-1101 in these events is unclear; nonclinical evaluations of pulmonary function and pathology do not indicate a direct toxic effect of GS-1101 on the lungs [Gilead Sciences 2011] and disease-related factors or toxicity from prior or concomitant therapies may have contributed to these clinical events. Rituximab-related noninfectious pneumonitis has been described [Subramanian 2010] with an incidence of ~4.3% [Salmasi 2010]. In patients developing rituximab-associated pneumonitis, the mean time from the first rituximab infusion to the onset of respiratory symptoms was 3 months, with a peak incidence after administration of a mean cumulative dosage of 1600 mg/m^2 [Lioté 2010].

Given the potential for infectious or drug-related adverse events, clinicians should be particularly observant for evidence of respiratory events in subjects participating in this trial. Subjects should be evaluated who describe pulmonary symptoms (eg, dyspnea on exertion, cough, shortness of breath); manifest a decline from baseline of ≥5% in oxygen saturation, or demonstrate evidence of pulmonary inflammation (eg, focal or diffuse interstitial pattern or ground-glass opacities on chest CT). Potential bacterial, fungal, or viral etiologies should be assessed. *Pneumocystis (carinii) jiroveci* should be considered, especially if the subject is not receiving pneumocystis prophylaxis. Depending upon the changes observed and the response to antibiotic intervention, recommended diagnostic work-up may include blood and sputum cultures; polymerase chain reaction or antigen testing for pneumocystis and respiratory viruses (eg, CMV, influenza virus, respiratory syncytial virus, parainfluenza virus, rhinovirus); chest X-ray, CT or other imaging methods; pulmonary function testing and diffusing capacity of the lung for carbon monoxide (DLCO); bronchoscopic lavage and/or biopsy; or open-lung biopsy. Noninfectious etiologies such as pulmonary edema or thromboembolism should also be considered.

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

For subjects with a symptomatic pneumonitis in the absence of infection (eg, onset of cough without fever and lack of response to anti-infective measures), study drug should be interrupted and therapy with corticosteroids should be instituted [Lioté 2010]. Resumption of study drug at Dose Level -1 should only be considered if the subject is experiencing evidence of substantial clinical benefit from therapy and other options for treating the subject's CLL are very limited; reoccurrence of drug-related pneumonitis upon rechallenge should result in permanent discontinuation of study treatment.

5.4.8. Tumor Lysis Syndrome

Patients with tumor lysis syndrome may experience hyperkalemia, hypocalcemia, hyperuricemia, hyperphosphatemia, cardiac dysrhythmias, and acute renal failure.

Tumor lysis syndrome has not been observed with GS-1101 monotherapy. However, if tumor lysis were to occur in a subject participating in this study, the subject should receive rapid reversal of hyperkalemia, intravenous hydration, antihyperuricemic agents, and appropriate cardiac and renal support, including dialysis as indicated. Upon recovery to baseline functioning, such subjects should continue study therapy to maintain tumor control.

5.4.9. Pregnancy, Lactation, and Reproduction

GS-1101 was not overtly teratogenic when administered to pregnant female rats in a dose-range-finding study [Gilead Sciences 2011]. However, definitive reproductive toxicology studies in animals have not yet been performed and the specific effects of GS-1101 on human embryogenesis or fetal development are unknown. Whether GS-1101 is excreted in human breast milk is unknown. General toxicology studies in rats and dogs indicated dose-dependent reductions in testicular weights, with persistent minimal to mild degeneration of the seminiferous tubules and decreased spermatozoa in rats and hypospermatogenesis in dogs. The implications of these testicular changes for animal or human fertility are unknown.

Given the preliminary nature of data regarding the risks to a fetus or infant as a result of exposure to GS-1101, women of reproductive potential entering this study must have a negative serum pregnancy test at baseline and must not be breastfeeding. Males and females of childbearing potential should abstain from sexual intercourse or use an effective form of contraception (see Section 5.6.4). If a female study participant becomes pregnant or decides to breastfeed during the course of the study, all study therapy must be discontinued. Study candidates will be informed of the testicular findings through the informed consent process.

5.5. Emergency Unblinding

Every attempt should be made to preserve the integrity of study drug dose assignment blinding. Unblinding in individual subjects who experience adverse events is rarely required to provide effective intervention and support. For subjects having adverse events or laboratory abnormalities that require drug cessation or medical intervention, the investigational staff should strive to provide necessary support to the subject without

breaking the blind. In the exceptional circumstance that knowledge of the study drug dose assignment appears essential for providing appropriate medical management, the investigator should contact the Gilead Sciences medical monitor to discuss the rationale for breaking the blind and the adverse consequences of the unblinding for the subject's continued participation in the study. If the investigator still believes that unblinding is warranted, the investigator will be able to access the allocation system in order to obtain the treatment assignment for that subject. No randomization lists or other unblinding information will be provided to the site. After breaking the blind, the investigational site staff should record details regarding the reasons for breaking the blind and any adverse events leading to the breaking of the blind in the source documents and in the appropriate eCRF.

If the site breaks the blind, the appropriateness of continued study drug therapy should be discussed with the Gilead Sciences medical monitor. Subjects who intentionally subvert the blind (eg, through chemical analysis of the drug) should be discontinued from study drug therapy.

5.6. Concomitant and Supportive Therapy

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

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

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

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

5.6.1. Anticancer or Experimental Therapies Other than Investigational Treatments

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 therapeutic clinical study.

5.6.2. Antibiotics

Except in a subject who has a contra-indication, investigators should consider initiation of antibiotic prophylaxis against pneumocystis infection (eg, with trimethoprim-sulfamethoxazole, dapsone, aerosolized pentamidine, or atovaquone) beginning prior to study

drug administration. Such support may also offer the benefit of reducing the risk for other bacterial infections [Green 2007]. Investigator discretion and local practices or guidelines may be followed.

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

5.6.3. Antiemetics and Antidiarrheals

Drug-related nausea and/or vomiting have not been commonly observed with GS-1101 in prior studies. However, subjects who experience nausea or vomiting while on study therapy may receive antiemetics based on the judgment of the treating physician and local institutional practices. At the occurrence of persistent nausea or vomiting of severity Grade ≥1, it is suggested that the subject receive an oral or transdermal serotonin antagonist (eg, dolasetron, granisetron, ondansetron, tropisetron, palonosetron). The neurokinin receptor antagonist, aprepitant, may be considered but is a mild inhibitor of CYP3A4 and so may modestly increase GS-1101 plasma exposures. Other classes of antiemetic medications that may be employed include dopamine antagonists or benzodiazepines. If possible, systemic corticosteroids should be avoided (see Section 5.6.5).

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

5.6.4. Contraception

In the context of this protocol, a female subject is considered to be of childbearing potential unless she has had a hysterectomy, a bilateral tubal ligation, or a bilateral oophorectomy; has medically documented ovarian failure (with serum estradiol and FSH levels within the institutional postmenopausal range and a negative serum or urine βHCG); or is menopausal (age ≥55 years with amenorrhea for ≥6 months).

Sexually active females of childbearing potential must accept continuous heterosexual abstinence as a lifestyle choice or agree to use a protocol-recommended method of contraception during heterosexual intercourse throughout the study treatment period and for 30 days following discontinuation of the study drug. The investigator should counsel subjects on the most effective methods for avoiding pregnancy during the trial. Protocol-recommended contraceptive methods are described in Table 5-3.

Table 5-3. Protocol-Recommended Contraceptive Methods

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

Abbreviation: IUD=intrauterine device

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

Sexually active male subjects who can father a child must accept continuous heterosexual abstinence as a lifestyle choice; limit intercourse to female partners who are surgically sterile, post-menopausal, or using effective contraception (as noted in Table 5-3); or agree to use a protocol-recommended method of contraception during heterosexual intercourse throughout the study treatment period and for 90 days following discontinuation of the study drug (as noted in Table 5-3).

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

5.6.5. Corticosteroids

Subjects may receive topical, inhaled, or enteric corticosteroids while on study. The use of systemic corticosteroids is discouraged because their potential antineoplastic activity in patients with CLL may confound interpretation of antitumor effects mediated by study drug therapy. 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.

5.6.6. Granulocyte Colony-Stimulating Factors and Erythropoietin

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

G-CSF (filgrastim, PEG-filgrastim, lenograstim) may be administered in response to Grade 4 neutropenia or neutropenic complications; use should be particularly considered if providing hematopoietic support might help to maintain study drug treatment (see Table 5-2).

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

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

5.6.7. Drugs that Inhibit CYP3A4-Dependent Metabolism

GS-1101 is metabolized in part by CYP3A4. However, a clinical drug-drug interaction study indicated that administration of a potent CYP3A4 inhibitor together with GS-1101 induced only a modest increase in GS-1101 plasma exposure (see Section 1.3.5.1). Thus, co-administration of CYP3A4 inhibitors and GS-1101 is not contraindicated and does not require special monitoring.

5.6.8. Immunization

Because of its actions to inhibit PI3Kδ-dependent B-cell function, high doses of GS-1101 can impair primary or secondary responses to immunization in animals [Gilead Sciences 2011].

The specific clinical relevance of these findings with GS-1101 is unknown. However, for subjects who are at substantial risk of an infection (eg, influenza) that might be prevented by immunization, consideration should be given to providing the vaccine prior to initiation of study therapy.

Of note, the safety of immunization with live viral vaccines following GS-1101 therapy has not been studied and vaccination with live virus vaccines during study treatment is not recommended.

5.6.9. Surgery

There are no known effects of GS-1101 on coagulation or wound healing. Pending receipt of additional information, study drug may be continued in the peri-procedural period in subjects who require surgery or invasive procedures.

5.6.10. Diet

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

5.7. Duration of Study Therapy

Subjects may continue receiving study drug until the earliest of the inability to tolerate a second rechallenge with protocol-described, dose-modified GS-1101 Dose Level –1 (see Section 5.3.6) or the occurrence of any events requiring treatment discontinuation as defined in Section 5.8.

5.8. Discontinuation of Study Treatment

All study participants may receive study drug indefinitely; however:

- Any subject has the right to withdraw from the study at any time.
- Any subject who has objective evidence of definitive CLL progression while receiving study treatment should be withdrawn from the study treatment.
- 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. Such subjects should be withdrawn from study treatment if continuing would place them at risk.

- Any subject who becomes pregnant or begins breastfeeding should be removed from study treatment.
- Any subject who becomes significantly noncompliant with study drug administration, study procedures, or study requirements should be withdrawn from study treatment in circumstances that increase risk or substantially compromise the interpretation of study results.
- Any subject for whom the blind is intentionally broken by the subject or the study site should discontinue study treatment.
- The investigator, in consultation with the Gilead Sciences medical monitor, may withdraw any subject from the study treatment, 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 treatment to commercial drug supply when GS-1101 becomes commercially available in the country where the subject is living.

The date the subject is withdrawn from study treatment or from the study (including long-term follow-up) and the reason for discontinuation will be recorded with the IWRS and also should be described on the appropriate eCRF.

When a subject is withdrawn from study treatment or is permanently removed from study treatment (regardless of the reason), all of the evaluations required at the end-of-treatment visit should be performed and any additional evaluations should be completed that may be necessary to ensure that the subject is free of untoward effects. The subject should be encouraged to seek appropriate follow-up for any continuing health problems.

Subjects who discontinue study treatment may still continue on study follow-up. Thus, all subjects receiving ≥1 dose of study drug will be followed during the immediate post-treatment and during the long-term follow-up periods unless the subject withdraws consent for such follow-up to be conducted.

5.9. Study Treatment Rationale

Subjects will be assigned to treatment (Arm A or Arm B) in this study based on their randomization in the primary study. The 1:1 randomization in the primary trial (GS-US-312-0116) ensures that sufficient Arm B subjects will cross over from rituximab alone to single-agent GS-1101 at the 150-mg/dose BID starting dose level in this extension trial (GS-US-312-0117) to allow an adequate evaluation of efficacy and safety in this trial. The randomization and allocation processes will be established and performed through an IWRS; the intent is to maximize the integrity and security of the subject disposition and to ensure appropriate access and convenience-of-use by the investigational sites.

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

Selection of the GS-1101 treatment regimen (including starting dose level, dose-modifications and supportive care, schedule, duration, and conditions of administration) for this study program has been based primarily on safety, exposure, and activity profiles from previous Phase 1 clinical studies involving healthy volunteers, patients with allergic rhinitis, and patients with refractory/relapsed lymphoid malignancies [Webb 2010, Coutre 2011, Kahl 2011]. The following information was considered in selecting the study drug dosing regimen for the primary study and this companion extension study:

- GS-1101 was symptomatically well tolerated in patients with lymphoid malignancies receiving dose levels of 50 mg/dose BID through 350 mg/dose BID (the highest dose level tested). No specific MTD was apparent over the dose range tested. However, monitorable, reversible transaminase elevations were observed in some patients and may have been more frequent at higher dose levels (~10% rate among patients with CLL receiving starting doses of ≥150 mg/dose). Thus, while doses through 350 mg/dose BID are tolerable, the starting dose of 150 mg/dose BID appears to appropriately balance safety with efficacy in GS-1101-naïve subjects. The starting dose of 300 mg/dose BID in this study also appears appropriate for evaluation; it is lower than the dose level of 350 mg/dose BID that has been tolerable in prior studies and is likely to be suitable in subjects who have already been tolerating GS-1101 therapy at ≥100 mg/dose BID.
- Upon disease progression, permitting escalation from 150 mg/dose BID to 300 mg/dose BID among subjects allocated to Arm A offers a systematic evaluation of higher doses in subjects who are tolerating GS-1101 treatment and might benefit from increased PI3Kδ inhibition. The pharmacological basis for considering such an intervention is based on the concept that some individuals might have lower-than-expected plasma exposures or dose-dependent resistance to the compound at 150 mg/dose BID and might benefit from a higher dose. The intent is to determine if the higher dose can reestablish disease control or whether absolute resistance to PI3Kδ inhibition has been acquired. The safety data obtained in these subjects would add to the overall safety database.
- In an allergic rhinitis study, GS-1101 induced statistically significant improvements in clinical and pharmacodynamic endpoints when administered at 100 mg/dose BID over 7 days. These data support the pharmacological relevance of GS-1101-mediated PI3Kδ inhibition when administered at the dose-levels to be used in this study.
- A positive correlation was noted between GS-1101 dose and measures of tumor control and chemokine normalization in patients with B-cell malignancies. The majority of patients appear to have tumor responses and protracted PFS when receiving starting doses of ≥100 mg/dose BID. Thus, treatment with a GS-1101 at a starting dose of 150 mg/dose BID appears to offer most patients the potential to benefit from therapy and the dose level of 300 mg/dose BID may provide additional benefit in patients with disease resistance as systematically evaluated in this trial.

