CLINICAL STUDY PROTOCOL

Study Title:	A Phase 1b/2 Open-Label, Dose Escalation and Expansion Study Evaluating the Safety and Efficacy of Entospletinib (GS-9973) with Vincristine and Dexamethasone in Adult Subjects with Relapsed or Refractory Acute Lymphoblastic Leukemia (ALL)
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404
IND Number: **EudraCT Number:** **NCT:**	116416 2015-002768-18 02404220
Indication:	Acute Lymphoblastic Leukemia
Protocol ID:	GS-US-339-1560
Gilead Clinical Program Manager:	Name: PPD Telephone: PPD Email: PPD
Gilead Medical Monitor:	Name: PPD Telephone: PPD Email: PPD
Protocol Version/Date:	Original: 18 December 2014 Amendment 1: 18 June 2015 Amendment 2: 09 December 2015 Amendment 3: 21 November 2016 Amendment 4: 31 August 2017 Amendment 5: 13 April 2018

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

Study Title:	A Phase 1b/2, Open-Label, Dose Escalation and Expansion Study Evaluating the Safety and Efficacy of Entospletinib (GS-9973) with Vincristine and Dexamethasone in Adult Subjects with Relapsed or Refractory Acute Lymphoblastic Leukemia (ALL)
IND Number:	116416
EudraCT Number:	2015-002768-18
Study Centers Planned:	Approximately 20 sites in North America and Europe
Objectives:	The primary objective of this study is: • To evaluate safety of entospletinib (GS-9973) in combination with vincristine (VCR) and dexamethasone in adult subjects with previously treated relapsed or refractory B-cell lineage ALL The secondary objectives of this study are: • To determine the recommended dose of GS-9973 in combination with VCR and dexamethasone in adult subjects with previously treated relapsed or refractory B-cell lineage ALL • To evaluate the therapeutic response of GS-9973 in combination with VCR and dexamethasone in adult subjects with previously treated relapsed or refractory B-cell lineage ALL The exploratory objectives of this study are: PPD [redacted]

Study Design: This is an open-label, Phase 1b dose-escalation and Phase 2 expansion study evaluating the safety, efficacy, tolerability, and pharmacokinetics of GS-9973 in combination with VCR and dexamethasone.

There will be four dose levels in the dose escalation phase where cohorts of 3 to 6 subjects will sequentially enroll into one of the dose levels using a 3+3 dose escalation design. The starting dose level for the first cohort is defined as Dose Level 1.

Dose Level	GS-9973	Vincristine (VCR)
1	200 mg BID	0.5 mg per dose
2	400 mg BID	0.5 mg per dose
3	400 mg BID	1 mg per dose
4	400 mg BID	2 mg per dose

Dose Escalation: Induction (Lead-in, Cycle 1 and Cycle 2)

Lead-in (GS-9973 Monotherapy): Beginning on Day -7 of Lead-in, GS-9973 will be administered orally twice daily (BID) for 7 days as a single agent.

Cycle 1 and Cycle 2 (GS-9973, VCR, dexamethasone, CNS Prophylaxis):

GS-9973 will be continuously administered orally BID in combination with chemotherapy for the duration of the study treatment.

VCR will be administered on Days 1, 8, 15 and 22 of each 28-day cycle for Cycle 1 and Cycle 2 only.

Dexamethasone (20 mg twice daily for 4 days) will be administered orally during Cycle 1 on Days 8-11 and Days 22-25 and during Cycle 2 on Days 1-4 and Days 15-18.

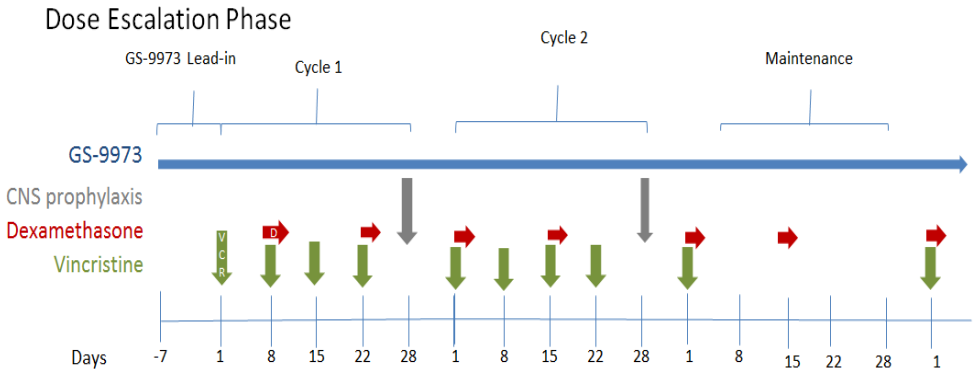
CNS prophylaxis per institutional standard will be given on Day 28 (±3 days) of Cycle 1 and Cycle 2.

Bone marrow (BM) aspirate/biopsy will be performed during screening (within 28 days prior to the start of study treatment), Cycle 1 on Day 8 and during both Cycle 1 and Cycle 2 on Day 28.

Imaging (computerized tomography [CT] with contrast or Positron Emission Tomography (PET) scan should be performed for subjects with extramedullary disease (EMD) if these are the only sites of evaluable disease (no BM involvement) to evaluate disease status and response, at screening, Cycle 1 Day 8 and Day 28, and Cycle 2 Day 28. Imaging will be evaluated using the NCCN guidelines version 2.2016 (Patients with no BM involvement and only EMD will not require BM aspirate/biopsy on cycle 1 day 8 and day 28, and cycle 2 day 28).

Subjects will continue on their assigned dose level throughout all cycles and through maintenance. Intra-subject dose escalations are not permitted. Dose modifications are not permitted during the GS-9973 Lead-in or Cycle 1 as this is used to assess dose limiting toxicities (DLT). Following the completion of Cycle 1, if a GS-9973 related AE of Grade ≥ 3 occurs, the subject will have GS-9973 held until the AE improves to Grade ≤ 1 and then may resume study therapy at the prior dose (or decreased by 1 dose level after discussion with Sponsor). For subjects assigned to Dose Level 1, the decreased dose of GS-9973 will be defined as 100 mg orally twice daily.

Dose Escalation treatment schedule is outlined in the schema below:



Dose Expansion:

At the time of this amendment, there have been no DLTs in the Phase 1 portion of the study. However, due to the low response rate to ENTO + vincristine + dexamethasone in relapsed/refractory ALL patients, it has been decided not to proceed with the dose expansion (Phase 2) portion of this trial. Prior to this amendment, dose expansion had been initiated at 400 mg BID, but was subsequently closed with no subjects enrolled.

Maintenance:

It is anticipated that most subjects who are transplant eligible will receive hematopoietic stem cell transplant (HSCT) or therapy with curative intent if a complete remission (CR) is reached. In the absence of a suitable alternative therapeutic option, subjects who obtain clinical benefit (at least partial response [PR]) after completing both cycles of induction therapy in dose escalation may continue GS-9973 at the assigned dose level during maintenance for up to 36 cycles. Subjects will continue GS-9973 and VCR at their assigned dose. GS-9973 will continue to be taken orally twice daily with VCR to be administered on Day 1 of each 28-day cycle and dexamethasone 20 mg total dose daily for 4 days (either 10 mg twice daily or 20 mg once daily) on Days 1-4 and Days 15-18 of each 28-day cycle.

Bone marrow evaluations and additional central nervous system (CNS) directed therapy can be performed as clinically indicated during maintenance.

Number of Subjects Planned:	Approximately 30
Target Population:	Adult subjects with relapsed or refractory B-cell lineage ALL
Duration of Treatment:	Subjects may continue receiving GS-9973 until refractory disease at the end of induction, relapsed disease, start of new therapy, unacceptable toxicity, withdrawal of consent by subject, or withdrawal from study by investigator.
Diagnosis and Main Eligibility Criteria: (see Protocol for Details)	**Inclusion Criteria** Subjects must meet all of the following inclusion criteria to be eligible for participation in this study: 1) ≥18 years of age 2) Previously treated ALL including Philadelphia chromosome (BCR-Abl) positive ALL who meet all of the following criteria: a) Diagnosis of precursor B-cell ALL based on flow cytometry and histology b) Previously treated subjects with primary refractory disease OR after first or subsequent relapse c) Subjects with >10% lymphoblasts in bone marrow or extramedullary disease (EMD) that is radiographically measureable and amenable to imaging studies and repeat biopsies d) Patients with Ph+ ALL must have failed treatment with at least one 2nd generation (eg. dasatanib) or 3rd generation (eg. ponatinib) tyrosine kinase inhibitor

3) Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2
4) Adequate organ function defined by the screening laboratory value inclusion and absence of known cardiac dysfunction
5) Required screening laboratory data (within 7 days prior to administration of GS-9973) (Table 4-1)
6) Discontinuation of all therapy (including radiotherapy, chemotherapy, tyrosine-kinase inhibitors [TKIs], immunotherapy, or investigational therapy) for the treatment of cancer as follows:
    a) At least 1 week or 5 half-lives (whichever is longer) from the last dose of prior anti-cancer therapy and the initiation of study therapy
    b) Exceptions or modifications to the above are as follows: Medications that are typically part of a maintenance therapy for ALL, such as glucocorticoids or mercaptopurine, may be administered up to 3 days prior to the first dose, except vinca alkaloids which must be discontinued at least 14 days prior to the start of study treatment. TKIs are not permitted to be continued at screening (eg, Gleevec). Subjects may receive hydroxyurea or leukapheresis if indicated for rapidly rising white blood cell count
    c) CNS prophylaxis should be dosed up at least one week prior to first dose of GS-9973
    d) For biologics (eg, monoclonal antibodies), washout period of at least 4 weeks or 5 half-lives (whichever is shorter) since the last dose
    e) If prior stem cell transplant, subject must be at least 100 days from stem cell infusion and off all systemic anti-graft versus host disease (GVHD) medications
    f) If prior donor lymphocyte infusion (DLI), subject must be at least 4 weeks from DLI and off all systemic anti-graft versus host disease (GVHD) medications and have no evidence of any infection
    g) If prior Chimeric Antigen Receptor (CAR) T-Cell Therapy, subject must be at least 4 weeks from CART infusion
7) All acute toxic effects of any prior antitumor therapy must be resolved to Grade ≤ 1 before enrollment, with the exception of alopecia (any grade permitted), or bone marrow parameters (any grades permitted)
8) For female subjects of childbearing potential, willingness to abstain from heterosexual intercourse or use a recommended method of contraception from the screening visit (Visit 1) throughout the study treatment period and to 30 days from the last dose of GS-9973 (See Appendix 5)

9) For male subjects 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 GS-9973 throughout the study treatment period and for 90 days following the last dose of GS-9973. Also, male subjects should refrain from sperm donation from the start of the GS-9973 throughout the study treatment period and for 3 months following the last dose of GS-9973

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

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

Exclusion Criteria

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

1) Diagnosis of mature B-cell ALL (Burkitt's leukemia), or lymphoid blast crisis of chronic myelogenous leukemia (CML)

2) A life threatening illness, medical condition or organ system dysfunction which, in the investigator's opinion, could compromise the subject's safety or interfere with the absorption or metabolism of GS-9973

3) Active or symptomatic central nervous system (CNS) disease

   For study purposes a subject will NOT be considered as having active CNS disease if the subject has documentation of prior CNS disease and has received treatment (IT or radiation) and are:

   a) asymptomatic for the last 28 days prior to screening, and

   b) has documented at least 2 negative cerebrospinal fluid (CSF) cytology (which must include 1 lumbar puncture [LP] within the study screening window)

4) Uncontrolled intercurrent illness including, but not limited to, unstable angina pectoris or psychiatric illness/social situations that would limit compliance with study requirements. Subjects with active infection are permitted to enroll provided that the infection is documented to be under control and after discussion with study Sponsor

5) History of myelodysplastic syndrome or solid organ transplantation

6) History of a non-lymphoid malignancy except for the following: adequately treated local basal cell or squamous cell carcinoma of the skin, cervical carcinoma in situ, superficial bladder cancer, asymptomatic prostate cancer without known metastatic disease and with no requirement for therapy or requiring only hormonal therapy and with normal prostate specific antigen for > 1 year prior to the start of GS-9973, or any other cancer that has been in complete remission without treatment for ≥ 5 years prior to enrollment
7) Known hypersensitivity or intolerance to any of the active substances or excipients in the formulations for GS-9973
8) Evidence of uncontrolled systemic bacterial, fungal, or viral infection at the start of GS-9973
Note: *Subjects with localized fungal infections of skin or nails are eligible. Subjects may be receiving prophylactic antiviral, antifungal, or antibacterial regimens (eg, anti-pneumocystis prophylaxis at the discretion of the investigator per institutional guidelines. If azoles are used for antifungal prophylaxis, subjects must be monitored for possible DDI with VCR*)
9) Ongoing drug-induced liver injury, chronic active hepatitis C (HCV), chronic active hepatitis B (HBV), HIV, alcoholic liver disease, non-alcoholic steatohepatitis, primary biliary cirrhosis, extrahepatic obstruction caused by cholelithiasis, cirrhosis of the liver, or portal hypertension
10) Prior allogeneic bone marrow progenitor cell transplant within 100 days or on active systemic immunosuppression for graft versus host disease (GVHD) treatment or prophylaxis within 28 days prior to enrollment
11) Active (symptomatic or requiring current medical treatment within 28 days prior to the start of study treatment) for GVHD
12) Ongoing immunosuppressive therapy other than corticosteroids (corticosteroids being used for GVHD treatment are not permitted).
Note: *Subjects may use topical, enteric, inhaled, or systemic corticosteroids as therapy for manifestations of comorbid conditions*
13) Current therapy with proton pump inhibitors (PPI) must be avoided (as there is the potential to interfere with GS-9973 absorption)
Note: *H2 blockers and antacids will be allowed for the use during the study*
14) Pregnancy or breastfeeding
15) Ongoing active pneumonitis
16) Concurrent participation in an investigational drug trial with therapeutic intent defined as prior study therapy within 28 days prior to GS-9973 administration
17) Ongoing or recent treatment with an excluded medication, as defined in Section 5.3, Excluded Medication

Test Product, Dose, and Mode of Administration:	Study drug, GS-9973 is available as 200 mg strength tablets. 200 mg or 400 mg of GS-9973 will be administered orally twice daily (BID) while in a fasted state. Intravenous administration of up to 2 mg Vincristine (VCR) per protocol schedule. Oral administration of 20 mg dexamethasone twice daily, taken for up to two courses of 4 days each in both Cycle 1 and Cycle 2 and per protocol during Maintenance. CNS prophylaxis regimen per institutional standard, given once at the end of each cycle during Induction period. Please refer to the package inserts for standard of care products for more information.

Criteria for Evaluation:

Safety: The primary endpoint is safety. Safety will be evaluated by the occurrence of adverse events and laboratory abnormalities defined as dose limiting toxicities (DLTs) and also the Occurrence of AEs and laboratory abnormalities not defined as DLTs.

Efficacy: Efficacy endpoints are considered secondary and will include:

- Overall Remission (CR or CRi) rate at end of induction - defined as the proportion of subjects who achieve a complete remission (CR) or complete remission with incomplete hematologic recovery (CRi) at end of induction
- Complete remission (CR) rate at end of induction
- Partial response (PR) rate at end of induction - defined as the proportion of subjects who achieve a partial response of marrow (as defined in Appendix 4 of the protocol) or by imaging criteria for patients with extramedullary disease (NCCN guidelines version 2.2016) as the best response.
- Overall Response (CR, CRi, or PR) rate at end of induction - defined as the proportion of subjects who achieve a complete remission (CR), complete remission with incomplete hematologic recovery (CRi) or partial response (PR) at end of induction

Exploratory Endpoints

Pharmacokinetics	Plasma drug concentrations will be analyzed to evaluate pharmacokinetics of GS-9973

Statistical Methods:

Appropriate data analysis sets will be defined. The full-analysis set will include data from all subjects who receive at least 1 dose of study treatment. DLT analysis set includes subjects in Full Analysis Set (FAS) with sufficient drug exposure (Section 3.3.1) or who experience a DLT during the DLT assessment window.

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

Based on the FAS, information regarding study treatment administration, study drug compliance, safety variables, and post-study therapies will be described and summarized. Study drug plasma concentrations, and will also be described and summarized using pharmacokinetics set.

Sample Size Calculation

Sequential dose-escalation is consistent with usual oncologic paradigms for dose ranging. The intent is to limit the number of subjects who are exposed to excessively toxic doses of a drug in an early phase evaluation of an anticancer agent. The trial employs the standard National Cancer Institute (NCI) definition of MTD (starting dose associated with DLT in < 33.3% of subjects during the DLT assessment window) to determine dose escalation. The cohort size and dose-escalation rules establish a low probability of increasing the dose if the true rate of DLT is high while there is a high likelihood of escalating or proceeding to the next cohort of the study if the true underlying probability of DLT is low. For example, if the true underlying probability of DLT is low (e.g, < 10%) at the current dose level, there is a high probability (> 0.91) of dose escalation to the next dose level. Conversely, if the true underlying proportion of DLT is high (e.g, > 60%) at the current dose level, there is a low probability (< 0.08) of escalation to the next dose level.

Assuming that 4 planned dose levels are tested for escalation and 3, 3, 6 and 6 subjects are tested at each dose level, respectively (18 subjects for escalation), and assuming 10% subjects are not evaluable during dose escalation, 20 subjects will be enrolled during dose escalation.