- Based on evaluations of GS-1101 steady-state plasma C_{max}, AUC, and C_{trough} values over a range of doses, administration of starting doses of GS-1101 of ≥150 mg/dose BID appears appropriate to ensure adequate exposure in the majority of patients.
- In Phase 1 studies, the mean plasma $t_{1/2}$ of GS-1101 was ~6.5 to 9.8 hours across all dose levels and there was no substantive plasma accumulation over 7 or 28 days. The collective data support a study drug administration schedule of BID administration to maintain GS-1101 plasma C_{trough} values without inducing excessively high plasma C_{max} values.
- The changes in exposure observed when administering GS-1101 after a high-fat, high-calorie meal are modest (~40% increase in mean AUC with no change in mean C_{max}). Thus, GS-1101 can be administered with or without food.
- Clinical evidence suggests that potent inhibitors of CYP3A4 may induce a modest increase in GS-1101 plasma concentrations in humans. However, given the fact that GS-1101 is well tolerated and appears to be a relatively weak substrate for CYP3A4, administration of drugs that inhibit CYP3A4 together with GS-1101 does not appear to be contraindicated and special precautionary measures do not appear necessary.
- The GS-1101 dose modification provisions described in the protocol are designed to balance a primary concern for subject safety with the potential for observing pharmacological and antitumor activity in circumstances under which a subject experiencing an adverse event may still be able to continue on therapy at a lower GS-1101 dose level. The enhanced monitoring to be performed and the actions to be taken in response to toxicity are based on experience with interruption, dose-modification, rechallenge, and re-escalation already piloted in GS-1101 Phase 1 trials. In addition, GS-1101 antitumor activity has been observed in the Phase 1 studies across all dose levels tested, including doses in the range of the modified dose levels planned for this protocol. Thus, use of the lower dose level to accommodate individual subject tolerability in this protocol is justified because subjects receiving such a GS-1101 dose level still have the potential for benefit.
- In both the primary and extension studies, study treatment will be continued for each subject until the occurrence of disease progression. Such a strategy is considered appropriate under the assumption that persistent interference with PI3Kδ signaling is likely to extend treatment effect. In addition, this design permits collection of further single-agent safety information and thus is likely to enhance understanding of the overall safety profile of GS-1101.
- Appropriate disincentives for unblinding of study drug are included in the trial (see Section 5.5). Investigational personnel will not have access to information at the site that would permit unblinding and must obtain the individual subject treatment assignment code only through the treatment allocation system. Clinic staff will be made aware that such unblinding may preclude a subject from continuing with study drug administration. Unblinding will also involve discussion between the investigator and the Gilead Sciences medical monitor; this provision is not intended to prevent an investigator from proceeding with unblinding, but to ensure that appropriate consultation is obtained, that

the investigator is aware of the consequences of the unblinding for the subject's continued participation in the study, and that appropriate permission is granted to the treatment allocation system to release the treatment assignment only for that subject.

6. STUDY PROCEDURES

6.1. Enrollment and Study Management Procedures

6.1.1. Subject Recruitment

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

The study sponsor will post a description of the study on the ClinicalTrials.gov website. Any promotional information generated by the sponsor or investigational sites will be submitted for IRB/IEC review.

6.1.2. Subject Compensation for Participation

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

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

6.1.3. Screening

The investigator must inform each prospective subject of the nature of the study, explain the potential risks, and obtain written informed consent from the subject and/or a legal guardian prior to performing any study-related screening procedures. At the time the study candidate signs the informed consent, a site representative should access the IWRS to indicate that a study candidate is being screened. The user will need to supply the IWRS with required information identifying the site and the subject number as already assigned in Study GS-US-312-0116.

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

6.2. Explanation of Study Visits

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

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

At visits involving GS-1101 administration and pharmacokinetic sampling in the clinic, care should be taken to perform procedures with the appropriate timing relative to GS-1101 administration. The actual sample collection times of pharmacokinetic blood specimens should be recorded. If a heparinized venous catheter is placed for sample collection in order to avoid repeated needle sticks, at least 2 mL of blood should be removed and discarded prior to each sample collection in order to avoid heparin contamination of the sample.

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

In addition to clinical assessments of tumor status, CT or MRI imaging of the neck, chest, abdomen, and pelvis will be performed as a component of tumor assessments during the study based on the rationale provided in Section 3.2.1; the same method of assessment (CT or MRI) and the same technique should be used to characterize each identified and reported lesion at baseline and while on study.

6.2.1. Visit 1 and Screening Period (Clinic Visit)

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

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

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

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

Assessment or Procedure	Explanation[a]
Informed consent	To be obtained before any screening procedures are initiated
IWRS access	Access IWRS to document that subject is in screening and provide the subject number from Study GS-US-312-0116
CIRS assessment	Recording of current comorbid conditions using the CIRS scoring instrument (see Appendix 6)
Concomitant medications	Recording of ongoing concomitant medication use
Performance status	Using Karnofsky performance status criteria (see Appendix 3)
Oxygen saturation	To be assessed by pulse oximetry while subject is breathing room air
Physical examination	Including height, weight, evidence of palpable lymphadenopathy, hepatomegaly, and/or splenomegaly
Serum β-HCG	Women of childbearing potential only
CLL peripheral blood evaluation	Including FISH for chromosome 11q deletion, 13q deletion, 17p deletion and 12 trisomy; DNA mutational analysis for p53, IgHV (including IgHV3-21), and other genes of interest in CLL (eg, Notch); flow cytometry for CD5, CD10, CD11c, CD19, CD20, CD23, CD38, CD45, kappa and lambda light chains, and ZAP-70; cytology for karyotyping; bone marrow aspirate may be used if peripheral blood lymphocyte count is too low
CLL serology	Serum β2 microglobulin
PPD	[redacted]
Hematology	Including hematocrit, hemoglobin, erythrocyte count; absolute counts of leukocytes, neutrophils, lymphocytes, monocytes, eosinophils, basophils, platelet count
Serum chemistry	Including sodium, potassium, chloride, glucose, urea, creatinine, calcium, phosphorus, total protein, albumin, ALT, AST, ALP, GGT, total bilirubin, LDH, uric acid, cholesterol, triglycerides
Circulating cells	Including cells for analysis of PI3K/AKT/mTOR pathway activation and quantitation of absolute number of CD4+, CD8+, CD16/CD56+, CD19+, and CD+20 cells by flow cytometry
Biomarkers	Collection of plasma and serum for evaluation of circulating chemokines and cytokines
Serum Igs	Including quantitative levels of IgA, IgE, IgG, and IgM
Radiology assessment	CT or MRI imaging of neck, chest, abdomen, and pelvis, to be scheduled prior to initiation of study treatment at Visit 2; the same method of assessment (CT, MRI) and the same technique should be used to characterize each identified and reported lesion at baseline and while on study
Bone marrow biopsy and aspirate	To be performed at investigator discretion to determine extent of CLL involvement and bone marrow cellularity.

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

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

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

Subjects will be assessed to determine if they still meet eligibility criteria and can initiate study treatment. The procedures outlined in Table 6-2 will be performed at Visit 2 (Day 1).

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

Assessment or Procedure	Explanation
Pre-Dose Procedures and Assessments	
FACT-Leu	HRQL instrument (Appendix 2) to be administered before any other procedures are performed and before any study-related information is communicated to the subject
EQ-5D	Health utility instrument (Appendix 4) to be administered after FACT-Leu but before any other procedures are performed and before any study-related information is communicated to the subject
Adverse events	Recording of adverse events occurring since the initiation of the screening period
Concomitant medications	Recording of concomitant medication use since the initiation of the screening period
Performance status	Using Karnofsky performance status criteria (see Appendix 3)
Oxygen saturation	To be assessed by pulse oximetry while subject is breathing room air
Physical examination	Including weight, evidence of palpable lymphadenopathy, hepatomegaly, and/or splenomegaly
β-HCG	For women of child-bearing potential only; serum β-HCG or urine dipstick pregnancy test must be negative prior to initial study treatment
Hematology	Including hematocrit, hemoglobin, erythrocyte count; absolute counts of leukocytes, neutrophils, lymphocytes, monocytes, eosinophils, basophils, platelet count
Serum chemistry	Including sodium, potassium, chloride, glucose, urea, creatinine, calcium, phosphorus, total protein, albumin, ALT, AST, ALP, GGT, total bilirubin, LDH, uric acid, cholesterol, triglycerides
GS-1101 pharmacokinetics	Pre-dose collection of plasma sample for GS-1101 pharmacokinetics (with recording of the date and actual clock time of blood collection)
IWRS access	Access of IWRS to obtain study drug blister card number
Study Therapy Administration	
Study drug administration	First dose of study drug to be administered to the subject (with recording of the date and actual clock time of the study drug administration)
Post-Therapy Procedures and Assessments	
GS-1101 pharmacokinetics	Post-dose collection of plasma sample for GS-1101 pharmacokinetics at 1.5 hours after study drug administration (with recording of the date and actual clock time of blood collection)
Study drug dispensing	Dispensing of 4-week supply of study drug to the subject with instructions for self-administration at home
Instruction regarding study drug dosing at next full clinic visit	Instruction to the subject that the morning dose of study drug should not be taken on the day of Visit 3.

Abbreviations: β-HCG=beta human chorionic gonadotropin, ALP=alkaline phosphatase, ALT=alanine aminotransferase, AST=aspartate aminotransferase, EQ-5D=EuroQoL Five-Dimension, FACT-Leu=Functional Assessment of Cancer Therapy-Leukemia, HRQL=health-related quality of life, GGT=gamma-glutamyltransferase, IWRS=interactive web response system, LDH=lactate dehydrogenase, RNA=ribonucleic acid

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

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

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

Assessment or Procedure	Explanation
Pre-Dose Procedures and Assessments	
FACT-Leu	HRQL instrument (Appendix 2) to be administered before any other procedures are performed and before any study-related information is communicated to the subject
EQ-5D	Health utility instrument (Appendix 4) to be administered after FACT-Leu but before any other procedures are performed and before any study-related information is communicated to the subject
Adverse events	Recording of adverse events occurring since the initiation of the screening period
Concomitant medications	Recording of concomitant medication use since the initiation of the screening period
Performance status	Using Karnofsky performance status criteria (see Appendix 3)
Oxygen saturation	To be assessed by pulse oximetry while subject is breathing room air
Hematology	Including hematocrit, hemoglobin, erythrocyte count; absolute counts of leukocytes, neutrophils, lymphocytes, monocytes, eosinophils, basophils, platelet count
Serum chemistry	Including sodium, potassium, chloride, glucose, urea, creatinine, calcium, phosphorus, total protein, albumin, ALT, AST, ALP, GGT, total bilirubin, LDH, uric acid, cholesterol, triglycerides
Circulating cells	Including cells for analysis of PI3K/AKT/mTOR pathway activation and quantitation of absolute number of CD4+, CD8+, CD16/CD56+, CD19+, and CD+20 cells by flow cytometry
Biomarkers	Collection of plasma and serum for evaluation of circulating chemokines and cytokines
Serum Igs	Including quantitative levels of IgA, IgE, IgG, and IgM
GS-1101 pharmacokinetics	Recording of the date and actual clock time of the last prior subject self-administration of study drug (should be the prior evening dose)Pre-dose collection of plasma sample for GS-1101 pharmacokinetics (with recording of the date and actual clock time of the date and actual clock time of blood collection)
IWRS access	Access of IWRS to document subject visit
Study Therapy Administration	
Study drug administration	Study drug to be administered to the subject (with recording of the date and actual clock time of the study drug administration)
Post-Therapy Procedures and Assessments	
GS-1101 pharmacokinetics	Post-dose collection of plasma sample for GS-1101 pharmacokinetics at 1.5 hours after study drug administration (with recording of the date and actual clock time of blood collection)
Instruction regarding study drug dosing at next full clinic visit	Instruction to the subject that the morning dose of study drug should not be taken on the day of Visit 4.

Abbreviations: ALP=alkaline phosphatase, ALT=alanine aminotransferase, AST=aspartate aminotransferase, EQ-5D=EuroQoL Five-Dimension, FACT-Leu=Functional Assessment of Cancer Therapy-Leukemia, HRQL=health-related quality of life, GGT=gamma-glutamyltransferase, IWRS=interactive web response system, LDH=lactate dehydrogenase

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

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

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

Assessment or Procedure	Explanation
Pre-Therapy Procedures and Assessments	
FACT-Leu	HRQL instrument (Appendix 2) to be administered before any other procedures are performed and before any study-related information is communicated to the subject
EQ-5D	Health utility instrument (Appendix 4) to be administered after FACT-Leu but before any other procedures are performed and before any study-related information is communicated to the subject
Adverse events	Recording of adverse events occurring since Visit 3
Concomitant medications	Recording of concomitant medication used since Visit 3
Study drug return/accounting	Counting returned study drug. Recording of the date and actual clock time of the last prior subject self-administration of study drug (should be the prior evening dose)
Performance status	Using Karnofsky performance status criteria (see Appendix 3)
Oxygen saturation	To be assessed by pulse oximetry while subject is breathing room air
Physical examination	Including weight, evidence of palpable lymphadenopathy, hepatomegaly, and/or splenomegaly
Hematology	Including hematocrit, hemoglobin, erythrocyte count; absolute counts of leukocytes, neutrophils, lymphocytes, monocytes, eosinophils, basophils, platelet count
Serum chemistry	Including sodium, potassium, chloride, glucose, urea, creatinine, calcium, phosphorus, total protein, albumin, ALT, AST, ALP, GGT, total bilirubin, LDH, uric acid, cholesterol, triglycerides
Circulating cells	Including cells for analysis of PI3K/AKT/mTOR pathway activation and quantitation of absolute number of CD4+, CD8+, CD16/CD56+, CD19+, and CD+20 cells by flow cytometry
Biomarkers	Collection of plasma and serum for evaluation of circulating chemokines and cytokines
Serum Igs	Including quantitative levels of IgA, IgE, IgG, and IgM
GS-1101 pharmacokinetics	Pre-dose collection of plasma sample for GS-1101 pharmacokinetics (with recording of the date and actual clock time of the date and actual clock time of blood collection)
IWRS access	Access of IWRS to obtain study drug blister card number
Study Therapy Administration and Dispensing	
Study drug administration	Dose of study drug to be administered to the subject (with recording of the date and actual clock time of the study drug administration)
Post-Therapy Procedures and Assessments	
GS-1101 pharmacokinetics	Post-dose collection of plasma sample for GS-1101 pharmacokinetics at 1.5 hours after study drug administration (with recording of the date and actual clock time of blood collection)
Study drug dispensing	Dispensing of 4-week supply of study drug to the subject with instructions for self-administration at home
Instruction regarding dosing at next full clinic visit	Instruction to the subject that the morning dose of study drug should not be taken on the day of Visit 5.

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

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

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

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

Assessment or Procedure	Explanation
Pre-Dose Procedures and Assessments	
FACT-Leu	HRQL instrument (Appendix 2) to be administered before any other procedures are performed and before any study-related information is communicated to the subject
EQ-5D	Health utility instrument (Appendix 4) to be administered after FACT-Leu but before any other procedures are performed and before any study-related information is communicated to the subject
Adverse events	Recording of adverse events occurring since the initiation of the screening period
Concomitant medications	Recording of concomitant medication use since the initiation of the screening period
Performance status	Using Karnofsky performance status criteria (see Appendix 3)
Oxygen saturation	To be assessed by pulse oximetry while subject is breathing room air
Hematology	Including hematocrit, hemoglobin, erythrocyte count; absolute counts of leukocytes, neutrophils, lymphocytes, monocytes, eosinophils, basophils, platelet count
Serum chemistry	Including sodium, potassium, chloride, glucose, urea, creatinine, calcium, phosphorus, total protein, albumin, ALT, AST, ALP, GGT, total bilirubin, LDH, uric acid, cholesterol, triglycerides
IWRS access	Access of IWRS to document subject visit
Study Therapy Administration	
Study drug administration	Study drug to be administered to the subject (with recording of the date and actual clock time of the study drug administration)
Post-Therapy Procedures and Assessments	
Instruction regarding study drug dosing at next full clinic visit	Instruction to the subject that the morning dose of study drug should not be taken on the day of Visit 6.
Scheduling of Visit 6 radiology assessment	CT or MRI imaging of neck, chest, abdomen, and pelvis to be scheduled for Visit 6; the same method of assessment (CT, MRI) should be used as was used at baseline.

Abbreviations: ALP=alkaline phosphatase, ALT=alanine aminotransferase, AST=aspartate aminotransferase, EQ-5D=EuroQoL Five-Dimension, FACT-Leu=Functional Assessment of Cancer Therapy-Leukemia, HRQL=health-related quality of life, GGT=gamma-glutamyltransferase, IWRS=interactive web response system, LDH=lactate dehydrogenase

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

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

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

Assessment or Procedure	Explanation
Pre-Visit Tumor Assessment	
Radiology assessment	CT or MRI imaging of neck, chest, abdomen, and pelvis within 1 week prior to the visit; the same method of assessment (CT or MRI) should be used as was used at baseline and the assessment should be done even if study drug has been interrupted.
Pre-Therapy Procedures and Assessments	
FACT-Leu	HRQL instrument (Appendix 2) to be administered before any other procedures are performed and before any study-related information is communicated to the subject
EQ-5D	Health utility instrument (Appendix 4) to be administered after FACT-Leu but before any other procedures are performed and before any study-related information is communicated to the subject
Adverse events	Recording of adverse events occurring since Visit 5
Concomitant medications	Recording of concomitant medication used since Visit 5
Study drug return/accounting	Counting returned study drug. Recording of the date and actual clock time of the last prior subject self-administration of study drug (should be the prior evening dose)
Performance status	Using Karnofsky performance status criteria (see Appendix 3)
Oxygen saturation	To be assessed by pulse oximetry while subject is breathing room air
Physical examination	Including weight, evidence of palpable lymphadenopathy, hepatomegaly, and/or splenomegaly
Hematology	Including hematocrit, hemoglobin, erythrocyte count; absolute counts of leukocytes, neutrophils, lymphocytes, monocytes, eosinophils, basophils, platelet count
Serum chemistry	Including sodium, potassium, chloride, glucose, urea, creatinine, calcium, phosphorus, total protein, albumin, ALT, AST, ALP, GGT, total bilirubin, LDH, uric acid, cholesterol, triglycerides
Circulating cells	Including cells for analysis of PI3K/AKT/mTOR pathway activation and quantitation of absolute number of CD4+, CD8+, CD16/CD56+, CD5+, CD19+, and CD+20 cells by flow cytometry
Biomarkers	Collection of plasma and serum for evaluation of circulating chemokines and cytokines
Serum Igs	Including quantitative levels of IgA, IgE, IgG, and IgM
Bone marrow biopsy and aspirate	To be performed post-baseline to confirm response category in subjects with potential CR by radiological assessments. If the subject does not otherwise meet criteria for CR, it is not necessary to obtain a follow-up bone marrow biopsy/aspirate to establish CR.
GS-1101 pharmacokinetics	Pre-dose collection of plasma sample for GS-1101 pharmacokinetics (with recording of the date and actual clock time of the date and actual clock time of blood collection)
IWRS access	Access of IWRS to obtain study drug bottle number
Study Therapy Administration	
Study drug administration	Dose of study drug to be administered to the subject (with recording of the date and actual clock time of the study drug administration)
Post-Therapy Procedures and Assessments	
GS-1101 pharmacokinetics	Post-dose collection of plasma sample for GS-1101 pharmacokinetics at 1.5 hours after study drug administration (with recording of the date and actual clock time of blood collection)
Study drug dispensing	Dispensing of 4-week supply of study drug to the subject with instructions for self-administration at home
Instruction regarding dosing at next full clinic visit	Instruction to the subject that the morning dose of study drug should not be taken on the day of Visit 8.

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

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

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

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

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

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

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

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

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

Assessment or Procedure	Explanation
Pre-Therapy Procedures and Assessments	
FACT-Leu	HRQL instrument (Appendix 2) to be administered before any other procedures are performed and before any study-related information is communicated to the subject
EQ-5D	Health utility instrument (Appendix 4) to be administered after FACT-Leu but before any other procedures are performed and before any study-related information is communicated to the subject
Adverse events	Recording of adverse events occurring since Visit 6
Concomitant medications	Recording of concomitant medication used since Visit 6
Study drug return/accounting	Counting returned study drug. Recording of the date and actual clock time of the last prior subject self-administration of study drug (should be the prior evening dose)
Performance status	Using Karnofsky performance status criteria (see Appendix 3)
Oxygen saturation	To be assessed by pulse oximetry while subject is breathing room air
Physical examination	Including weight, evidence of palpable lymphadenopathy, hepatomegaly, and/or splenomegaly
Hematology	Including hematocrit, hemoglobin, erythrocyte count; absolute counts of leukocytes, neutrophils, lymphocytes, monocytes, eosinophils, basophils, platelet count
Serum chemistry	Including sodium, potassium, chloride, glucose, urea, creatinine, calcium, phosphorus, total protein, albumin, ALT, AST, ALP, GGT, total bilirubin, LDH, uric acid, cholesterol, triglycerides
Circulating cells	Including cells for analysis of PI3K/AKT/mTOR pathway activation and quantitation of absolute number of CD4+, CD8+, CD16/CD56+, CD19+, and CD+20 cells by flow cytometry
Biomarkers	Collection of plasma and serum for evaluation of circulating chemokines and cytokines
Serum Igs	Including quantitative levels of IgA, IgE, IgG, and IgM
GS-1101 pharmacokinetics	Pre-dose collection of plasma sample for GS-1101 pharmacokinetics (with recording of the date and actual clock time of the date and actual clock time of blood collection)
IWRS access	Access of IWRS to obtain study drug blister card number
Study Therapy Administration and Dispensing	
Study drug administration	Dose of study drug to be administered to the subject (with recording of the date and actual clock time of the study drug administration)
Post-Therapy Procedures and Assessments	
GS-1101 pharmacokinetics	Post-dose collection of plasma sample for GS-1101 pharmacokinetics at 1.5 hours after study drug administration (with recording of the date and actual clock time of blood collection)
Study drug dispensing	Dispensing of 4-week supply of study drug to the subject with instructions for self-administration at home
Instruction regarding dosing at next full clinic visit	Instruction to the subject that the morning dose of study drug should not be taken on the day of Visit 9.
Scheduling of Visit 9 radiology assessment	CT or MRI imaging of neck, chest, abdomen, and pelvis to be scheduled for Visit 9; the same method of assessment (CT, MRI) should be used as was used at baseline.

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

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

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

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

Assessment or Procedure	Explanation
Pre-Visit Tumor Assessment	
Radiology assessment	CT or MRI imaging of neck, chest, abdomen, and pelvis within 1 week prior to the visit; the same method of assessment (CT or MRI) should be used as was used at baseline and the assessment should be done even if study drug has been interrupted.
Pre-Therapy Procedures and Assessments	
FACT-Leu	HRQL instrument (Appendix 2) to be administered before any other procedures are performed and before any study-related information is communicated to the subject
EQ-5D	Health utility instrument (Appendix 4) to be administered after FACT-Leu but before any other procedures are performed and before any study-related information is communicated to the subject
Adverse events	Recording of adverse events occurring since Visit 8
Concomitant medications	Recording of concomitant medication used since Visit 8
Study drug return/accounting	Counting returned study drug. Recording of the date and actual clock time of the last prior subject self-administration of study drug (should be the prior evening dose)
Performance status	Using Karnofsky performance status criteria (see Appendix 3)
Oxygen saturation	To be assessed by pulse oximetry while subject is breathing room air
Physical examination	Including weight, evidence of palpable lymphadenopathy, hepatomegaly, and/or splenomegaly
Hematology	Including hematocrit, hemoglobin, erythrocyte count; absolute counts of leukocytes, neutrophils, lymphocytes, monocytes, eosinophils, basophils, platelet count
Serum chemistry	Including sodium, potassium, chloride, glucose, urea, creatinine, calcium, phosphorus, total protein, albumin, ALT, AST, ALP, GGT, total bilirubin, LDH, uric acid, cholesterol, triglycerides
Circulating cells	Including cells for analysis of PI3K/AKT/mTOR pathway activation and quantitation of absolute number of CD4+, CD8+, CD16/CD56+, CD5+, CD19+, and CD+20 cells by flow cytometry
Biomarkers	Collection of plasma and serum for evaluation of circulating chemokines and cytokines
Serum Igs	Including quantitative levels of IgA, IgE, IgG, and IgM
Bone marrow biopsy and aspirate	To be performed post-baseline to confirm response category in subjects with potential CR by radiological assessments. If the subject does not otherwise meet criteria for CR, it is not necessary to obtain a follow-up bone marrow biopsy/aspirate to establish CR.
GS-1101 pharmacokinetics	Pre-dose collection of plasma sample for GS-1101 pharmacokinetics (with recording of the date and actual clock time of the date and actual clock time of blood collection)
IWRS access	Access of IWRS to obtain study drug blister card number
Study Therapy Administration	
Study drug administration	Dose of study drug to be administered to the subject (with recording of the date and actual clock time of the study drug administration)
Post-Therapy Procedures and Assessments	
GS-1101 pharmacokinetics	Post-dose collection of plasma sample for GS-1101 pharmacokinetics at 1.5 hours after study drug administration (with recording of the date and actual clock time of blood collection)
Study drug dispensing	Dispensing of 4-week supply of study drug to the subject with instructions for self-administration at home
Instruction regarding dosing at next full clinic visit	Instruction to the subject that the morning dose of study drug should not be taken on the day of Visit 10.

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

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

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

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

Assessment or Procedure	Explanation
Pre-Therapy Procedures and Assessments	
FACT-Leu	HRQL instrument (Appendix 2) to be administered before any other procedures are performed and before any study-related information is communicated to the subject
EQ-5D	Health utility instrument (Appendix 4) to be administered after FACT-Leu but before any other procedures are performed and before any study-related information is communicated to the subject
Adverse events	Recording of adverse events occurring since Visit 9
Concomitant medications	Recording of concomitant medication used since Visit 9
Performance status	Using Karnofsky performance status criteria (see Appendix 3)
Study drug return/accounting	Counting returned study drug. Recording of the date and actual clock time of the last prior subject self-administration of study drug (should be the prior evening dose)
Physical examination	Including weight, evidence of palpable lymphadenopathy, hepatomegaly, and/or splenomegaly
Hematology	Including hematocrit, hemoglobin, erythrocyte count; absolute counts of leukocytes, neutrophils, lymphocytes, monocytes, eosinophils, basophils, platelet count
Serum chemistry	Including sodium, potassium, chloride, glucose, urea, creatinine, calcium, phosphorus, total protein, albumin, ALT, AST, ALP, GGT, total bilirubin, LDH, uric acid, cholesterol, triglycerides
Circulating cells	Including cells for analysis of PI3K/AKT/mTOR pathway activation and quantitation of absolute number of CD4+, CD8+, CD16/CD56+, CD19+, and CD+20 cells by flow cytometry
Biomarkers	Collection of plasma and serum for evaluation of circulating chemokines and cytokines
Serum Igs	Including quantitative levels of IgA, IgE, IgG, and IgM
GS-1101 pharmacokinetics	Pre-dose collection of plasma sample for GS-1101 pharmacokinetics (with recording of the date and actual clock time of the date and actual clock time of blood collection)
IWRS access	Access of IWRS to obtain study drug blister card number
Study Therapy Administration	
Study drug administration	Dose of study drug to be administered to the subject (with recording of the date and actual clock time of the study drug administration)
Post-Therapy Procedures and Assessments	
GS-1101 pharmacokinetics	Post-dose collection of plasma sample for GS-1101 pharmacokinetics at 1.5 hours after study drug administration (with recording of the date and actual clock time of blood collection)
Study drug dispensing	Dispensing of 4-week supply of study drug to the subject with instructions for self-administration at home
Instruction regarding dosing at next full clinic visit	Instruction to the subject that the morning dose of study drug should not be taken on the day of Visit 11.
Scheduling of Visit 11 radiology assessment	CT or MRI imaging of neck, chest, abdomen, and pelvis to be scheduled for Visit 11; the same method of assessment (CT, MRI) should be used as was used at baseline.