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

GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

°C	degrees Celsius
°F	degrees Fahrenheit
AE	adverse event
ALC	absolute lymphocyte count
ALT	alanine aminotransferase
AM	Morning
ANC	absolute neutrophil count
ARA-C	Cytarabine-(Cytosine arabinoside)
AST	aspartate aminotransferase
ATP	adenosine triphosphate
AUC	area under the concentration versus time curve
AUCtau	area under the plasma concentration versus time curve over the dosing interval (tau)
BCR	B-cell receptor
BID	bis in die (twice a day)
BM	bone marrow
BUN	blood urea nitrogen
Cmax	maximum observed concentration of drug
CFR	(United States) Code of Federal Regulations
CI	confidence interval
CLL	chronic lymphocytic leukemia
cm/s	centimeter per second
CNS	central nervous system
CR	complete remission
CRi	Morphologic CR with incomplete blood count recovery
CRO	contract research organization
CSF	cerebrospinal fluid
CT	computed tomography
CTA	clinical trial application
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DLBCL	diffuse large B-cell lymphoma
dL	Deciliter
DLT	Dose limiting toxicities
DNA	deoxyribonucleic acid
DOR	duration of response
DSPH	Drug Safety and Public Health
EC	ethics committee
EC50	50% effective inhibitory concentration
ECG	Electrocardiogram

ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form(s)
EFS	event-free survival
EDC	electronic data capture
EOS	end of study
EU	European
EMD	extramedullary disease
ENTO	entospletinib (GS-9973)
FAS	Full analysis set
FDA	(United States) Food and Drug Administration
FL	follicular lymphoma
FSH	follicle stimulating hormone
g	Gram
GCP	Good Clinical Practice (Guidelines)
G-CSF	granulocyte colony-stimulating factor
GM-CSF	granulocyte-macrophage colony-stimulating factor
GSI	Gilead Sciences, Inc.
GVHD	Graft versus host disease
h, hr	Hour
HBc	hepatitis B core
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
β-HCG	beta human chorionic gonadotropin
HSCT	hematopoietic stem cell transplant
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HL	Hodgkin lymphoma
IB	investigator's brochure
IC	immune-complex
IC50	concentration necessary to achieve 50% inhibition of target
ICF	informed consent form
ICH	International Conference on Harmonisation
ID	Identification
IEC	independent ethics committee
IND	Investigational New Drug (Application)
iNHL	indolent non-Hodgkin lymphoma
IRB	institutional review board
ITAM	immunoreceptor tyrosine-based activation motifs
IXRS	Interactive Voice/Web Response System
kg	Kilogram
L	Liter

LD	longest diameter
LDH	lactate dehydrogenase
LP	lumbar puncture
MAPK	mitogen-activated protein kinase
MCL	mantle cell lymphoma
mg	Milligram
mL	Milliliter
mm	Millimeter
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
MZL	marginal zone lymphoma
NCI	National Cancer Institute
ND	no disease
NE	not evaluable
ng	Nanogram
NHL	non-Hodgkin lymphoma
nM	Nanomolar
OS	overall survival
ORR	objective response rate
PBMC	peripheral blood mononuclear cells
PD	progressive disease
PFS	progression-free survival
Ph+	Philadelphia chromosome positive
PI	prescribing information
PI3K	phosphatidylinositol 3-kinase
PK	pharmacokinetic(s)
PM	Evening
PPD	product of the perpendicular diameters
PPI	proton pump inhibitor
PR	partial response
pSyk	phospho-spleen tyrosine kinase
QD	once-daily
REB	research ethics board
RFS	relapse-free survival
RNA	ribonucleic acid
SD	stable disease
SDD	Spray-dried dispersion
StD	standard deviation
SADR	serious adverse drug reactions
SAE	serious adverse event
SLL	small lymphocytic lymphoma

SOP	standard operating procedure
SPD	sum of the products
SPEP	serum protein electrophoresis
SUSAR	Suspected Unexpected Serious Adverse Reaction
Syk	spleen tyrosine kinase
Tmax	time (observed time point) of Cmax
T½	an estimate of the terminal elimination half-life of the drug, calculated by dividing the natural log of 2 by the terminal elimination rate constant (λz)
TKI	Tyrosine-kinase inhibitors
TTC	time to peripheral blast clearance
TNF	tumour necrosis factor
TNF-α	tumour necrosis factor-α
TTR	time to response
ULN	upper limit of the normal range
US	United States
VCR	Vincrsitine
WHO	World Health Organization
WM	Waldenström macroglobulinemia
αIgM	anti-IgM
β	population mean slope
λz	terminal elimination rate constant, estimated by linear regression of the terminal elimination phase of the concentration of drug versus time curve

1. INTRODUCTION

1.1. Acute Lymphoblastic Leukemia

Acute lymphoblastic leukemia (ALL) is a biologically heterogeneous disease of the hematopoietic system characterized by clonal accumulation and expansion of immature lymphoid cells (B or T cells) either in the bone marrow (ALL) or presenting as a mass lesion (lymphoblastic lymphoma, LBL). There are an estimated 6,000 new cases of ALL diagnosed annually in the USA {American Cancer Society 2014}. While the majority of cases of ALL occur in children, the majority of deaths (approximately 4/5) occur in adults {American Society of Clinical Oncology (ASCO) 2014}. Survival in childhood ALL currently approaches 90%, but results of therapy in adults remains unsatisfactory {Bassan 2011, Hunger 2012}. The long-term survival of adults with ALL who are intensively treated is about 40%. However, despite hematologic remissions being obtained in up to 90% of subjects, after further consolidation therapy and maintenance chemotherapy, less than half will have long-term leukemia-free survival; the majority of adults with ALL will ultimately relapse. In addition, up to 20 % will have primary resistant disease {Goldstone 2008}.

Treatment for ALL typically spans 2 to 2.5 years, and comprises of three phases: induction of remission, intensification/consolidation, and maintenance/continuation therapy {Pui 2008}. Most of the drugs currently used in the treatment of ALL were developed before 1970 and while few of the individual components of therapy have been evaluated rigorously in randomized trials, their dosages and schedule in combination have been empirically optimized over time based on risk assessment, biological features, response to treatment, and pharmacodynamic and pharmacogenomics findings in subjects {Inaba 2013}. The primary goal of induction therapy is to achieve an initial complete remission (CR), defined as eradication of all detectable leukemia cells (< 5%blasts) from the bone marrow and blood and the restoration of normal hematopoiesis (> 25% percent cellularity and normal peripheral blood counts) {National Comprehensive Cancer Network (NCCN) 2014}. Subjects with BCR-Ab1-positive disease have poor prognoses but benefit from early treatment with tyrosine-kinase inhibitors (imatinib, dasatinib), which improve complete remission rates and event-free survival when added to combination chemotherapy regimens {Schultz 2009}. Subjects who do not achieve a CR with initial induction therapy are considered to have resistant disease. Consolidation and maintenance/continuation therapy are meant to eradicate residual leukemic cells without additional cytotoxic therapy, virtually all subjects will relapse within weeks or months.

Because further intensification of existing chemotherapy regimens is unlikely to substantially improve survival, new agents and treatment regimens should be investigated. In addition, treatment for relapsed disease, defined as the reappearance of leukemia cells in the bone marrow or peripheral blood any time after the attainment of a complete remission, remains generally unsuccessful. Emerging evidence suggests that chemoresistance is frequently driven by subpopulations of cells harboring specific genetic alterations that confer resistance. This highlights the need for novel therapeutic strategies either alone or in combination with existing treatment regimens to improve on the currently dismal prognosis for relapsed/refractory ALL subjects, particularly in the adult age group.