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

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

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

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

Assessment or Procedure	Explanation
Pre-Visit Tumor Assessment	
Radiology assessment	CT or MRI imaging of neck, chest, abdomen, and pelvis within 1 week prior to the visit; the same method of assessment (CT or MRI) should be used as was used at baseline and the assessment should be done even if study drug has been interrupted.
Pre-Therapy Procedures and Assessments	
FACT-Leu	HRQL instrument (Appendix 2) to be administered before any other procedures are performed and before any study-related information is communicated to the subject
EQ-5D	Health utility instrument (Appendix 4) to be administered after FACT-Leu but before any other procedures are performed and before any study-related information is communicated to the subject
Adverse events	Recording of adverse events occurring since Visit 10
Concomitant medications	Recording of concomitant medication used since Visit 10
Study drug return/accounting	Counting returned study drug. Recording of the date and actual clock time of the last prior subject self-administration of study drug (should be the prior evening dose)
Performance status	Using Karnofsky performance status criteria (see Appendix 3)
Oxygen saturation	To be assessed by pulse oximetry while subject is breathing room air
Physical examination	Including weight, evidence of palpable lymphadenopathy, hepatomegaly, and/or splenomegaly
Hematology	Including hematocrit, hemoglobin, erythrocyte count; absolute counts of leukocytes, neutrophils, lymphocytes, monocytes, eosinophils, basophils, platelet count
Serum chemistry	Including sodium, potassium, chloride, glucose, urea, creatinine, calcium, phosphorus, total protein, albumin, ALT, AST, ALP, GGT, total bilirubin, LDH, uric acid, cholesterol, triglycerides
Circulating cells	Including cells for analysis of PI3K/AKT/mTOR pathway activation and quantitation of absolute number of CD4+, CD8+, CD16/CD56+, CD19+, and CD+20 cells by flow cytometry
Biomarkers	Collection of plasma and serum for evaluation of circulating chemokines and cytokines
Serum Igs	Including quantitative levels of IgA, IgE, IgG, and IgM
Bone marrow biopsy and aspirate	To be performed post-baseline to confirm response category in subjects with potential CR by radiological assessments. If the subject does not otherwise meet criteria for CR, it is not necessary to obtain a follow-up bone marrow biopsy/aspirate to establish CR.
GS-1101 pharmacokinetics	Pre-dose collection of plasma sample for GS-1101 pharmacokinetics (with recording of the date and actual clock time of the date and actual clock time of blood collection)
IWRS access	Access of IWRS to obtain study drug blister card numbers
Study Therapy Administration	
Study drug administration	Dose of study drug to be administered to the subject (with recording of the date and actual clock time of the study drug administration)
Post-Therapy Procedures and Assessments	
GS-1101 pharmacokinetics	Post-dose collection of plasma sample for GS-1101 pharmacokinetics at 1.5 hours after study drug administration (with recording of the date and actual clock time of blood collection)
Study drug dispensing	Dispensing of 12-week supply of study drug to the subject with instructions for self-administration at home

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

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

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

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

Assessment or Procedure	Explanation
FACT-Leu	HRQL instrument (Appendix 2) to be administered before any other procedures are performed and before any study-related information is communicated to the subject
EQ-5D	Health utility instrument (Appendix 4) to be administered after FACT-Leu but before any other procedures are performed and before any study-related information is communicated to the subject
Adverse events	Recording of adverse events occurring since Visit 11
Concomitant medications	Recording of concomitant medication used since Visit 11
Performance status	Using Karnofsky performance status criteria (see Appendix 3)
Oxygen saturation	To be assessed by pulse oximetry while subject is breathing room air
Physical examination	Including weight, evidence of palpable lymphadenopathy, hepatomegaly, and/or splenomegaly
Hematology	Including hematocrit, hemoglobin, erythrocyte count; absolute counts of leukocytes, neutrophils, lymphocytes, monocytes, eosinophils, basophils, platelet count
Serum chemistry	Including sodium, potassium, chloride, glucose, urea, creatinine, calcium, phosphorus, total protein, albumin, ALT, AST, ALP, GGT, total bilirubin, LDH, uric acid, cholesterol, triglycerides
Circulating cells	Including cells for analysis of PI3K/AKT/mTOR pathway activation and quantitation of absolute number of CD4+, CD8+, CD16/CD56+, CD19+, and CD+20 cells by flow cytometry
Biomarkers	Collection of plasma and serum for evaluation of circulating chemokines and cytokines
Serum Igs	Including quantitative levels of IgA, IgE, IgG, and IgM
IWRS access	Access of IWRS to document subject visit
Study drug administration	Subject to continue with study drug as prescribed.
Scheduling of Visit 13 radiology assessment	CT or MRI imaging of neck, chest, abdomen, and pelvis to be scheduled for Visit 13; the same method of assessment (CT, MRI) should be used as was used at baseline.

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

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

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

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

Assessment or Procedure	Explanation
Pre-Visit Tumor Assessment	
Radiology assessment	CT or MRI imaging of neck, chest, abdomen, and pelvis within 1 week prior to the visit; the same method of assessment (CT or MRI) should be used as was used at baseline and the assessment should be done even if study drug has been interrupted.
During-Visit Procedures and Assessments	
FACT-Leu	HRQL instrument (Appendix 2) to be administered before any other procedures are performed and before any study-related information is communicated to the subject
EQ-5D	Health utility instrument (Appendix 4) to be administered after FACT-Leu but before any other procedures are performed and before any study-related information is communicated to the subject
Adverse events	Recording of adverse events occurring since Visit 10
Concomitant medications	Recording of concomitant medication used since Visit 10
Study drug return/accounting	Counting returned study drug.
Performance status	Using Karnofsky performance status criteria (see Appendix 3)
Oxygen saturation	To be assessed by pulse oximetry while subject is breathing room air
Physical examination	Including weight, evidence of palpable lymphadenopathy, hepatomegaly, and/or splenomegaly
Hematology	Including hematocrit, hemoglobin, erythrocyte count; absolute counts of leukocytes, neutrophils, lymphocytes, monocytes, eosinophils, basophils, platelet count
Serum chemistry	Including sodium, potassium, chloride, glucose, urea, creatinine, calcium, phosphorus, total protein, albumin, ALT, AST, ALP, GGT, total bilirubin, LDH, uric acid, cholesterol, triglycerides
Circulating cells	Including cells for analysis of PI3K/AKT/mTOR pathway activation and quantitation of absolute number of CD4+, CD8+, CD16/CD56+, CD19+, and CD+20 cells by flow cytometry
Biomarkers	Collection of plasma and serum for evaluation of circulating chemokines and cytokines
Serum Igs	Including quantitative levels of IgA, IgE, IgG, and IgM
Bone marrow biopsy and aspirate	To be performed post-baseline to confirm response category in subjects with potential CR by radiological assessments. If the subject does not otherwise meet criteria for CR, it is not necessary to obtain a follow-up bone marrow biopsy/aspirate to establish CR.
IWRS access	Access of IWRS to obtain study drug blister card numbers
Study drug administration	Subject to continue with study drug as prescribed.
Study drug dispensing	Dispensing of 12-week supply of study drug to the subject with instructions for self-administration at home

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

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

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

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

Assessment or Procedure	Explanation
FACT-Leu	HRQL instrument (Appendix 2) to be administered before any other procedures are performed and before any study-related information is communicated to the subject
EQ-5D	Health utility instrument (Appendix 4) to be administered after FACT-Leu but before any other procedures are performed and before any study-related information is communicated to the subject
Adverse events	Recording of adverse events occurring since Visit 10
Concomitant medications	Recording of concomitant medication used since Visit 10
Performance status	Using Karnofsky performance status criteria (see Appendix 3)
Oxygen saturation	To be assessed by pulse oximetry while subject is breathing room air
Physical examination	Including weight, evidence of palpable lymphadenopathy, hepatomegaly, and/or splenomegaly
Hematology	Including hematocrit, hemoglobin, erythrocyte count; absolute counts of leukocytes, neutrophils, lymphocytes, monocytes, eosinophils, basophils, platelet count
Serum chemistry	Including sodium, potassium, chloride, glucose, urea, creatinine, calcium, phosphorus, total protein, albumin, ALT, AST, ALP, GGT, total bilirubin, LDH, uric acid, cholesterol, triglycerides
Circulating cells	Including cells for analysis of PI3K/AKT/mTOR pathway activation and quantitation of absolute number of CD4+, CD8+, CD16/CD56+, CD19+, and CD+20 cells by flow cytometry
Biomarkers	Collection of plasma and serum for evaluation of circulating chemokines and cytokines
Serum Igs	Including quantitative levels of IgA, IgE, IgG, and IgM
IWRS access	Access of IWRS to document subject visit
Study drug administration	Subject to continue with study drug as prescribed.
Scheduling of Visit 15 radiology assessment	CT or MRI imaging of neck, chest, abdomen, and pelvis to be scheduled for Visit 15; the same method of assessment (CT, MRI) should be used as was used at baseline.

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

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

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

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

Assessment or Procedure	Explanation
Pre-Visit Tumor Assessment	
Radiology assessment[a]	CT or MRI imaging of neck, chest, abdomen, and pelvis within 1 week prior to the visit; the same method of assessment (CT or MRI) should be used as was used at baseline and the assessment should be done even if study drug has been interrupted.
During-Visit Procedures and Assessments	
FACT-Leu	HRQL instrument (Appendix 2) to be administered before any other procedures are performed and before any study-related information is communicated to the subject
EQ-5D	Health utility instrument (Appendix 4) to be administered after FACT-Leu but before any other procedures are performed and before any study-related information is communicated to the subject
Adverse events	Recording of adverse events occurring since prior visit
Concomitant medications	Recording of concomitant medication used since prior visit
Study drug return/accounting	Counting returned study drug.
Performance status	Using Karnofsky performance status criteria (see Appendix 3)
Oxygen saturation	To be assessed by pulse oximetry while subject is breathing room air
Physical examination	Including weight, evidence of palpable lymphadenopathy, hepatomegaly, and/or splenomegaly
Hematology	Including hematocrit, hemoglobin, erythrocyte count; absolute counts of leukocytes, neutrophils, lymphocytes, monocytes, eosinophils, basophils, platelet count
Serum chemistry	Including sodium, potassium, chloride, glucose, urea, creatinine, calcium, phosphorus, total protein, albumin, ALT, AST, ALP, GGT, total bilirubin, LDH, uric acid, cholesterol, triglycerides
Circulating cells	Including cells for analysis of PI3K/AKT/mTOR pathway activation and quantitation of absolute number of CD4+, CD8+, CD16/CD56+, CD19+, and CD+20 cells by flow cytometry
Biomarkers	Collection of plasma and serum for evaluation of circulating chemokines and cytokines
Serum Igs	Including quantitative levels of IgA, IgE, IgG, and IgM
Bone marrow biopsy and aspirate	To be performed post-baseline to confirm response category in subjects with potential CR by radiological assessments. If the subject does not otherwise meet criteria for CR, it is not necessary to obtain a follow-up bone marrow biopsy/aspirate to establish CR.
IWRS access	Access of IWRS to obtain study drug blister card numbers
Study drug administration	Subject to continue with study drug as prescribed.
-Study drug dispensing	Dispensing of 12-week supply of study drug to the subject with instructions for self-administration at home
Scheduling of next visit radiology assessment	CT or MRI imaging of neck, chest, abdomen, and pelvis to be scheduled for next clinic visit (every 12 weeks); the same method of assessment (CT, MRI) should be used as was used at baseline.

a For follow-up visits after Week 96, CT or MRI is only required at the end-of-treatment visit (see Table 6-16).

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

6.2.16. End-of-Treatment Visit (Clinic Visit)

At the time of discontinuation from the study, the subject should have the procedures and assessments performed as documented in Table 6-16. An end-of-study CT/MRI tumor assessment should be performed unless the subject already has radiographic confirmation of definitive disease progression ≤4 weeks prior to study drug discontinuation.

Table 6-16. Procedures and Assessments at End-of-Treatment Visit

Assessment or Procedure	Explanation
Radiology assessment[a]	CT or MRI imaging of neck, chest, abdomen, and pelvis; the same method of assessment (CT or MRI) should be used as was used at baseline
FACT-Leu	HRQL instrument (Appendix 2) to be administered before any other procedures are performed
EQ-5D	Health utility instrument (Appendix 4) to be administered after FACT-Leu but before any other procedures are performed
Adverse events	Recording of adverse events occurring since prior visit; if a clinically significant adverse event or abnormal result is observed that is not resolved by the end-of treatment visit, repeat evaluations should be performed to document resolution or stabilization of the abnormality
Concomitant medications	Recording of concomitant medication used since prior visit
Study drug return/accounting	Counting returned study drug.
Performance status	Using Karnofsky performance status criteria (see Appendix 3)
Oxygen saturation	To be assessed by pulse oximetry while subject is breathing room air
Physical examination	Including weight, evidence of palpable lymphadenopathy, hepatomegaly, and/or splenomegaly
Serum β-HCG	Women of childbearing potential only
CLL peripheral blood evaluation	Including FISH for chromosome 11q deletion, 13q deletion, 17p deletion and 12 trisomy; DNA mutational analysis for p53, IgHV (including IgHV3-21), and other genes of interest in CLL (eg, Notch); flow cytometry for CD5, CD10, CD11c, CD19, CD20, CD23, CD38, CD45, kappa and lambda light chains, and ZAP-70; cytology for karyotyping; bone marrow aspirate may be used if peripheral blood lymphocyte count is too low
CLL serology	Serum β2 microglobulin
PPD	
Hematology	Including hematocrit, hemoglobin, erythrocyte count; absolute counts of leukocytes, neutrophils, lymphocytes, monocytes, eosinophils, basophils, platelet count
Serum chemistry	Including sodium, potassium, chloride, glucose, urea, creatinine, calcium, phosphorus, total protein, albumin, ALT, AST, ALP, GGT, total bilirubin, LDH, uric acid, cholesterol, triglycerides
Circulating cells	Including cells for analysis of PI3K/AKT/mTOR pathway activation and quantitation of absolute number of CD4+, CD8+, CD16/CD56+, CD19+, and CD+20 cells by flow cytometry
Biomarkers	Collection of plasma and serum for evaluation of circulating chemokines and cytokines
Serum Igs	Including quantitative levels of IgA, IgE, IgG, and IgM
IWRS	Access IWRS to document that subject has permanently discontinued study therapy and to indicate whether subject agrees to continue to undergo long-term follow-up

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

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

6.2.17. Immediate Post-Treatment Safety Follow-up

After the last dose of study treatment subjects should be followed for any drug-related adverse events and/or ongoing serious adverse events until those events have resolved or become stable, whichever occurs later. Follow-up may be obtained in person or by telephone contact.

6.2.18. Long-Term Follow-Up

Long-term, post-treatment follow-up will be requested of all subjects who withdraw from study therapy for any reason.

The long-term post-treatment follow-up will be conducted (as measured from the last dose of study drug) at ~6-month intervals during Year 1 and Year 2, and at ~12-month intervals during Years 3, 4, and 5. Data on post-study therapies for CLL, on the occurrence of new non-CLL-related health problems (eg, myelodysplasia, Richter's transformation, chronic hepatic abnormalities, etc), and on survival will be collected from all subjects who receive ≥1 dose of study drug.

Long-term follow-up information will be gathered during a routine clinic visit or other contact with the subject, or via telephone. These data will be collected in the source documents (eg, subject medical record) and transcribed into a specific electronic eCRF. Any unsuccessful efforts to contact the subject (eg, dates of unanswered phone calls, return of certified letter sent to subject's home, etc) will be documented.