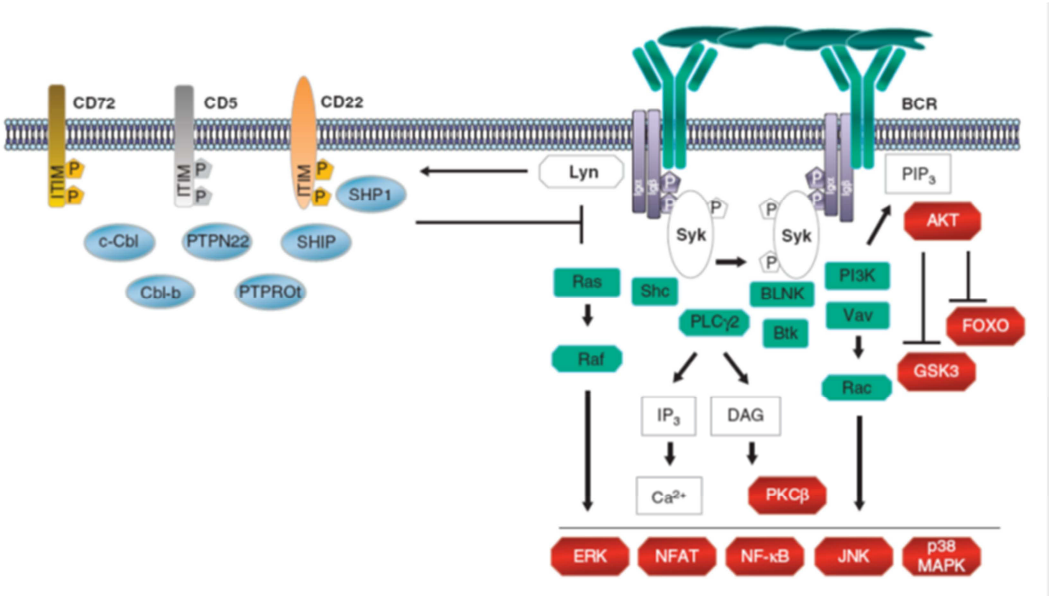
1.2. Spleen Tyrosine Kinase

1.2.1. Spleen Tyrosine Kinase in Hematologic Malignancies

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

Recent studies have suggested a role for the dysregulation of the tyrosine kinase Syk in B-cell malignancies. Syk is expressed in B-cells and is essentially involved in multiple signal transduction pathways downstream of the B-cell receptor (BCR). In this process, Syk trans-autophosphorylates, and activates effector molecules such as PLCy, PI3K, and mitogen-activated protein kinase (MAPK) and their associated signaling pathways, to induce a variety of responses including: proliferation, survival, differentiation, anergy, and apoptosis (Figure 1-1). In B-cells, the Syk inhibitor GS-9973 effectively blocks BCR-mediated activation and proliferation (data on file). Additionally, the BCR can deliver antigen-independent signals that have also been postulated to require Syk activity. Both antigen-dependent and independent signals have been implicated in the pathogenesis of several common B-cell malignancies, including chronic lymphocytic leukemia (CLL), diffuse large B cell lymphoma (DLBCL), follicular lymphoma (FL), mantle cell lymphoma (MCL) and marginal zone lymphoma (MZL). Importantly, signaling through the Syk-dependent pre-BCR and pre-BCR-independent pathways are required for the survival of pre-B lymphocytes and may contribute to the pathogenesis of B-cell lineage acute lymphoblastic leukemia (B-ALL) {Efremov 2011, Perova 2014}. As a result, inhibitors of Syk activity are an attractive therapeutic option for hematopoietic B-cell lymphomas and other Non-Hodgkin lymphoma (NHL) histologies where Syk inhibition would prevent B-cell receptor-mediated signaling and therefore the uncontrolled growth of lymphoma cells.

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



Source: {Efremov 2011}

1.2.2. Clinical Experience in Hematologic Malignancies treated with Syk Inhibitors

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

GS-9973 is currently in a Phase 2 clinical trial in subjects with relapsed or refractory CLL/NHL.

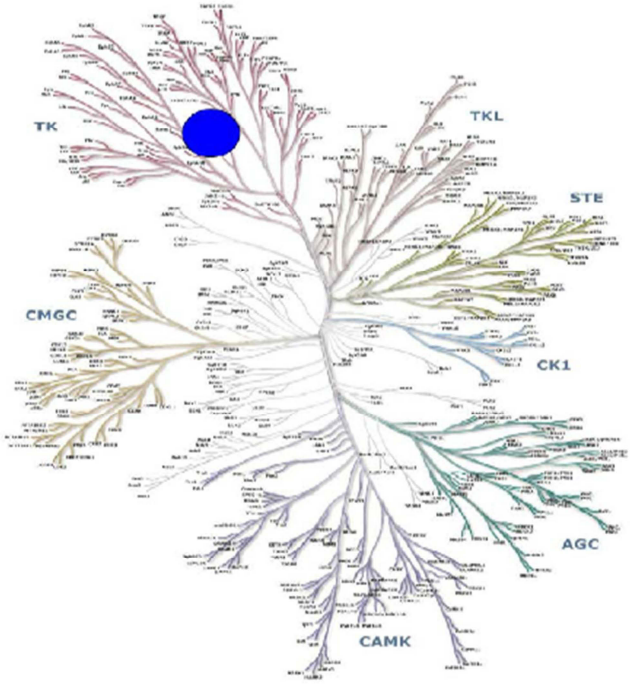
Subjects with relapsed or refractory chronic lymphocytic leukemia (CLL; n = 41) or non-Hodgkin's lymphoma (NHL; n = 104) were enrolled in a monotherapy trial of GS-9973. Subjects received 800 mg of GS-9973 twice daily. Initial data analysis has been completed for the CLL cohort and is ongoing in the MCL and FL cohorts. Efficacy outcomes have been reported in the CLL cohort (n = 41) and safety outcomes in all cohorts (N = 145). The primary end point was progression-free survival (PFS) rate at 24 weeks in subjects with CLL. PFS rate at 24 weeks is 69.8% (95% confidence interval [CI]: 50.9%, 82.6%). The objective response rate (ORR) was 56.1% (95% CI: 39.7%, 71.5%). Two subjects (4.9%) with stable disease achieved nodal response with persistent lymphocytosis. Forty-five subjects (31.0%) had serious adverse events (AEs). The most common treatment-emergent serious AEs included dyspnea, pneumonia, febrile neutropenia, and pyrexia. Common grade 3/4 lab abnormalities included neutropenia (14.5%) and reversible alanine aminotransferase (ALT)/aspartate aminotransferase (AST) elevations (14.5%). GS-9973 demonstrates clinical activity in subjects with relapsed or refractory CLL with acceptable toxicity.

1.3. Entospletinib (ENTO [GS-9973])

1.3.1. Nonclinical Pharmacology

GS-9973 is an adenosine triphosphate (ATP) competitive inhibitor of Syk with an IC50 of 8.5 ± 3.6 nM. GS-9973 binds in the ATP pocket of the Syk active site and disrupts the kinase activity of the enzyme. Kinase selectivity profiling showed a > 14-fold selectivity of GS-9973 for Syk versus 359 nonmutant kinases. Furthermore, there was < 50% binding of GS-9973 at 1 uM to any of a panel of 67 ion channels, transporters, and receptors. Therefore, GS-9973 demonstrated at least 14-fold selectivity against a total of 426 biological targets tested (See Figure 1-2).

Figure 1-2. GS-9973 Kinome Scan



The cellular activity of GS-9973 was evaluated in 2 anti-IgM (αIgM)-stimulated CD86 expression assays in human peripheral and mouse splenic B-cells. GS 9973 potently inhibited αIgM-stimulated CD86 expression with a mean EC50 of 125.0 ± 78.2 nM and 94.5 ± 19.6 nM in human peripheral and murine splenic B-cells, respectively. Additionally, GS 9973 was evaluated in vitro in an FcεRI-triggered αIgE stimulated β-hexosaminidase release assay in mouse bone marrow derived mast cell (BMMC) cultures. GS-9973 inhibited the FcεRI-stimulated hexosaminidase release into the media with a mean EC50 of 159.3 ± 14.8 nM. GS-9973 was evaluated in vitro in an immune-complex (IC) stimulated TNFα release assay in primary human monocytes. GS-9973 inhibited the IC stimulated TNFα release with a mean EC50 of 147.0 ± 15.6 nM. These data support the concept that Syk inhibition blocks with similar potency, B-cell, αIgE, and Fcγ receptor signaling in vitro.

The potency of GS-9973 was evaluated in human whole blood by a αIgE-stimulated CD63 expression assay in human basophils. GS-9973 inhibited the αIgE-stimulated CD63 expression on CD123+/HLADR- human basophils with a mean EC50 ± SD of 0.387 ± 0.220 nM. Additionally, GS-9973 inhibited the pervanadate-induced autophosphorylation of Syk at phospho-Syk (Y525) in whole blood with a mean EC50 ± SD of 830 ± 560 nM. These data support the concept that Syk inhibition can block Syk activity in whole blood as determined by functional inhibition of CD63 expression and direct target inhibition of SYK autophosphorylation.

GS-9973 was evaluated in a battery of safety pharmacology studies. The IC50 for the inhibitory effect of GS-9973 on human ether-à-go-go-related gene (hERG) potassium current in vitro was estimated to be greater than 1 μM. Because GS-9973 is 97.3% protein bound in human plasma and the total plasma concentrations of GS-9973 are in the 1 to 3 micromolar range, with a corresponding range of free GS-9973 of 27 to 81 nM, it is unlikely that a clinically relevant effect on QT interval would occur. No GS-9973 SS-related effects were noted on neurological or respiratory function in rats at doses up to 1000 mg/kg, the highest dose tested. In dogs, GS-9973 caused small increases in heart rates (during the night cycle) at doses ≥ 15 mg/kg but had no effects on electrocardiograms (ECGs) or blood pressure at up to 150 mg/kg, the highest dose evaluated.

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

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

1.3.2. Nonclinical Drug Metabolism and Pharmacokinetics

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

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

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

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

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

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

GS-9973 is an inhibitor of the uptake transporters OATP1B1 and OATP1B3 as well as the efflux transporters P-gp and BCRP with an IC50 value of approximately 2 μM for each of these transporters. GS-9973 may affect the activity of these transporters in vivo at the expected clinical concentrations and could transiently affect the disposition of other drugs. The high plasma protein binding of GS-9973 (> 97%) may mitigate some of the potential drug-drug interactions at clinically relevant doses.

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

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

1.3.3. Nonclinical Toxicology

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

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

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

Increases in total and/or indirect bilirubin in rats, rabbits, and dogs at ≥ 30 mg/kg/day may have been due to the inhibition of the enzyme UGT1A1. GS-9973 inhibits this uridine glucuronyl transferase enzyme with an IC50 of 2 µM. This enzyme is involved in glucuronidation of bilirubin, and inhibitors of UGT1A1 have the potential to produce increased levels of total and indirect (unconjugated) bilirubin in the circulation {Zhang 2005}. As no histological evidence of hepatobiliary toxicity was noted concurrently with bilirubin increases in GS 9973 treated rats or dogs, and GS-9973 levels above the IC50 for UGT1A1 were achieved in serum, this seems a plausible mechanism for the noted increases in bilirubin.

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

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

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

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

1.3.4. Monotherapy Clinical Trials of GS-9973

As of March, 2017, GS-9973 has been studied in single and multiple ascending dose studies in 470 healthy subjects (16 subjects with hepatic impairment), 464 subjects with hematologic malignancies, 7 subjects with cGVHD, and 7 subjects with RA have participated. Of these subjects, 948 received ENTO and 26 received placebo. Refer to the latest IB Edition for the most recent information.

In pharmacokinetics studies at steady state in healthy subjects, GS-9973 was well tolerated when given in a fasted state for 7 days at doses of 25, 75, 200, 600, 900, and 1200 mg twice daily (GS-US-245-0101) and when given in a fed state for 6 days at doses of 100 and 900 mg twice daily (GS-US-245-0106), for 4 days at doses of 200 and 600 mg twice daily (GS-US-339-0101), and at 1200 mg twice daily for 5 days (GS-US-339-0109).Exposure, as measured by AUC and maximum concentration C_{max}, did not increase appreciably at doses of 600 mg and above under fasted condition. See Figure 1-3 and Figure 1-4.

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

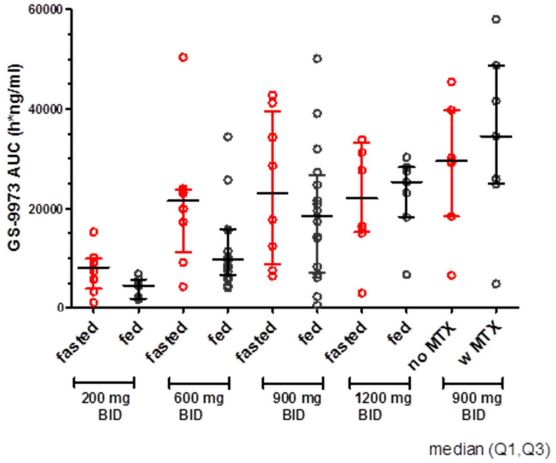
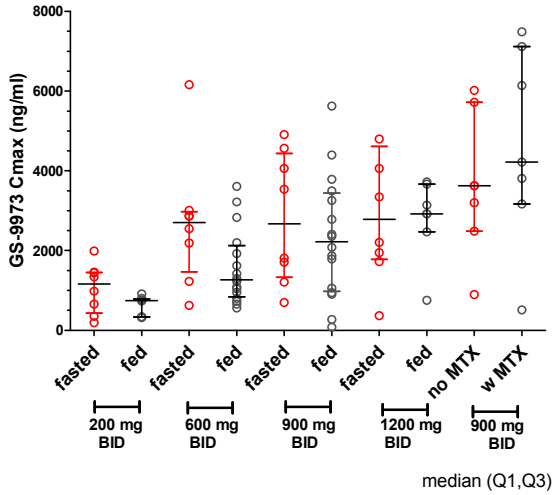


Figure 1-4. GS-9973 C_{max} at Steady State



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

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

1.3.5. GS-9973 Target Drug Concentrations

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

Figure 1-5. Inhibition of Basophil Activation

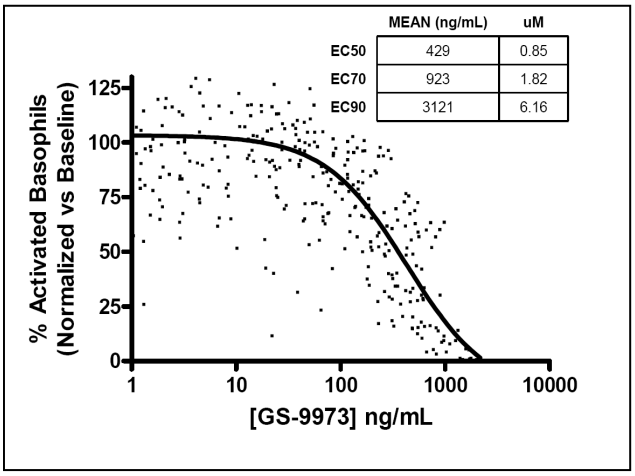
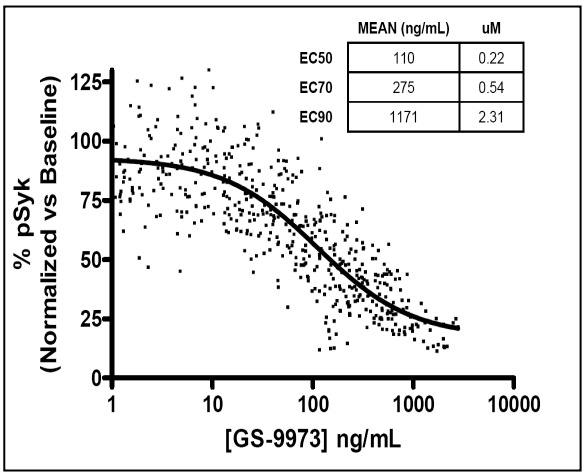


Figure 1-6. Inhibition of pSyk



1.3.6. Use of Concomitant Medications with GS-9973

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

Studies in healthy volunteers have demonstrated a significant reduction in Entospletinib exposure when proton pump inhibitors are co-administered. Therefore, proton pump inhibitors are prohibited in combination with Entospletinib. Use of a proton pump inhibitor should be avoided for 1 week prior to study drug administration. Examples of, strong CYP3A and CYP2C9 inducers, moderate CYP2C9 inducers and proton pump inhibitors that are prohibited in this study are provided in Section 5.3 (see Table 5-1).

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

In a study in healthy volunteers, Entospletinib 400 mg twice daily increased rosuvastatin exposure by approximately 4-fold, which may theoretically increase the risk of rhabdomyolysis. In reviewing the safety of subjects whom have received a statin with Entospletinib there have been no reports of rhabdomyolysis nor a different adverse events profile, but in the interest of caution, restrictions apply to the use of HMG-CoA reductase inhibitors with Entospletinib in this study. These restrictions are included in Section 5.3.

1.4. Rationale for This Study

Despite progress made in understanding the biology and improvements in the treatment of ALL, the majority of adults with ALL will ultimately relapse after initial complete remission (CR) and up to 25 percent will have primary resistant disease. Retreatment of such subjects is generally unsuccessful, and most will die of their disease, underscoring the need for novel therapeutic approaches. Allogeneic hematopoietic stem cell transplantation (HSCT) after initial cytoreduction or in second CR offers a chance of cure in a small, highly selected group of subjects. As such, induction of a second CR is the first step in the treatment of relapsed disease. Increased activity of Syk in ALL cells may play a role in leukemia cell survival and proliferation, and inhibition of Syk has shown to attenuate the growth of B-cell ALL *in vitro* and *in vivo* in mouse models {Perova 2014}. Thus, Syk activation sustains the growth of multiple B-ALL subtypes, suggesting that Syk inhibitors may improve outcomes for high risk and relapsed B-ALL.

The potential for enhanced antiproliferative activity of the combination of GS-9973 and VCR was investigated in vitro. At concentrations of each agent that were minimally growth inhibitory, combination of doses of GS-9973 that approximated trough concentrations with doses of VCR (< 10um) resulted in strong growth inhibition in human ALL cell lines in vitro. These data suggest that the combination of GS-9973 and VCR may have increased anti-tumor activity and warrants clinical investigation. We therefore propose this early phase clinical trial of dose escalated GS-9973 in combination with chemotherapy for fit subjects with relapsed or refractory ALL.

GS-9973 is an adenosine triphosphate (ATP) competitive inhibitor that disrupts the kinase activity of purified Syk protein with a concentration that results in 50% inhibition (IC50) ± standard deviation (StD) of 8.6 ± 3.6 nM (Study PC-245-2006).

1.4.1. Rationale for the GS-9973 Dose Selection

GS-9973 administered twice daily in previous studies was well tolerated up to 1200 mg (7 days in the fasted state) in healthy subjects and 900 mg (6 days in the fed state) in rheumatoid arthritis (RA) subjects. A GS-9973 dose of 800 mg twice daily is being evaluated in the Phase 2 program in subjects with CLL, indolent NHL, mantle cell lymphoma, diffuse large B-cell lymphoma, follicular lymphoma, and non-FL iNHL. Pharmacodynamic evaluation at exposures equivalent to an 800 mg twice daily dose, resulted in trough concentrations that inhibited 70-80% of Syk activity in normal healthy volunteers. In CLL patients, this level of target suppression resulted in clinical benefit.

In the current protocol, a new spray-dried dispersion (SDD) formulation will be used. With this formulation, a 400 mg dose resulted in exposures similar to the 800 mg dose of the original formulation. Among the subjects treated with GS-9973 SDD formulation (N = 28), there were no SAEs reported. In the study, 3 subjects (10.7%) had AEs resulting in study drug discontinuation. Overall, 19 subjects (67.9%) reported an AE. The most common AEs included: headache (11 subjects, 39.3%); back pain and nausea (6 subjects each, 21.4%); ALT increased, rash, and pruritus (4 subjects each, 14.3%); and (3 subjects each, 10.7%) reported AST increased and constipation. No Grade 3 or 4 AEs were reported.