6.3. Blood Collection

Computations of blood drawing requirements for this study are shown in Table 6-17. The maximum amount of blood to be drawn at a visit is 105 mL and the total amount of blood to be drawn over the initial 52-week study period (including the 4-week screening period and through Week 48 of the study including a possible end-of-therapy visit) is ~551 mL. For a 40-kg person (the smallest participant expected to enroll in the study), this equates to maximum blood volume per body weight per visit of ~2.8 mL/kg and a total blood volume per body weight per average 6-week period of ~1.6 mL/kg. These quantities of blood are within accepted limits of 3.0 mL/kg of body weight for a single blood draw and 7.0 mL/kg of body weight for a 6-week period [National Institutes of Health 2003].

Table 6-17. Blood Drawing Requirements Through Visit 15 (Week 48)

Test		Sample Type	Tube Type	Blood Per Tube (mL)	Tubes (n)		Blood Volume (mL)	
					Maximum Per Visit	Total in Study[a]	Maximum Per Visit	Total in Study[a]
CLL peripheral blood evaluation		Plasma	Sodium heparin	50	1	2	50	100
Genotyping and expression analysis	DNA RNA	Cells	K_2-EDTA Paxgene	12	1	2	12	24
	Protein	Cells	K_2-EDTA	8	1	2	8	16
Coagulation		Plasma	Citrate	4	1	1	4	4
Hematology		Plasma	K_2-EDTA	3	1	16	3	48
Serum chemistry (including β-HCG and CLL serology)		Serum	Clot	5	1	16	5	80
Circulating cells for PI3K/AKT/mTOR pathway activation and immunophenotyping		Cells	K_2-EDTA	4	1	13	4	52
Biomarkers		Plasma	K_2-EDTA	5	1	13	5	65
		Serum	Clot	5	1	13	5	65
Serum Igs		Serum	Clot	5	1	13	5	65
GS-1101 pharmacokinetics		Plasma	K_2-EDTA	2	2	8	4	32
Total							105	551

a Computed for initial 52-week period (considering 4 weeks for screening and 48 weeks on study)

Abbreviations: β-HCG=beta human chorionic gonadotropin, AKT =AKT (a serine/threonine protein kinase), CLL=chronic lymphocytic leukemia, DNA=deoxyribonucleic acid, Ig=immunoglobulin, K_2-EDTA=potassium-ethylenediaminetetraacetic acid, mTOR=mammalian target of rapamycin, PI3K=phosphatidylinositol 3-kinase, RNA=ribonucleic acid

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

PPD

6.4. Study Procedure Rationale

The planned study assessments and timing have been selected as appropriate for screening of subjects, for determination of GS-1101-related or disease-related toxicities, for dose modification during the study, for characterization of drug exposure and desired pharmacological effects, and for evaluation of drug activity. The scheduling of testing is designed to collect a complete safety and pharmacology data set while maintaining subject tolerance of study procedures. The planned schedule of tumor assessments is consistent with expected rate of changes and appropriately balances precise measurement of tumor control

with the expense and subject inconvenience associated with clinical and radiological procedures. For discussion of the rationale for endpoint selection, see Section 3.2.

7. EFFICACY ASSESSMENTS

7.1. Tumor Status Assessments

The determination of CLL response and progression will be based on standardized IWCLL criteria [Hallek 2008], as specifically modified for this study considering the pharmacology of GS-1101 and the methods to be used in evaluation. Treatment decisions by the investigator in this study will be based on these assessments. Radiographic and clinical tumor assessments will be subject to independent confirmation by the IRC (see Section 10.4.3).

7.2. Method of Assessment

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

For radiographic evaluations, the same method of assessment and the same technique (eg, scan type, scanner, subject position, dose of contrast, injection/scan interval) should be used to characterize each identified and reported lesion at baseline and during study treatment and follow-up. 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.

7.3. Timing of Assessments

All baseline clinical and CT/MRI tumor assessments should be performed within 4 weeks prior to the start of treatment. In order to optimize scheduling convenience for the subject and for the investigational staff, clinical and CT/MRI tumor assessments performed as part of Study GS-US-312-0116 need not be repeated and can be used as baseline tumor assessments for Study GS-US-312-0117 if performed within 4 weeks prior to initiation of study drug therapy on Study GS-US-312-0117. Clinical tumor assessments should be performed at each clinical visit. On-study CT/MRI tumor assessments should be performed at ~8- to 12-week intervals as dictated by the study protocol. For follow-up visits after Week 96, CT or MRI is only required at the end-of-treatment visit. An end-of-treatment CT/MRI tumor assessment should be performed unless the subject already has radiographic confirmation of disease progression ≤4 weeks prior to study drug discontinuation.

7.4. Identification and Measurement of Tumor Lesions and Organomegaly

7.4.1. Index Lesions

At baseline, up to 6 lymph nodes should be selected as index lesions that will be used to quantitate the status of the disease during study treatment. Ideally, the index lesions should be located in disparate regions of the body. Only peripheral nodes need be selected as index

lesions. However, it is optimal if mediastinal and retroperitoneal areas of disease are assessed whenever these sites are involved.

A nodal mass may be selected as a nodal index lesion if it is both abnormal and measurable at baseline. A nodal lesion is considered abnormal and measurable if it has 2 perpendicular diameters that can be accurately measured in cross section and each of the perpendicular diameters measures ≥1.0 cm. Abnormal, measurable nodal lesions will be subcategorized as either large or small. Large nodal lesions have a longest diameter (LD) that is >1.5 cm and a longest perpendicular diameter (LPD) that is ≥1.0 cm. Small nodal lesions have an LD that is >1.0 cm and ≤1.5 cm and an LDP 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.

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 × LPD) will be recorded (in cm) for each index lesion. The product of the perpendicular diameters (PPD) (in cm^2) will be calculated. The PPDs and the sum of the products (SPDs) (in cm^2) for all index lesions will be calculated and recorded. The baseline and nadir PPDs for individual lesions and the baseline and nadir SPDs will be used as references by which tumor response and progression will be characterized during treatment.

At follow-up time points, the PPDs 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.

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, only those elements that are >1.0 cm in at least 1 diameter will be considered abnormal and used in calculating the SPD. Progression of the lesion can only be based on the SPD of abnormal sub-components. Lesion sub-components that are considered normal but measurable will have the true PPDs calculated, with the result used only for calculating an accurate nadir. 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), stored only for the purposes of calculating the nadir SPD value.

7.4.2. Spleen and Liver

Both the spleen and liver will be assessed by CT/MRI scan and by physical examination.

By imaging, the spleen will be considered enlarged if it is >10 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).

Physical examination of the spleen should comprise assessment of its vertical dimension below the left costal margin by palpation. By physical examination, the spleen will be considered enlarged if it is palpable below the left costal margin. If the spleen is not palpable below the left costal margin, it should be assigned a value of 0 cm for physical examination assessment.

By imaging, the liver will be considered enlarged if it is >18 cm in LVD [Erturk 2006], with the LVD being obtained by multiplying the number of sections on which the liver is visualized by the thickness of the sections (eg, if the liver is seen in 34 contiguous cross-sectional images with 0.5-cm thickness, the LVD is recorded as 17 cm).

Physical examination of the liver should comprise assessment of its LVD at the right midclavicular line by percussion. The liver will be considered enlarged if it is >15 cm in LVD as assessed by percussion [Walker 1990].

The spleen and liver should be measured clinically and radiographically at baseline and at the stipulated intervals during treatment. The baseline and nadir values will be used as references by which tumor response and progression will be characterized during treatment. For subjects with splenomegaly at baseline or at the splenic LVD nadir, respective response and progression evaluations of the spleen will consider only changes relative to the enlargement of the spleen at baseline or nadir, not changes relative to the total splenic LVD. For subjects with hepatomegaly at baseline or at the liver LVD nadir, respective response and progression evaluations of the liver will consider only changes relative to the enlargement of the liver at baseline or nadir, not changes relative to the total hepatic LVD.

7.4.3. Non-Index Lesions

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

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

7.5. Definitions of Tumor Response and Progression

Responses will be categorized as CR, PR, stable disease (SD), progressive disease (PD). In addition, a response category of not evaluable (NE) is provided for situations in which there is inadequate information to otherwise categorize response status. While enrollment is limited to subjects who have measurable disease, a response category of no disease (ND) is

included solely to account for the unexpected situation in which a subject is found to have no evidence of tumor either at baseline or on treatment.

The date of response, date of progression, and best overall response will be determined. The best nodal, splenic, hepatic, and peripheral blood counts response will be characterized. The best overall response is the best response recorded from the start of treatment until disease progression (taking as a reference for disease progression the smallest measurements recorded at baseline or post-baseline). All relevant clinical and radiographic information required to make each tumor status assessment must be made available for source verification and for submission to the IRC (see Section 10.4.3). Where imaging data are available, these data will supersede physical examination data in determining tumor status.

7.5.1. Complete Response

To satisfy criteria for a CR, all of the following criteria must be met and must persist for ≥8 weeks (minimum of 49 days to allow for CT/MRI scheduling):

- No evidence of new disease
- ALC in peripheral blood of $<4 \times 10^9$/L
- 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 LPD for nodes that were considered small at baseline) (see Section 7.4.1 for definitions of large and small nodes)
- 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
- No known disease-related constitutional symptoms
- Peripheral blood counts meeting all of the following criteria:
  - ANC $\geq 1.5 \times 10^9$/L without need for exogenous growth factors (eg, G-CSF)
  - Platelet count $\geq 100 \times 10^9$/L without need for exogenous growth factors
  - Hemoglobin ≥110 g/L (11.0 g/dL) without red blood cell transfusions or need for exogenous growth factors (eg, erythropoietin)

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

7.5.2. Partial Response

To satisfy criteria for a PR, all of the following criteria must be met and must persist for ≥8 weeks (minimum of 49 days to allow for CT/MRI scheduling):

- No evidence of new disease
- A change in disease status meeting ≥2 of the following criteria:
  - Decrease in peripheral blood ALC by ≥50% from baseline
  - 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: normal spleen size or a decrease by ≥50% from baseline (minimum 2-cm decrease or reduction in LVD to normal) in the pretreatment enlargement of the splenic LVD
  - In a subject with enlargement of the liver at baseline: normal liver size or a decrease by ≥50% from baseline (minimum 2-cm decrease or reduction in LVD to normal) in the pretreatment enlargement of the liver LVD
  - A decrease by ≥50% from baseline in the CLL marrow infiltrate or in B-lymphoid nodules
- No index, splenic, liver, or non-index disease with worsening that meets the criteria for definitive PD
- Peripheral blood counts meeting ≥1 of the following criteria:
  - ANC ≥1.5 x 10^9/L or ≥50% increase over baseline without need for exogenous growth factors (eg, G-CSF)
  - Platelet count ≥100 x 10^9/L or ≥50% increase over baseline without need for exogenous growth factors
  - Hemoglobin ≥110 g/L (11.0 g/dL) or ≥50% increase over baseline without red blood cell transfusions or need for exogenous growth factors (eg, erythropoietin)

7.5.3. Stable Disease

To satisfy criteria for stable disease (SD), the following criteria must be met:

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

7.5.4. Definitive Progressive Disease

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

- Evidence of any new disease:
  - A new node that measures >1.5 cm in any diameter
  - A new node that measures >1.0 cm to ≤1.5 cm in the LD and >1.0 cm in the LPD
  - New splenomegaly or recurrent splenomegaly (in a subject for whom spleen size had normalized) with a splenic LVD that now measures >2 cm larger than the cut-off value for the normal splenic LVD

- New hepatomegaly or recurrent hepatomegaly (in a subject for whom liver size had normalized) with an hepatic LVD that now measures >2 cm larger than the cut-off value for the normal hepatic LVD
- New non-index disease (eg, effusions, ascites, or other organ abnormalities related to CLL)

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

- Evidence of worsening of lymph nodes, spleen or liver, or non-index disease:
  - Increase by ≥50% from the nadir in the SPD of index lesions
  - Evidence of worsening of individual index lymph nodes or nodal masses:
    - Increase from the nadir by ≥50% in the PPD for any individual node if the node now has a LD of >1.5 cm and there is an absolute change from the nadir of ≥0.5 cm in the LD or LPD and to ≥2.0 cm.
    - Increase from the nadir by ≥50% in the LD for any individual node if the node now has a LD of >1.5 cm and there is an absolute change from the nadir of ≥0.5 cm in the LD
    - Increase from the nadir by ≥50% in the LPD for any individual node if the node now has a LPD of >1.5 cm and there is an absolute change from the nadir of ≥0.5 cm in the LPD
    - If a lesion had been classified as a small lymph node, there is an additional requirement that the lesion has an LD of >1.0 cm and an LPD of >1.0 cm
  - In a subject with enlargement of the spleen at splenic nadir, there is an increase by ≥50% from the nadir value (minimum 2-cm increase) in the nadir enlargement of the LVD and the splenic LVD now measures >2 cm larger than the cut-off value for the normal splenic LVD
  - In a subject with enlargement of the liver at hepatic nadir, there is an increase by ≥50% from the nadir value (minimum 2-cm increase) in the nadir enlargement of the LVD with an hepatic LVD that now measures >2 cm larger than the cut-off value for the normal hepatic LVD
  - Unequivocal increase in the size of non-index disease (eg, effusions, ascites, or other organ abnormalities related to CLL)
  - Transformation to a more aggressive histology (eg, Richter syndrome) as established by lymph node biopsy
- Decrease in platelet count or hemoglobin that is attributable to CLL, is not attributable to an autoimmune phenomenon, and is confirmed by bone marrow biopsy showing an infiltrate of clonal CLL cells

- The current platelet count is <100 x 10^9/L and there has been a decrease by >50% from the highest on-study platelet count
- The current hemoglobin is <110 g/L (11.0 g/dL) and there has been a decrease by >20 g/L (2 g/dL) from the highest on-study hemoglobin

7.5.5. Non-Evaluable

Subjects have a status of NE if any of the following conditions occur:

- No data or the data are inadequate or missing such that a response determination cannot be made

7.5.6. No Disease

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

- No index disease noted at baseline or on-treatment
- No non-index disease noted at baseline or on-treatment.
- No enlargement of the liver or spleen at baseline or on-treatment
- No abnormalities of peripheral blood counts (elevated ALC or abnormally low ANC, platelet count, or hemoglobin) and no evidence of CLL in bone marrow (if available) at baseline or on treatment

7.5.7. Lymphocytosis During Therapy

GS-1101 can mobilize CLL cells from tissues into the peripheral blood. This characteristic pharmacological action can be prominent early in therapy but can persist over time and should not be confused with disease progression in subjects who have persistent control of other CLL-related signs and symptoms. ***In the absence of other objective evidence of disease progression, lymphocytosis alone will not be considered evidence of disease progression.*** 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 as described in Section 5.8. 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. If disease progression is suspected, CT/MRI and peripheral blood counts should be obtained and bone marrow biopsy should be considered in order to provide objective evidence of CLL status.