Subjects enrolled in the first cohort will receive 200 mg of GS-9973 and 0.5 mg of VCR. These conservative doses were selected to minimize the potential safety risk to subjects. Nonclinical studies suggest that these low doses in combination can have anti-proliferative activity.

The doses of GS-9973 SDD proposed in the current study, from 200 mg twice daily to 400 mg twice daily, provides a wide range of daily doses (2-fold between 200 mg twice daily vs. 400 mg twice daily) to evaluate the dose/exposure/PD relationship which may be helpful in dose selection for ongoing/future GS-9973 SDD ALL studies. Vincristine will be dose escalated up to 2 mg, which is the commonly used dose cap for VCR, in combination with 400 mg of GS-9973.

1.5. Information about Chemotherapy Agents

1.5.1. Vincristine

Vincristine (VCR) is a vinca alkaloid mitotic inhibitor used in the treatment of leukemia and lymphoma. The compound is delivered via intravenous infusion, and binds to tubulin dimers, inhibiting assembly of microtubule structures and arresting mitosis in metaphase. Because vincristine's mechanism of action targets all rapidly dividing cell types, it not only inhibits cancerous cells but can also affect the intestinal epithelium and bone marrow. Side effects include peripheral neuropathy, hyponatremia, constipation, and hair loss. Please see package insert/label for product details.

1.5.2. Dexamethasone

Dexamethasone is a corticosteroid with anti-inflammatory and immunosuppressant effects used in the treatment of a variety of diseases. It is 25 times more potent than cortisol in its glucocorticoid effect, while having minimal mineralocorticoid effect. Dexamethasone is commonly used as part of combination chemotherapy regimens for the treatment of leukemia and lymphoma. Side effects include increased risk of infection, osteonecrosis, and increased risk of bone fractures, psychosis, and myopathy. Please see package insert/label for product details.

1.6. OVERALL RISK AND BENEFIT ASSESSMENT

Potential Risks Based On Nonclinical Safety Data with GS-9973

Spleen tyrosine kinase deficiency and SYK-deficient bone marrow in rodents have been associated with hemorrhage. In an ex vivo platelet function assay, GS-9973 showed no biologically relevant inhibition or activation of platelets at concentrations up to 12.3 μM. No evidence of altered coagulation parameters was noted at any dose level in the GS-9973 nonclinical studies.

The target organ(s) of toxicity identified in rats was the duodenum, and in rabbits and dogs were predominantly the gastrointestinal tract and lymphoid organs. No target organs were identified in the cynomolgus monkey. In rats treated with 500 mg/kg/day ENTO for 4 weeks, slight villus alteration in the duodenum was noted; this finding was not observed following administration of up to 100 mg/kg/day to rats for 26 weeks. In rabbits and dogs, the predominant organs affected were the GI tract and lymphoid tissues including spleen, lymph nodes, and/or the thymus. Oral administration of GS-9973 to rats for up to 26 weeks or cynomolgus monkeys for up to 39 weeks showed no evidence of GI toxicity or lymphoid changes at exposures which overlapped with or exceeded those in dogs. Clinical assessments will monitor for signs and symptoms of infection, hemorrhage, GI distress, and changes in clinical pathology parameters (changes in hemoglobin, neutrophils, lymphocytes, liver enzymes, and total and indirect bilirubin) that could occur after GS-9973 administration. Because evidence of lymphoid tissue depletion was noted in rabbits and dogs at high doses, clinical assessments will also include monitoring for signs and symptoms of infection.

Coadministration of ENTO with vincristine (VCR) did not exacerbate VCR-related hematological toxicity in male rats. Addition of GS-9973 to low dose VCR resulted in a mild slowing of caudal nerve conduction velocity compared with low dose VCR; no contributive effects of GS-9973 to nerve conduction velocity at high dose VCR were observed. The effect may be mitigated by the high plasma protein binding of ENTO (> 97%).

Administration of ENTO to pregnant female rats and rabbits resulted in dose-dependent developmental findings. The study will exclude females who are pregnant or breastfeeding, and only include female subjects of child bearing potential who are willing to use a protocol-recommended method of contraception from the screening visit throughout the study and to 30 days from the last dose of ENTO. For male subjects having intercourse with females of childbearing potential, must be willing to abstain from heterosexual intercourse or use a protocol-recommended method of contraception from the start of ENTO throughout the study treatment period and for 90 days following the last dose of ENTO.

Also, male subjects should refrain from sperm donation from the start of the ENTO throughout the study treatment period and for 90 days from the last dose of ENTO.

Potential Risks Based On Clinical Safety Data with Entospletinib (ENTO [GS-9973])

As of March 2017, 18 clinical studies have been conducted in which 470 healthy subjects (including16 subjects with hepatic impairment), 464 subjects with hematologic malignancies, 7 subjects with cGVHD, and 7 subjects with RA have participated. Of these subjects, 948 received ENTO and 26 received placebo. Overall, ENTO was generally well tolerated when administered as a single dose or as multiple doses. Treatment emergent AEs commonly reported across the studies involving healthy volunteer subjects include headache, somnolence, and GI symptoms (nausea and abdominal pain), all of which were mild and reversible.

Increased transaminases levels were noted in some subjects which is reversible.

ENTO is an inhibitor of UGT1A1 and may transiently inhibit UGT1A1 activity in vivo at the expected clinical concentrations. Administrations of drugs such as ENTO that inhibit UGT1A1 are expected to increase total bilirubin due to decreased conjugation rather than liver dysfunction. The elevations in indirect bilirubin observed in clinical trials with ENTO were generally self-limited and did not result in discontinuation of ENTO. In the absence of symptoms or other hepatic laboratory abnormalities, ENTO dose modification is not required for elevated indirect bilirubin levels.

The bis-MSA spray-dried dispersion (SDD) formulation will be used in this study and was chosen because it had less interaction with acid reducing agents. Administration of the bis-MSA formulation in studies GS-US-339-0111 and GS-US-245-1222, demonstrated that the change in ENTO exposure upon coadministration with omeprazole was less than the reduction in exposure observed in Study GS-US-245-0106 using the original formulation. The new formulation did not completely annul the DDI effect of a coadministered PPI agent, however the interaction of ENTO new formulation with an H2 receptor antagonist (H2RA) (eg famotidine) is not considered clinically meaningful.

In study GS-US-245-1222, the administration of food with the bis-MSA formulation of ENTO resulted in a reduction in ENTO exposure compared to fasted conditions. Due to this, ENTO should be taken under fasted conditions, as described in the administration instructions in this protocol.

Peripheral neuropathy has been reported with the use of vincristine. Subjects that have current or ongoing neuropathy (sensory or motor) Grade > 1 or any history of Grade ≥ 3 neuropathy with prior VCR or chemotherapy exposure are excluded from the study.

Based on the clinical experience with ENTO and VCR administered as single agents, and the absence of notable additive effects with the combination in nonclinical studies, ENTO alone or in combination with VCR demonstrates an acceptable benefit/risk profile for the proposed treatment of hematological malignancies in adults.

The available nonclinical and clinical data support the evaluation of ENTO in eligible subjects with relapsed or refractory ALL.

Refer to the IB for complete details of the compound including completed and ongoing preclinical and clinical studies including summary safety and response data.

1.7. Compliance

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

2. OBJECTIVES AND ENDPOINTS

2.1. Objectives

The primary objective of this study is:

- To evaluate safety of entospletinib (GS-9973) in combination with vincristine (VCR) and dexamethasone in adult subjects with previously treated relapsed or refractory B-cell lineage ALL

The secondary objectives of this study are:

- To determine the recommended dose of GS-9973 in combination with VCR and dexamethasone in adult subjects with previously treated relapsed or refractory B-cell lineage ALL

- To evaluate the therapeutic response of GS-9973 in combination with VCR and dexamethasone in adult subjects with previously treated relapsed or refractory B-cell lineage ALL

The exploratory objectives of this study are:

3. STUDY DESIGN

3.1. Endpoints

The endpoints for this study are described in Section 8.1.2.

3.2. Study Design

This is an open-label, Phase 1b dose-escalation and Phase 2 expansion study evaluating the safety, efficacy, tolerability, and pharmacokinetics of GS-9973 in combination with VCR, and dexamethasone.

3.3. Study Treatment

This study consists of two parts: dose escalation and dose expansion. The dose escalation begins with a 7-day lead-in of GS-9973 monotherapy where subjects are enrolled into dose level cohorts as outlined in Table 3-1. For the dose expansion, the 7-day GS-9973 monotherapy Lead-in is omitted and the dosage is based on the maximum tolerated dose (MTD) or recommended dose determined from dose escalation results. However, after completion of dose escalation, it was decided not to move forward with dose expansion.

3.3.1. Dose Escalation

During dose escalation, there will be four dose levels (outlined in Table 3-1) investigated in dose escalation where subjects in cohorts of 3 to 6 will sequentially enroll into one of the dose levels using the 3+3 dose escalation design. The starting dose level for the first cohort is defined as Dose Level 1.