7.5.8. Documentation of Definitive CLL Progression

Of importance, tumor size data collected from the primary study will be subjected to IRC review (see Section 10.4.3). ***Subjects must have confirmation by the sponsor working in collaboration with the IRC that the disease has progressed on the primary clinical trial (Study GS-US-312-0116) before being permitted to receive secondary GS-1101 therapy on this extension trial (GS-US-312-0117).*** If there is uncertainty regarding whether there is definitive progression, the subject should continue study treatment and remain under close observation (eg, evaluated at 4-week intervals) pending confirmation of progression status. CT/MRI should be attempted in order to document definitive disease progression. If obtained

within the specified screening period for the extension study, this scan can serve as the baseline scan for the extension study.

8. SAFETY ASSESSMENTS

8.1. Adverse Event Definitions

8.1.1. Adverse Event

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

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

- Any complication that occurs as a result of a protocol-mandated procedure (eg, venipuncture, biopsy) in the screening, on-treatment, or post-treatment periods.
- Any pre-existing condition that increases in severity or changes in nature during or as a consequence of study drug administration. Worsening manifestations of the underlying cancer (eg, increase in pain, tumor flare reaction, tumor lysis syndrome) may be considered adverse events in this study.
- Any injury or accident occurring during the screening, on-treatment, or post-treatment periods. If a medical condition is known to have caused the injury or accident (eg, a fall secondary to dizziness), the medical condition (dizziness) and the accident (fall) should be reported as 2 separate adverse events.
- Any abnormality in physiological testing or a physical examination finding that requires clinical intervention or further investigation (beyond ordering a repeat [confirmatory] test).
- Any laboratory (eg, clinical chemistry, hematology, urinalysis) or investigational abnormality (eg, ECG, X-ray) independent of the underlying medical condition that requires clinical intervention, results in further investigation (beyond ordering a repeat [confirmatory] test), or leads to investigational medicinal product interruption or discontinuation unless it is associated with an already reported clinical event. If the laboratory abnormality is part of a syndrome, the syndrome or diagnosis (eg, anemia) not the laboratory result (eg, decreased hemoglobin) should be recorded.
- A complication related to pregnancy or termination of a pregnancy (see Section 8.9 for additional information).

None of the following events is considered an adverse event:

- Lymphocytosis
- Laboratory abnormalities not requiring clinical intervention or further investigation. Such abnormalities will be captured as part of overall laboratory monitoring.
- A diagnostic, medical or surgical procedure (eg, surgery, endoscopy, tooth extraction, transfusion). However, the medical condition for which the procedure was performed should be reported if it meets the definition of an adverse event. For example, an acute

appendicitis that begins during the adverse event reporting period should be reported as the adverse event and the resulting appendectomy should be recorded in the source documents.

- A pre-existing disease or condition or laboratory abnormality present or detected before the initial screening visit and that does not worsen.
- An intervention not associated with an untoward medical occurrence (eg, hospitalization for elective surgery or for social and/or convenience reasons).

8.1.2. Serious Adverse Event

A serious adverse event is defined is an untoward medical occurrence that results in any of the following outcomes:

- Death (ie, all deaths occurring between signing of the consent form to within 30 days after last study drug administration), including deaths due to disease progression. Deaths that occur as a result of an adverse event that started during the study period should be reported. The reported adverse event should be the event that caused the death. Death is the outcome of this serious adverse event.
- Life-threatening situation (ie, with an immediate risk of death from the event as it occurred but not including an event that, had it occurred in a more serious form, might have caused death).
- In-patient hospitalization or prolongation of existing hospitalization. Of note, an untoward medical occurrence that occurs during hospitalization is an adverse event but a complication that prolongs hospitalization is a serious adverse event. In-patient hospitalization comprises formal admission to a hospital for medical reasons, for any length of time, whether or not hospitalization extends overnight. However, hospital admissions for administration of the study drug, procedures required by the study protocol, or tumor-related diagnostic procedures are not considered serious.
- Persistent or significant disability/incapacity.
- Congenital anomaly/birth defect in the offspring of a subject who received the investigational medicinal product.
- Other medically significant event. Such events 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 might include:
    - Allergic bronchospasm requiring intensive treatment in an emergency room or at home
    - New cancers or blood dyscrasias
    - Convulsions that do not result in hospitalization
    - Development of drug dependency or drug abuse

8.1.3. Unexpected Adverse Event

An unexpected adverse event is defined as an event that has a nature or severity, or specificity that is not consistent with the applicable investigator 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 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 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.

8.2. Eliciting Adverse Event Information

The investigator is to report all directly observed adverse events and all adverse events spontaneously reported by the study subject. In addition, each study subject will be questioned about adverse events at each scheduled clinic visit or during each telephone contact with the subject following initiation of study treatment. The type of question asked should be open-ended, eg, *"Have you had any new health problems?"* or a similar type of query.

8.3. Recording Adverse Events

All adverse events will be assessed by the investigator or qualified designee and recorded in the eCRFs. 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 adverse event and/or serious adverse event and not described as the individual signs or symptoms. The following information should be recorded:

- Description of the adverse event using concise medical terminology
- Description as to whether or not the adverse event is serious (see Section 8.1.2)
- The start date (date of adverse event onset)
- The stop date (date of adverse event resolution)
- The severity of the adverse event (see Section 8.4)
- A description of the potential relatedness of the adverse event to study drug or a study procedure (see Section 8.5)
- The action taken due to the adverse event
- The outcome of the adverse event

8.4. Grading of the Severity of an Adverse Event

The severity of adverse events will be graded using the CTCAE, Version 4.03 (provided in study manual and available at *http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-*

14_QuickReference_8.5x11.pdf). For each episode, the highest severity grade attained should be reported.

If a CTCAE criterion does not exist, the investigator should use the grade or adjectives: Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), Grade 4 (life-threatening), or Grade 5 (fatal) to describe the maximum intensity of the adverse event. For purposes of consistency with the CTCAE, these intensity grades are defined in Table 8-1.

Table 8-1. Grading of Adverse Event Severity

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

The distinction between the seriousness and the severity of an adverse event should be noted. Severe is a measure of intensity; thus, a severe reaction is not necessarily a serious reaction. For example, a headache may be severe in intensity, but would not be classified as serious unless it met one of the criteria for serious events listed in Section 8.1.2 above.

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

The relationship of an adverse event to study drug 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 adverse event had an etiology other than the study drug. For serious adverse events, an alternative causality must be provided (eg, pre-existing condition, underlying disease, intercurrent illness, or concomitant medication).
- Yes: A temporal relationship exists between the adverse event onset and administration of the investigational medicinal product that cannot be readily explained by the subject's clinical state or concomitant therapies. Furthermore, the adverse event appears with some degree of certainty to be related to the study drug based on the known therapeutic and pharmacologic actions or adverse event profile of the investigational medicinal product. In case of cessation or reduction of the dose, the adverse event abates or resolves. In case of interruption and rechallenge, the event reappears upon rechallenge.

Of note, even in circumstances when the study drug is given intermittently or is interrupted temporarily before the onset of the adverse event, consideration should be given as to whether the study drug may have contributed to the event.

As noted in Section 5.5, unblinding should be avoided unless absolutely necessary for a subject's well-being; breaking the blind should not be performed merely to obtain enhanced certainty regarding the relationship of an adverse event to study drug.

The relationship to protocol-mandated study procedures (eg, procedures such as venipuncture or biopsy) should be assessed using the following considerations:

- No: Evidence exists that the adverse event has an etiology other than the study procedure.
- Yes: The adverse event occurred as a result of a protocol-mandated procedure.

8.6. Adverse Event Reporting Period

The start of the adverse event reporting for a study subject will coincide with signing of the informed consent for Study GS-US-312-0117. Any new adverse events occurring thereafter should not be reported within Study GS-US-312-0116, but instead should be reported within Study GS-US-312-0117. The end of the adverse-event-reporting period for Study GS-US-312-0117 occurs 30 days after the completion of study treatment or when any ongoing drug-related adverse events and/or serious adverse events have resolved or become stable. A subject withdrawn from the study because of an adverse event must be followed until the clinical outcome from the adverse event is determined. The investigator should use appropriate judgment in ordering additional tests as necessary to monitor the resolution of events ongoing at the completion of study treatment. Gilead Sciences may request that certain adverse events be followed longer. A longer reporting period applies in the case of pregnancy (see Section 8.9).

8.7. Adverse Event Reporting Requirements

8.7.1. Site Reporting Requirements

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

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

Table 8-2. Site Reporting Requirements for Adverse Events

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

a See contact information in Table 8-3 below.
b Subject name, address, and other personal identifiers should be obscured but without losing the traceability of a document to the study subject identifiers.
c CLL progression or death due to CLL progression should be reported by the investigator as a serious adverse event only if it is assessed that the study drugs caused or contributed to the CLL progression (ie, by a means other than lack of effect). Unrelated events of CLL progression should be captured on the appropriate eCRF.

Abbreviations: CLL = chronic lymphocytic leukemia, eCRF=case report form, IRB/IEC= Institutional Review Board/Independent Ethics Committee

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

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

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

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

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

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

8.7.2. Gilead Sciences Reporting Requirements

Gilead Sciences is required to expedite reports to regulatory authorities worldwide relating to serious adverse events including events related to study procedures; serious adverse drug reactions (SADRs); or suspected, unexpected, serious adverse reactions (SUSARs) consistent with relevant legislation or regulations, including the applicable US FDA Code of Federal Regulations (CFR), the European Commission Clinical Trials Directive (2001/20/EC, and revisions), and other country-specific legislation or regulations.

Each serious adverse event report received from the investigator through PPD Pharmacovigilance will be evaluated by Gilead Sciences Drug Safety and Public Health (DSPH). Gilead Sciences DSPH will assess the seriousness of the event (see Section 8.1.2), the expectedness of the event (see Section 8.1.3), and the relationship to participation in the study (see Section 8.5). For regulatory reporting purposes, expectedness will be determined by Gilead Sciences using reference safety information specified in the investigator brochure and the event will be classified as related if either the investigator or Gilead Sciences determines that the event may be related to the study drug (see Section 8.5).

Gilead Sciences or its designee will also provide all investigators and the DMC with 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.

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

To maintain the integrity of the study, serious adverse events that are associated with the following disease-related effects, and that are assessed as unrelated to study treatment, will not be reported in an expedited fashion by Gilead Sciences:

- Progression of CLL
- Death related to progression of CLL

These events will be exempt from global expedited reporting requirements for the duration of the study because they define the primary efficacy endpoint for this study. They will be reported, as appropriate, in the final clinical study report and in any relevant aggregate safety reports.

The safety information from this study will also be reviewed by an independent DMC on an ongoing basis. The DMC can have access to partially blinded or unblinded data in order to determine if it is safe to continue the study according to the protocol.

8.8. Study Drug Overdose

An overdose is ingestion or administration of an amount of study drug that exceeds the dose mandated by the protocol (see Sections 5.2.8), any misuse or abuse of study drug, or any misuse or abuse of any other product taken as a concomitant medication. An overdose is considered to have occurred if this definition is met, whether or not the administration is accidental or intentional, is suspected or confirmed, and whether or not the overdose is associated with an adverse experience.

An overdose must be reported using the Gilead Sciences DSPH Clinical Overdose form. The completed DSPH Clinical Overdose form must be forwarded within 24 hours to DSPH or if applicable, to the CRO. Any questions or concerns should be discussed with the Gilead Sciences medical monitor.

Along with information regarding the circumstances of the overdose, any clinical sequelae in association with the overdose should be reported as an adverse event or serious adverse event according to the reporting requirements for those events (see Section 8.6). Overdose will be considered a serious adverse event only if any of the seriousness criteria are met (see Section 8.1.2). Details of signs or symptoms, clinical management and outcome should be reported, if available.

8.9. Pregnancy Requirements

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 the last ingestion of 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 prior 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 has been 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 adverse event; such occurrences should be reported on the appropriate pregnancy report forms. However, if the outcome of the pregnancy meets the criteria for classification as a serious adverse event (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 serious adverse events, ie, report the event to PPD Pharmacovigilance by telephone and follow up by submission of the appropriate adverse event eCRFs (see Section 8.7.1).

Additional information about pregnancy outcomes that are classified as serious adverse events includes:

- Any spontaneous abortion, including miscarriage and missed abortion will be reported as an serious adverse event.
- A induced therapeutic abortion to terminate any pregnancy due to complications or other medical reasons will be recorded as an serious adverse event. The underlying medical reason for this procedure should be recorded as the adverse event term.
- All neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as serious adverse events. 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.
- 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.

9. STATISTICAL CONSIDERATIONS

9.1. Analysis Conventions

9.1.1. Analysis Sets

9.1.1.1. Full Analysis Set

The full-analysis set includes all subjects who receive ≥1 dose of any study treatment (high-dose GS-1101 or standard-dose GS-1101). In the full-analysis set, study drug assignment will be designated according to initial allocation in this study, regardless of whether subjects receive a different study therapy from that to which they were allocated.

This analysis set will be used in the analyses of subject characteristics, PFS, ORR, TTF, and OS. Subjects in the full-analysis set who do not have sufficient baseline or on-study tumor status information to be adequately assessed for ORR will be counted as failures in the analysis of ORR.

9.1.1.2. Responding Analysis Set

The responding analysis set includes subjects in the full-analysis set who have measurable nodal disease, who can be evaluated for tumor response with both baseline and on-study tumor evaluations, and who achieve a CR or PR. The subjects will be grouped for analyses with treatment assignments designated according to the actual study drug received.

This analysis set will be used in the analyses of TTR and DOR.

9.1.1.3. Evaluable Analysis Sets

The evaluable 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 percent changes in lymph node area, lymph node response rate, splenomegaly response rate, hepatomegaly response rate, platelet response rate, hemoglobin response rate, neutrophil response rate, changes in HRQL, and changes in performance status.

9.1.1.4. Safety Analysis Set

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

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

9.1.1.5. Pharmacodynamic/Pharmacokinetic Analysis Sets

The pharmacodynamic/pharmacokinetic analysis sets include subjects in the safety 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 AKT phosphorylation, chemokines/cytokines, and GS-1101 plasma concentrations.

9.1.2. Data Handling Conventions

9.1.2.1. General Methods

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

Time-to-event analyses will be performed with reference to the date of first treatment on this clinical trial (Study GS-US-312-0117). Similarly, evaluations of on-therapy changes will reference the baseline values obtained prior to treatment in this study. The baseline value used in each analysis will be the last (most recent) pre-treatment value. 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.

Analyses will generally focus on evaluation of outcomes within each treatment arm; formal analyses comparing outcomes in Arm A to those in Arm B are not planned. Unless otherwise specified, all analyses will be 2-sided at the 0.05 level of significance.

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

Tumor control assessments will be based on standardized IWCLL criteria [Hallek 2008], as specifically modified for this study considering the pharmacology of GS-1101. The individual and composite endpoints of response and progression (considering changes in lymph node area, liver and spleen size, bone marrow, platelet counts, hemoglobin, neutrophil counts, and peripheral blood lymphocyte counts) will be determined. Tumor control will be documented at each assessment by response category (eg, CR, PR, SD, definitive PD, NE, ND) as defined for each response parameter, SPD value, percentage change in SPD values from baseline or nadir, date that response is first documented, date that response is confirmed, and date of definitive CLL progression.

The date of definitive CLL progression will be the timepoint at which progression is first identified by CT/MRI, physical examination, or by worsening platelet count or hemoglobin. However, where imaging data are available, these data will supersede physical examination data in determining tumor status. For purposes of analysis, subjects who have only physical examination evidence of definitive disease progression that is not confirmed by CT/MRI will be considered to have progressed at the time of the physical examination finding. Because of the characteristic redistribution lymphocytosis that expected with PI3Kδ inhibition,

lymphocyte count will be ignored in the evaluation of progression. Calculations of progression considering lymphocyte count will be described but not analyzed.

Changes in tumor status as provided by the investigator and changes in tumor status as adjudicated by the IRC (see Section 10.4.3) will be described and compared. The findings of the IRC will be considered primary for analyses of all tumor control endpoints.

For time-to-event endpoints other than OS, only events occurring ≤30 days following the permanent discontinuation of study treatment will be considered as events; for subjects with events occurring >30 days following the permanent discontinuation of study treatment, the data will be censored. The following censoring conventions will be applied:

- PFS: Data from surviving, non-progressing subjects will be censored at the earliest of the time of initiation of antitumor treatment other than the study treatment or the last time that lack of definitive CLL progression was objectively documented while on study treatment.
- DOR: Data from surviving, non-progressing subjects will be censored at the earliest of the time of initiation of antitumor treatment other than the study treatment or the last time that lack of definitive CLL progression was objectively documented while on study treatment.
- TTF: Data from surviving subjects who do not have treatment failure will be censored at the earliest of the time of initiation of antitumor treatment other than the study treatment or the last on-therapy time that lack of treatment failure was objectively documented.
- OS: Data from surviving subjects will be censored at the last time that the subject was known to be alive.
- Time to definitive increment in HRQL: Data from subjects who do not have definitive HRQL increment by the specified amount (10%, 20%, or 40%) will be censored at the earliest of the time of initiation of antitumor treatment other than the study treatment or the last HRQL assessment while on study treatment.
- Time to definitive decrement in HRQL: Data from surviving subjects who do not have definitive HRQL decrement by the specified amount (10%, 20% or 40%) will be censored at the earliest of the time of initiation of antitumor treatment other than the study treatment or the last HRQL assessment while on study treatment.
- Time to definitive performance status improvement: Data from subjects who do not have definitive performance status improvement will be censored at the earliest of the time of initiation of antitumor treatment other than the study treatment or the last performance status assessment while on study treatment.
- Time to definitive performance status worsening: Data from surviving subjects who do not have definitive performance status worsening will be censored at the earliest of the time of initiation of antitumor treatment other than the study treatment or the last performance status assessment while on study treatment.

9.2. Analysis Plan

9.2.1. 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, allocated study drug assignment, actual study drug assignment, the longest duration of study drug treatment, and the reason for discontinuing study treatment. Available information on subjects who were screened or registered but not treated will be listed separately. A table will be created summarizing these categories in terms of number and percent for the full-analysis set.

Subject baseline characteristics will be listed and summarized by treatment arm for the full-analysis and responding analysis sets. As appropriate for the specific variable, subject baseline characteristics acquired in Study GS-US-312-0116 will be referenced in Study GS-US-312-0117. Subject characteristics between Arm A and Arm B may be compared using the Wilcoxon rank-sum test for continuous variables and the Fisher's exact test for categorical variables. Similarly, within each arm, subject characteristics between GS-US-312-0116 and GS-US-312-0117 may also be compared.

9.2.2. Efficacy Analyses

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

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

The Cox regression approach will be used to explore the influence of the primary study stratification factors and other baseline characteristics on PFS and OS. The stratification variables from the primary study and additional baseline subject characteristics may be included as covariates, focusing on those with expected prognostic significance. For the Cox regression modeling, a stepwise selection process will be applied to these variables to identify the final subset of relevant factors. Each prognostic factor will be preliminarily evaluated in the Cox regression model. Only the variables significant at the 0.20 level will be considered to build the multivariate model. A forward selection process will be applied to these variables to identify the final subset of relevant factors. .

9.2.2.2. 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 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.

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

9.2.2.3. Continuous Endpoints

Changes in lymph node area and changes in performance status, PI3K/AKT/mTOR pathway activation, and plasma chemokines/cytokines will be assessed by treatment group. Both

changes from baseline to each subsequent timepoint and best overall on-study changes will be analyzed using appropriate methods (eg, analysis of covariance [ANCOVA] or paired t-tests). Means and standard errors will be presented.

9.2.2.4. Health-Related Quality of Life and Performance Status

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

Because a significant portion of the study subjects will have CLL disease progression during the course of the study and no HRQL or performance status data will be collected after disease progression, the duration of data collection for these variables will vary among the study subjects. Hence, at each HRQL or performance status assessment timepoint, changes from baseline in HRQL parameters or in performance status in the 2 treatment groups will be described by treatment group. considering both: 1) all subjects in the evaluable analysis sets for HRQL or performance status with the worst score assigned to those subjects who have progressed at the time of the analysis, and 2) all subjects in the evaluable analysis sets for HRQL or performance status who have not progressed at the time of the analysis. Subjects who are lost-to-follow-up without disease progression will be excluded, ie, missing data will not be imputed. In addition, Kaplan-Meier methods will be used for each of the FACT-Leu subscale scores, assessing time to changes in each variable by increments or decrements of 10%, 20%, and 40% from baseline. Similarly Kaplan-Meier methods will be used assessing time to definitive performance status improvement or worsening from baseline. For these analyses, medians, ranges, and corresponding 95% CIs for each treatment group will be presented. In the analyses of FACT-Leu data, particular focus will be placed on changes in subject reports relating to CLL (focusing specifically on fever, chills, night sweats, lymphadenopathy, and fatigue).

9.2.3. Exposure and Safety Analyses

9.2.3.1. Treatment Administration and Study Drug Compliance

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

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

9.2.3.2. GS-1101 Plasma Concentrations

Bioanalytical analyses will performed independently so that the study team and investigators will not have knowledge of data from individual subjects. GS-1101 plasma concentrations immediately pre-dose and at 1.5 hours after administration of the dose of study drug at each relevant clinic visit will be summarized by treatment and visit using descriptive statistics.

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

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

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

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

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

9.2.3.4. Adverse Events

All adverse events will be listed. The focus of adverse event summarization will be on treatment-emergent adverse events. A treatment-emergent adverse event is defined as an adverse event that occurs or worsens in the period from the first dose of study treatment to 30 days after the last dose of study treatment. Adverse events that occur before the first dose of study treatment or >30 days after the subject has been discontinued from study treatment will be included in data listings.

Adverse events will be classified using MedDRA (http://www.meddramsso.com) with descriptions by System Organ Class, High-Level Group Term, High-Level Term, Preferred Term, and Lower-Level Term. The severity of adverse events will be graded by the investigator according to the CTCAE, Version 4.03 (*http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf*), whenever possible. If a CTCAE criterion does not exist for a specific type of adverse event, the grade corresponding to the appropriate adjective will be used by the investigator to describe the maximum intensity of the adverse event: Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), Grade 4 (life threatening), or Grade 5 (fatal). The relationship of the adverse event to the study drug will be categorized as related or unrelated.

Treatment-emergent adverse events will be summarized by treatment arm and by visit. Summary tables will be presented to show the number of subjects reporting treatment-emergent adverse events by severity grade and corresponding percentages. A subject who reports multiple treatment-emergent adverse events within the same Preferred Term (or

System Organ Class) is counted only once for that Preferred Term (or System Organ Class) using the worst severity grade. Adverse event descriptions will be presented 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 adverse events:

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

Separate listings and summaries will be prepared for long-term follow-up safety data (see Section 6.2.18).

9.2.3.5. 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 has been discontinued from study treatment will be included in data listings.

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

Hematological and serum biochemistry and their changes from baseline will be summarized by treatment arm and by visit. Summary tables will be presented for each relevant assay to show the number of subjects by CTCAE severity grade with corresponding percentages. For parameters for which a CTCAE scale does not exist, the frequency of subjects with values below, within, and above the normal ranges will be summarized. Subjects will be characterized only once for a given assay, based on their worst severity grade observed during a period of interest (eg, during the study or from baseline to a particular visit).

Shift tables for hematology and serum biochemistry will also be presented by showing change in CTCAE severity grade from baseline to 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.

9.2.3.6. Oxygen Saturation Values

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

9.2.4. Other Analyses

9.2.4.1. Between-Study Comparisons

It is expected that patients with a progressive malignancy like CLL will normally fare better with an earlier therapy than with a later therapy. However, if the converse situation proves true – eg, if an investigational treatment (GS-1101) administered later shows similar or greater benefit than a standard treatment (rituximab) administered earlier – strong evidence of investigational drug effect is demonstrated. Evaluating data derived from the same study subjects during their sequential participation in 2 clinical trials offers unique analytical challenges. However, in this integrated Phase 3 study program, it is likely that comparing baseline characteristics and outcomes among Arm B subjects participating in Study GS-US-312-0116 and Study GS-US-312-0117 will be informative. Such an evaluation characterizes how the subjects and the CLL disease process change with time and treatment. In addition, such an analysis provides relevant supporting information documenting the benefits of single-agent GS-1101 relative to single-agent rituximab in the same subjects.

Accordingly, the subject baseline characteristics at the start of Study GS-US-312-0116 relative to those at the start of Study GS-US-312-0117 will be evaluated. Subject baseline characteristics between the studies may be compared using the Wilcoxon rank-sum test for continuous variables and the Fisher's exact test for categorical variables.

Time-to-event efficacy variables (eg, PFS, TTR, DOR, TTF, time to performance status, or HRQL changes) will be evaluated using the paired Prentice-Wilcoxon test, comparing results in Study GS-US-312-0116 to those in Study GS-US-312-0117 among subjects who participate in Arm B of both studies. Within each study period, medians, ranges, hazard ratios and corresponding 95% CIs will be presented using Kaplan Meier methods. As appropriate, Cox regression techniques may be used to explore the influence of baseline characteristics on treatment differences when comparing these outcomes between the studies. For categorical variables (eg, ORR, lymph node response rate, splenomegaly response rate, hepatomegaly response rate), the Wilcoxon signed-rank test will be employed to compare outcomes between Study GS-US-312-0116 and Study GS-US-312-0117 for Arm B subjects. For all analyses, odds ratios and the corresponding 95% CIs will be presented. Differences between studies for Arm B subjects relating to continuous variables (eg, percentage changes

in lymph node area; changes in performance status, PI3K/AKT/mTOR pathway activation and plasma chemokines/cytokines) will be analyzed using appropriate methods (eg, analysis of covariance [ANCOVA] or paired t-tests). Means and standard errors will be presented. As appropriate, the potential influence of subject baseline characteristics on treatment effects may be explored with multiple logistic regression techniques.

9.2.4.2. Health Care Resource Utilization

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

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

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

The perspective of this analysis will be that of the third-party payer(s) and the hospital over a lifetime horizon in the base case. The costs will be described relative to the health care findings as measured by duration of tumor control, the symptom-free survival period, life-years, utility outcomes, or other measure of appropriate clinical benefits. In order to facilitate the calculation of utilities for use in the cost effectiveness analyses, the health status of subjects will be evaluated using PFS, Karnofsky performance status, FACT-Leu, and EQ-5D.

9.2.4.3. Data Explorations

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

9.3. Sample Size

The sample size for this extension study is not based upon a formal statistical hypothesis. The upper bound of the sample size in this study is determined by the sample size of the preceding primary study (Study GS-US-312-0116) in which ~160 subjects (~80 per arm) are expected to be enrolled. It is estimated that this extension study (Study GS-US-312-0117) will have a total GS-1101-treated N~130 (assuming a ~10% dropout rate during Study GS-US-312-0116 and a further ~10% dropout rate in the transition from the primary study to the extension study).

9.4. Timing of Analyses

9.4.1. Interim Analysis

The DMC will have access to serious adverse events requiring expedited reporting and will be provided with accumulating safety data on a regular basis. Interim safety reviews will be conducted by the DMC in conjunction with safety reviews of the primary clinical trial (Study GS-US-312-0116). Thus, interim safety reviews will be performed by the DMC at intervals of ~6 months; the specific frequency of these reviews will depend upon the rate at which the trials are enrolled, the nature of any emerging safety signals, and monitoring recommendations from the DMC. At each review, all available safety data will be summarized and evaluated.

An interim efficacy analysis of this clinical trial (Study GS-US-312-0117) is planned that take place at the time of the final analysis of the primary study (Study GS-US-312-0116). The intent is to provide the data from this extension study in support of regulatory review of data from the primary study. The blind will be broken to the study team at Gilead Sciences for analysis purposes. However, the study will be continued to obtain further follow-up efficacy and safety information; individual subjects, caregivers, and site personnel will not be informed of the treatment assignments until the implications of revealing such data for the overall GS-1101 study program have been determined.

9.4.2. Final Analysis

An additional, final analysis of efficacy and safety may be performed to satisfy regulatory requirements and to perform long-term efficacy, safety and OS follow-up. The timing of this analysis is expected to occur within 36 months of accrual of the final subject to Study GS-US-312-0117.

10. RESPONSIBILITIES

10.1. Investigator Responsibilities

10.1.1. Compliance with Ethical and Regulatory Guidelines

The investigator will ensure that this study is conducted in accordance with the principles of the "Declaration of Helsinki" (as amended in Edinburgh, Tokyo, Venice, Hong Kong, and South Africa), with ICH guidelines, or with the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the study subject. For studies conducted under a United States Investigational New Drug (IND) application, the investigator will ensure adherence to the basic principles of GCP as outlined in 21 CFR 312, subpart D, "Responsibilities of Sponsors and Investigators," 21 CFR, part 50, 1998, and 21 CFR, part 56, 1998.