Table 3-1. GS-9973/VCR Dose Escalation

Dose Level	GS-9973	Vincristine (VCR)
1	200 mg BID	0.5 mg per dose
2	400 mg BID	0.5 mg per dose
3	400 mg BID	1 mg per dose
4	400 mg BID	2 mg per dose

Subjects in Dose Level 1 will receive 200 mg GS-9973 taken orally twice daily (BID). Subjects in Dose levels 2 to 4 will receive 400 mg GS-9973 orally BID. Subjects in all dose levels will receive dexamethasone 20 mg BID for four days during Cycle 1 on Days 8-11 and Days 22-25 and during Cycle 2 on Days 1-4 and Days 15-18. Each treatment cycle is 28 days in length.

In the absence of toxicity requiring a drug interruption (as defined in Section 3.5.2.1), dosing of GS-9973 will be taken continuously without interruption.

Subjects will have evaluations for safety and provide blood for drug levels prior to starting Lead-in and 1.5 hours after the first dose of GS-9973.

Additional PK blood samples will be collected at (applies to both escalation and expansion):

- Pre-dose during Cycle 1 on Day 1 and 1.5 hours (± 30 minutes) post-dose of GS-9973
- Pre-dose during Cycle 1 on Day 8, and 1.5 hours (± 30 minutes) post-dose of GS-9973
- Pre-dose during Cycle 1 on Day 28 and Cycle 2 on Day 28, and 1.5 hour (± 30 minutes) post-dose of GS-9973
- A sample of cerebrospinal fluid (CSF) for PK analysis will be taken during Cycle 1 on Day 28 and Cycle 2 on Day 28 (untimed sample) prior to CNS prophylaxis administration

3.3.1.1. Treatment Plan in Dose Escalation

Subjects will be enrolled and dosed in accordance with the 3+3 dose escalation design (Table 3-1). Intra-subject dose escalation is not allowed. Up to 6 subjects will be dosed per dose level. Dose escalation will be performed based on assessments of DLTs and other adverse events data obtained within the DLT window (GS-9973 Lead-in and Cycle 1; study day 1 through day 35). Subjects with CR, CRi, or PR on Day 28 of Cycle 1 bone marrow, and /or subjects who in the investigator's opinion have obtained clinical benefit from Cycle 1 induction, will continue to Cycle 2 of induction.

During the DLT assessment window, subjects who fail to complete 21 days of GS-9973 or fail to receive sufficient exposure (> 50% of planned total dose) to VCR and dexamethasone for reasons other than treatment-related toxicity will not be evaluable for DLT assessment and an additional (replacement) subjects may be enrolled to that dose level in order to provide adequate safety data for dose escalation decisions.

Decision to open the next higher dose level to enrollment or expand the current cohort will be determined by the sponsor in consultation with study Principal Investigators (PIs).

The maximum tolerated dose (MTD) is defined as the highest tested dose associated with an observed DLT rate of < 33% during the DLT window.

A minimum of 6 subjects need to be treated at a dose level before this dose level can be determined as MTD or recommended dose.

3.3.2. Dose Expansion

At the time of this amendment, there have been no DLTs in the Phase 1 portion of the study. However, due to the low response rate to ENTO + vincristine + dexamethasone in relapsed/refractory ALL patients, it has been decided not to proceed with the dose expansion (Phase 2) portion of this trial. Prior to this amendment, dose expansion had been initiated at 400 mg BID, but was subsequently closed with no subjects enrolled.

3.3.3. Maintenance

It is anticipated that most subjects will receive hematopoietic stem cell transplant (HSCT) therapy with curative intent if a complete remission (CR) is reached. In the absence of suitable alternative therapeutic options, subjects who obtain clinical benefit (at least PR) after completing both cycles of induction therapy in dose escalation may continue GS-9973 at the assigned dose level in the maintenance phase for up to 36 cycles. Subjects will continue GS-9973 and VCR at their assigned dose. GS-9973 will continue to be taken orally twice daily with VCR given on Day 1 of each 28-day cycle. Dexamethasone may be administered as a single dose of 20 mg once daily or a divided dose of 10 mg twice daily on Days 1-4 and Days 15-18 of each 28-day cycle.

Bone marrow evaluations and additional central nervous system (CNS) directed therapy can be performed as clinically indicated in the maintenance phase.

3.4. Duration of Treatment

Dose escalation consists of a 7 day lead-in followed by 2 induction cycles (1 cycle=28 days). Subjects may be put on maintenance for up to 36 cycles with VCR on Day 1 of each cycle, if they have obtained clinical benefit from the assigned dose level. There may be up to a 7 day interval between Cycle 1 and Cycle 2.

3.5. Dose-Limiting Toxicity

The evaluation period for dose-limiting toxicity (DLT) will occur from the start of treatment through the end of Cycle 1 in the escalation phase. Subjects who fail to complete 21 days of GS-9973 or fail to receive sufficient exposure (> 50% of planned total dose) to VCR and dexamethasone for reasons other than treatment-related toxicity will be considered not evaluable for DLT assessment and additional (replacement) subjects may be enrolled to that dose level in order to provide adequate safety data on which to base dose escalation decisions. All toxicities will be graded using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03 (Appendix 3).

The occurrence of any of the following toxicities during Lead-in/Cycle 1 will be considered a DLT if judged by the Investigator to be possibly, probably, or definitely related to the administration of any drug in the treatment regimen (GS-9973, VCR, dexamethasone, institutional standard CNS prophylaxis):

- Grade 4 (or higher) non-hematologic toxicity
- Grade 3 non-hematologic toxicity lasting $\geq$ 7 days despite optimal supportive care
- Any Grade 3 non-hematologic laboratory value if:
  - Medical intervention is required to treat the patient, or
  - The abnormality leads to hospitalization, or
  - The abnormality persists for >1 week

- Grade 4 Neutropenia (ANC < 500 /µl) persistent for greater than 14 days or associated with febrile neutropenia
- Grade 4 thrombocytopenia (platelets < 25,000/µl) persisting for greater than 14 days (or greater than 25,000 /µl, but requiring prophylactic platelet transfusion to maintain this level)

The following will NOT be considered as a DLT for the purposes of this study, regardless of grade:

- Alopecia
- Fatigue
- Nausea or vomiting controllable with anti-emetic therapy
- Catheter-associated venous thrombosis
- Infection (or infection-related toxicities such as fever/sepsis, unless it is felt that the infection resulted from unexpectedly complicated myelosuppression due to study medication)
- Transient electrolyte abnormalities (any grade) that are not clinically significant and are correctable within 24 hours
- Transient liver function test abnormalities (AST, ALT, bilirubin, or alkaline phosphatase) that resolve to ≤ Grade 2 within 7 days

Table 3-2. Dose Escalation/DLT Guidelines

Number of subjects with DLT at a given level	Escalation Decision Rule
0 out of 3	Enroll 3 subjects at the next higher dose level. If this dose level is the highest dose level, it will be declared the maximally administered dose, and enroll 3 additional subjects at this dose level.
1 out of 3	Enter 3 additional subjects at this dose level. • If 0 of these 3 subjects experience DLT, proceed to the next higher dose level. • If 1 or more of them experience DLT, then dose escalation is stopped, and this dose is declared the maximally administered dose. Three additional subjects will be entered at the next lower dose level if only 3 subjects were treated previously at that dose.
≥ 2 out of 3	Dose escalation will be stopped. This dose level will be declared the maximally administered dose (highest dose administered). Three additional subjects will be entered at the next lower dose level if only 3 subjects were treated previously at that dose.
≤ 1 out of 6 at highest dose level at or below the maximally administered dose	This is the maximum tolerated dose (MTD) and generally the recommended dose. At least 6 subjects must be enrolled at MTD or the recommended dose.

3.5.1. Management of Dose Limiting Toxicities

It is recognized that drug-related toxicity in this population may be difficult to ascertain given the nature of hematologic disease. Investigators will attempt to assign attribution of toxicities to each drug if possible. The Cancer Therapy Evaluation Program (CTEP) Active Version of the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 will be utilized for AE reporting.

3.5.2. Guidelines for Dose Modifications

3.5.2.1. Dosing Delays/Dose Modifications Attributed to GS-9973 (beyond Cycle 1)

If the following signs or symptoms are medically manageable, they are not to be a consideration with respect to the subject's dosing or continuation on study: nausea/mild vomiting/diarrhea, drug-related fever or chills, transient and correctable laboratory test abnormalities, line associated thrombosis, or alopecia. See Appendix 3.

There will be no dose modifications during Lead-in or Cycle 1 for GS-9973, VCR, or dexamethasone. Subjects experiencing toxicity attributed to these agents during Cycle 1 requiring discontinuation of any drug shall be removed from study and will be considered a DLT.

Dose modification of GS-9973 in subsequent cycles is permitted following guidelines provided in Appendix 3. Subjects who experience a non-hematologic toxicity assessed as GS-9973 related that is Grade 3 or higher will hold dosing of GS-9973 until the toxicity resolves to ≤ Grade 1, and then may resume study therapy at the prior dose through the end of the cycle (or decreased by 1 dose level after discussion with Sponsor). For subjects assigned to Dose Level 1, the decreased dose of GS-9973 will be defined as 100 mg orally twice daily. Missed doses are not to be made up.