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

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

10.1.2. Institutional Review Board/Independent Ethics Committee

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

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

The investigator shall submit a progress report, at least once yearly, to the IRB/IEC, and must provide a copy to Gilead Sciences. As soon as possible after completion or termination of the study, the investigator will submit a final report to the IRB/IEC and to Gilead Sciences. This

report should include the dates of initiation and completion of the trial, a description of any changes in study procedures or amendments to the protocol, any deviations from the protocol, the number and type of subjects evaluated, the number of subjects who discontinued (and the reasons for discontinuation), the number of subjects who completed the trial, and the results of the trial, including a description of any adverse events.
Gilead Sciences will assist the investigator in the preparation of this report, as needed.

10.1.3. Informed Consent

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

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

10.1.4. Confidentiality

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

The investigator agrees that all information received from Gilead Sciences, including but not limited to the GS-1101 investigator brochure, this protocol, eCRFs, the investigational new drug, and any other study information, remain the sole and exclusive property of Gilead Sciences during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from Gilead Sciences. The investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the study site to any third party or otherwise into the public domain.

10.1.5. Study Files and Retention of Records and Biological Samples

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

The investigator's study file will contain the protocol/amendments, eCRF and query forms, the IRB/IEC and governmental approval with correspondence, informed consent, drug records, staff curriculum vitae and authorization forms, and other appropriate documents and correspondence.

The required source data referenced in the monitoring plan for the study, and should include sequential notes containing at least the following information for each subject:

- Subject identification (name, date of birth, gender)
- Documentation that subject meets eligibility criteria, eg, history, physical examination, and confirmation of diagnosis (to support inclusion and exclusion criteria)
- Participation in trial (including trial number)
- Trial discussed and date of informed consent
- Dates of all visits
- Documentation that protocol-specific procedures were performed
- Results of efficacy parameters, as required by the protocol
- Start and end date (including dose regimen) of trial medication (including relevant drug dispensing and return information)
- Record of all adverse events and other safety parameters (including start and end date, causality and intensity)
- Concomitant medication (including start and end date and dose if relevant dose changes occur)
- Date of trial completion and reason for discontinuation, if applicable

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

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

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

Biological samples retained by the investigator will be stored and maintained by the investigator until notification is received from Gilead Sciences that the retained samples and records no longer need to be retained. The investigator must obtain written permission from

Gilead Sciences before disposing of any retained samples. The investigator should promptly notify Gilead Sciences in the event of accidental loss or destruction of any study samples. With the permission of Gilead Sciences, the retained samples may be transferred to an acceptable designee, such as another investigator, another institution, a contract storage site, or to Gilead Sciences.

10.1.6. Case Report Forms

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

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

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

10.1.7. Drug Accountability

As described in the relevant section (see Section 5.2.7), the investigator is responsible for ensuring adequate accountability of all used and unused investigational medicinal product, placebos, and comparators. This responsibility includes acknowledgment of receipt of each shipment of study product (quantity and condition), subject dispensing records, and returned or destroyed study product. Dispensing records will document quantities received from Gilead Sciences and quantities dispensed to subjects, including lot number, date dispensed, subject identifier number, subject initials, and the initials of the person dispensing the medication.

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

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

10.1.8. Inspections

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

10.1.9. Protocol Compliance

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

10.2. Sponsor Responsibilities

10.2.1. Protocol Modifications

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

10.2.2. Communications with Regulatory Authorities

Gilead Sciences, working either directly or through designees, will assume responsibility for regulatory interactions with relevant regulatory authorities. Gilead Sciences will maintain an IND for GS-1101 in support of the study in the United States and will maintain similar regulatory applications with other regulatory authorities, as required for conduct of the study. In fulfilling this responsibility, Gilead Sciences (or a designee) will collect, assemble, and communicate all required regulatory documents (eg, Form FDA 1572, investigator financial disclosure forms, protocol and protocol amendments, investigator brochures, informed consent documents, annual reports) as required by regulation. Gilead Sciences (or a designee) will also assume responsibility for adverse event reporting to regulatory authorities as described in Section 8.7.2.

10.2.3. Data Management

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

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

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

10.2.4. Study Reporting and Publication

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

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

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

Investigators should not present or publish the data from the individual sites of this study without agreement among the principal investigators and Gilead Sciences. However, 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 the results of the trial if either of the following conditions is met:

- The results of the study in their entirety have been publicly disclosed in an abstract, manuscript, or presentation form by Gilead Sciences or with the consent of Gilead Sciences; or
- The primary clinical trial (Study GS-US-312-0116) and this companion extension trial (Study GS-US-312-0117) have been closed at all study sites for ≥2 years.

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

The investigator will submit to Gilead Sciences any proposed publication or presentation along with the respective scientific journal or presentation forum 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. If deemed necessary by Gilead Sciences, the investigator also agrees to withhold publication or presentation for an additional 60 days in order to obtain patent protection.

10.3. Joint Investigator/Sponsor Responsibilities

10.3.1. Access to Information for Monitoring

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

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

10.3.2. Access to Information for Auditing or Inspections

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

10.3.3. Public Notification of Study Conduct

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

10.3.4. Study Discontinuation

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

10.4. Study Committees

10.4.1. Study Steering Committee

A study steering committee (SSC) will be responsible for assisting Gilead Sciences with protocol development, review of any study amendments, coordination of study conduct, interpretation of data, and presentation and publication of study results. The SSC comprises the Gilead Sciences medical monitor for the study, the Gilead Sciences study director, and several clinicians with expertise in the care of subjects with CLL. Other specialists may be

invited to participate as members of the SSC at any time if additional expertise is desired. Academic SSC members may be involved in accruing subjects to the study. The Gilead Sciences study director serves as the chair of the SSC. It is expected that the members of the SSC will be the same as those for the SSC of the primary clinical trial (Study GS-US-312-0116).

10.4.2. Data Monitoring Committee

A DMC, operating autonomously from Gilead Sciences, the clinical investigators, and the SSC, will be responsible for providing independent recommendations to Gilead Sciences about evolving risk-benefit observed in the course of the study and any modifications required during the course of the study. The DMC will consist of a biostatistician and ≥2 physicians experienced in treating patients with lymphoid malignancies. The DMC will be chaired by one of these individuals. DMC members must not be actively involved in study design, conduct, or subject accrual and must not have financial, proprietary, professional, or other interests that may affect impartial, independent decision-making. Specialists may be invited to participate as non-voting members at any time if additional expertise is desired. The DMC will formally interact with the external SSC members through the sharing of meeting minutes. Informal interactions between the DMC and external SSC members will be limited. The DMC will operate under a charter developed as a collaborative document between Gilead Sciences and the DMC. It is expected that the members of the DMC will be the same as those for the primary study (Study GS-US-312-0116).

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

- Reviewing the general progress of the study as regards subject accrual, study conduct, and protocol violations
- Examining accumulated safety, efficacy, and other relevant data at prespecified points during the course of the study
- Reviewing major study design modifications prior to implementation of those modifications
- Making recommendations concerning continuation, modification, interruption, or termination of each study
- Advising the company on changes to informed consent documents
- Proposing updates to the DMC monitoring plan, changes in the DMC membership, actions to be taken relating to conflict of interest or confidentiality breaches, the need for additional expertise during DMC deliberations, revisions to the DMC charter, or alterations in the support provided to the DMC
- Providing expert advice to the Gilead Science medical monitor on an ad hoc basis regarding matters such as safety concerns or diagnostic evaluations in individual subjects

Based on the results of its deliberations during the course of the study, the DMC can recommend appropriate actions (eg, continuation of the study unchanged, continuation of the study with modifications in design or monitoring plan, interruption of study accrual, study termination).

10.4.3. Independent Review Committee

An IRC will be established to provide a blinded review of radiographic data and pertinent clinical data in order to provide expert interpretation of changes in tumor status. The IRC will include ≥1 independent board-certified radiologist and ≥1 independent board-certified hematologist or oncologist, and will be managed by a CRO selected by Gilead Sciences. The review of radiographic and clinical data by the IRC will be performed on an ongoing basis. The specifics of the IRC's processes and reading methods will be described in an independent review charter developed by the contracted imaging facility in conjunction with Gilead Sciences. The same organization that is providing IRC services for Study GS-US-312-0116 will provide IRC services for this study.

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12. APPENDICES

Appendix 1. Investigator Signature Page

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

STUDY ACKNOWLEDGEMENT

A Phase 3, Double-Blind Extension Study Evaluating the Efficacy and Safety of Two Different Dose Levels of Single-Agent GS-1101 (CAL-101) as Therapy for Patients with Previously Treated Chronic Lymphocytic Leukemia

GS-US-312-0117 Original Protocol, 23 January 2012

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

PPD

Gilead Sciences Study Director

PPD

Signature

23 January 2012

Date

INVESTIGATOR STATEMENT

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

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

Principal Investigator
Printed Name

Signature

Date

Site Number

Appendix 2. Functional Assessment of Cancer Therapy: Leukemia (FACT-Leu)

FACT-Leu (Version 4)

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

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

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

19 November 2007
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FACT-Leu (Version 4)

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

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

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

FACT-Leu (Version 4)

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

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

Appendix 3. Performance Status Scoring System

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

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

EuroQoL-5 Dimensions (EQ-5D)

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

Mobility

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

Self-Care

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

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

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

Pain/Discomfort

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

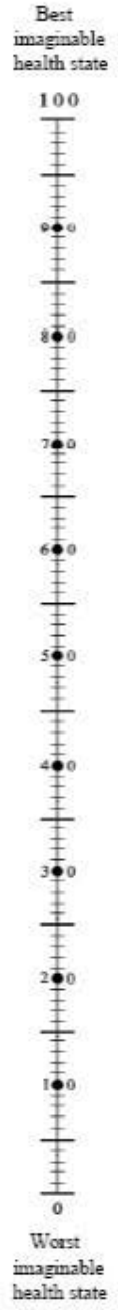
Anxiety/Depression

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

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

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

Your own health state today



Appendix 5. Cockcroft-Gault Method for Estimating Creatinine Clearance

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

Cockcroft-Gault Formulas for Calculating Estimated Creatinine Clearance

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

Abbreviation: eC_{cr}=estimated creatinine clearance

Appendix 6. Cumulative Illness Rating Scale (CIRS)

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

CIRS List of Comorbid Conditions

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

Organ System	Diagnosis	Comment
Respiratory	Asthma	
	Chronic obstructive pulmonary disease	
	Cystic fibrosis	
	Emphysema	
	Chronic bronchitis	
	Chronic pleural effusions	
	Pulmonary fibrosis	
	Sarcoidosis	
	Pulmonary embolism	
	Pulmonary arterial hypertension	
	Lung cancer	
	Other chronic respiratory condition:	
	Other chronic respiratory condition	
Ophthalmological/ otolaryngological	Loss of vision	
	Glaucoma	
	Cataract	
	Macular degeneration	
	Diabetic retinopathy	
	Loss of hearing	
	Otitis/chronic otitis	
	Vestibular impairment	
	Vertigo	
	Temporomandibular disorder	
	Sialolithiasis	
	Chronic sinusitis	
	Laryngeal/pharyngeal disorders	
	Other chronic ophthalmological or otolaryngological condition:	
Upper gastrointestinal	Chronic esophagitis	
	Dysphagia	
	Achalasia	
	Gastroduodenal ulceration	
	Celiac disease	
	Irritable bowel syndrome	
	Short bowel syndrome	
	Malnutrition	
	Malabsorption	
	Small bowel obstruction	
	Hernia	
	Pseudomyxoma peritonei	
	Upper gastrointestinal cancer	
	Other chronic upper gastrointestinal condition:	
	Other chronic upper gastrointestinal condition:	
Lower gastrointestinal	Diverticulitis	
	Inflammatory Hernia bowel disease	
	Volvulus	
	Colon cancer	
	Other chronic lower gastrointestinal condition:	
	Other chronic lower gastrointestinal condition:	
Hepatic/ pancreatic	Chronic hepatitis or hepatic cirrhosis	
	Biliary obstructive disorders	
	Pancreatitis	
	Hepatic, biliary, or pancreatic cancer	
	Other chronic hepatic or pancreatic condition:	
	Other chronic hepatic or pancreatic condition:	

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

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

Abbreviation: CIRS=Cumulative Illness Rating Scale

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

CIRS Rating Scale

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

Abbreviation: CIRS=Cumulative Illness Rating Scale

Appendix 7. Schedule of Study Procedures

Period	Screen	Treatment																Follow-up	
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16+	End of treatment	Post-therapy	Long-term
Week	-4	0	2	4	6	8	10	12	16	20	24	30	36	42	48	Q12 Weeks			
Study Day	Within -28 Days	1	15	29	43	57	71	85	113	141	169	211	253	295	337			Within +30 days	To +5 years
Visit Window			±2	±2	±2	±2	±2	±2	±3	±3	±3	±3	±3	±3	±3	±7			
Informed consent	X																		
CIRS assessment	X																		
β-HCG (women of childbearing potential)	X	X															X		
CLL peripheral blood evaluation	X																X		
CLL serology	X																X		
IWRS	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X		
PPD																			
HRQL/healthy utility – FACT-Leu/EQ-5D		X	X	X	X	X		X	X	X	X	X	X	X	X	X	X		
Adverse events		X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	
Concomitant medications	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	
Performance status	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X		
Physical exam (includes nodes, liver, spleen)	X	X		X		X		X	X	X	X	X	X	X	X	X	X		
Oxygen saturation (by pulse oximetry)	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X		
Hematology	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Serum chemistry	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Circulating cells	X		X	X		X		X	X	X	X	X	X	X	X	X	X		
Biomarkers	X		X	X		X		X	X	X	X	X	X	X	X	X	X		
Serum Igs	X		X	X		X		X	X	X	X	X	X	X	X	X	X		
Study drug administration in clinic		X	X	X		X		X	X	X	X								
GS-1101 pharmacokinetics		X	X	X		X		X	X	X	X								
Study drug dispensing/accounting		X		X		X		X	X	X	X		X		X	X	X		
Radiology assessment (CT/MRI)	X					X			X		X		X		X	X[a]	X[a]		
Bone marrow biopsy/aspirate	X					X[b]			X[b]		X[b]		X[b]		X[b]	X[b]	X[b]		
Post-treatment CLL therapy																			X
Long-term follow-up																			X

a For follow-up visits after Week 96, CT or MRI is only required at the end-of-treatment visit.

b At baseline, to be performed at investigator discretion to determine extent of CLL involvement and bone marrow cellularity. Post-baseline, to be performed to confirm response category in subjects with potential CR by physical examination and radiological assessments.

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