Adverse events and laboratory abnormalities will be graded using the CTCAE, Version 4.03.

3.5.2.2. Dose Modifications for Non-Hematologic Toxicity for VCR, and dexamethasone

If the subject experiences any non-hematologic clinically significant Grade 3 or greater toxicity felt to "possibly" be related to any agent, hold the protocol therapy until it resolves to ≤ Grade 2. If related to VCR, reduce the dose of VCR to by one dose level (per Table 3-1); if at lowest dose level, resuming treatment with VCR will be at Investigator's discretion after discussion with Sponsor. Refer to product label information for specific toxicity management. If related to dexamethasone, resuming treatment with dexamethasone will be at the discretion of the Investigators. If the toxicity recurs, subject will be removed from study. If protocol therapy is withheld for more than 2 weeks for toxicity possibly, probably, or definitely related to protocol-based therapy or up to 4 weeks for any other reason, subjects will be removed from protocol.

Subjects who have been dose-reduced cannot be returned to a higher dose level.

Toxicities in an individual subject must resolve to Grade 2 or to baseline levels before proceeding with the next cycle of treatment.

3.5.3. Dose Modifications for Hematologic Toxicity for GS-9973, VCR, and dexamethasone

It is recognized that drug-related hematologic toxicity in this population may be difficult to ascertain given the aggressive hematologic disease and the fact that multiple cycles of therapy may need to be administered for maximal clinical response. Therefore, there will be no dose modifications for hematologic toxicity due to GS-9973, VCR, or dexamethasone during Cycle 1. However, after the first cycle is administered, subjects suspected to have protocol therapy related ANC and/or platelet count toxicity (i.e. fail to recover to at least 50% of the prior cycle's baseline value), will have the dose of VCR reduced by one dose level (or 50% if at lowest dose level) dexamethasone and the dose of GS-9973 will be decreased one dose level. Dose modifications because of concern for drug induced cytopenias will be discussed with the study PIs. Dose modifications for hematologic toxicity for subjects who have achieved a CR or CRi are detailed below.

3.5.3.1. Neutropenia

In the event of Grade 4 neutropenia (ANC < 500/μL) that occurs after Cycle 1 and persists for 14 days or more or is associated with febrile neutropenia, further cycles of GS-9973/VCR will be decreased by 1 dose level. For subjects assigned to Dose Level 1, the decreased dose of GS-9973 will be defined as 100 mg twice daily. If Grade 4 neutropenia that persists for 14 days or more (or Grade 4 neutropenia associated with fever) recurs for the third time, GS-9973/VCR/dexamethasone should be discontinued. Refer to VCR product label for specific guidance.

3.5.3.2. Thrombocytopenia

In the event of Grade 4 thrombocytopenia (platelets < 25,000/μL) that occurs with the second or subsequent cycles of maintenance and persists for more than 14 days (or >25,000/uL but requiring prophylactic platelet transfusions to maintain this over the 14 day period), further cycles of GS-9973/VCR shall be decreased by 1 dose level. For subjects assigned to Dose Level 1, the decreased dose will be defined as 100 mg twice daily. If Grade 4 thrombocytopenia persisting for more than 14 days (or patient requires prophylactic platelet transfusions to maintain >25,000/μL over the 14 day period) recurs for the third time, discontinue the GS-9973/VCR/dexamethasone. Refer to VCR product label for specific guidance.

3.5.4. Management of Low Grade Chronic Toxicities

Since subjects will be receiving the GS-9973 daily, low grade chronic side effects such as nausea, fatigue and diarrhea, while not meeting the above definition for dose limiting toxicities, may not be tolerable when experienced for long periods of time. Following discussion with the Gilead Medical Monitor, dose reduction may be permitted if low grade chronic side effects cannot be managed effectively with supportive care.

3.5.5. Specific Considerations for Managing Hyperbilirubinemia

3.5.5.1. Unconjugated (Indirect) Bilirubin Elevations

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

3.6. End of Study

End of study will be defined as when all patients complete long term follow-up or discontinue their participation in the study due to death, withdrawal of consent or lost to follow up, or the time at which the Sponsor closes the study.

3.7. Post Study Care

Does not apply.

4. SUBJECT POPULATION

4.1. Number of Subjects and Subject Selection

4.2. Inclusion Criteria

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

1) ≥18 years of age

2) Previously treated ALL including Philadelphia chromosome (BCR-Abl) positive ALL who meet all of the following criteria:

   a) Diagnosis of precursor B-cell ALL based on flow cytometry and histology

   b) Previously treated subjects with primary refractory disease OR after first or subsequent relapse

   c) Subjects with >10% lymphoblasts in bone marrow (BM) or extramedullary disease (EMD) that is radiographically measureable and amenable to imaging studies and repeat biopsies

   d) Patients with Ph+ ALL must have failed treatment with at least one 2nd generation (ex. dasatanib) or 3rd generation (ex. ponatinib) tyrosine kinase inhibitor

3) Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2

4) Adequate organ function defined by the screening laboratory inclusion values (Table 4-1) and absence of known cardiac dysfunction

5) Required screening laboratory data (within 7 days prior to administration of GS-9973) as shown in (Table 4-1)
   Note: *Confirmation should be considered for out-of-range values to determine if the abnormality is real or artifactual. Values should be obtained within the screening period and should be the most recent measurement obtained*

Table 4-1. Required Screening Laboratory Values

Organ System	Parameter	Required Value
Hepatic	Serum total bilirubin	<2.0mg/dL or ≤ 1.5 x ULN (unless elevated due to Gilbert's syndrome)
	AST (SGOT)	≤ 2.5 x institutional ULN (unless due to disease then < 5 x ULN)
	ALT (SGPT)	
Renal	Creatinine	<2.0mg/dL
Pregnancy	β-HCG[a]	Negative
Infection[c]	HIV[b]	Negative HIV antibody/PCR
	HBV	Negative HBsAg and negative HBc antibody or positive HBc and negative HBV DNA by quantitative PCR
	HCV	Negative viral RNA (if HCV antibody is positive)

a For women of childbearing potential only; serum β-HCG must be negative during screening and serum β-HCG or urine dipstick pregnancy test must be negative at start of study drug
b If screening test is positive, a negative confirmatory test will be required for eligibility
c Screening for infection can be done up to 30 days prior to administration of study drug
Abbreviations: ULN=upper limit of normal, β-HCG=beta human chorionic gonadotropin, DNA=deoxyribonucleic acid, HBc antibody=anti-hepatitis B core antibody, HBsAg=hepatitis B surface antigen, HBV=hepatitis B virus, HCV=hepatitis C virus, HIV=human immunodeficiency virus, Ig=immunoglobulin, PCR=polymerase chain reaction, RNA=ribonucleic acid.

6) Discontinuation of all therapy (including radiotherapy, chemotherapy, tyrosine-kinase inhibitors [TKIs], immunotherapy, or investigational therapy) for the treatment of cancer as follows:

   a) At least 1 week or 5 half-lives (whichever is longer) from the last dose of prior anti-cancer therapy and the initiation of study therapy

   b) Exceptions or modifications to the above are as follows:

      Medications that are typically part of a maintenance therapy for ALL, such as glucocorticoids or mercaptopurine, may be administered up to 3 days prior to the first dose, except vinca alkaloids which must be discontinued at least 14 Days prior to the start of study treatment. TKIs are not permitted to be continued at screening (eg, Gleevec). Subjects may receive hydroxyurea or apheresis if indicated for rapidly rising white blood cell count

   c) CNS prophylaxis up to at least one week prior to first dose of GS-9973

   d) For biologics (eg, monoclonal antibodies), washout period of 1 month beyond the recommended dosing interval and at least 4 weeks or 5 half-lives (whichever is shorter) since the last dose

   e) If prior stem cell transplant, subject must be at least 100 days from stem cell infusion and off all systemic anti-graft versus host disease (GVHD) medications

f) If prior donor lymphocyte infusion (DLI), subject must be at least 4 weeks from DLI and off all systemic anti-graft versus host disease (GVHD) medications and have no evidence of any infection

g) If prior Chimeric Antigen Receptor (CAR) T-Cell Therapy, subject must be at least 4 weeks from CART infusion

7) All acute toxic effects of any prior antitumor therapy must be resolved to Grade ≤ 1 before enrollment, with the exception of alopecia (any grade permitted), or bone marrow parameters (any grades permitted)

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 to 30 days from the last dose of GS-9973. A negative serum pregnancy test is required for female subjects at screening. Lactating females must agree to discontinue nursing before GS-9973 is administered. See Appendix 5

9) For male subjects 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 GS-9973 throughout the study treatment period and for 90 days following the last dose of GS-9973. Also, male subjects should refrain from sperm donation from the start of the GS-9973 throughout the study treatment period and for 3 months following the last dose of GS-9973. See Appendix 5.

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

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

4.3. Exclusion Criteria

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

1) Diagnosis of mature B-cell ALL (Burkitt's leukemia), or lymphoid blast crisis of chronic myelogenous leukemia (CML)

2) A life threatening illness, medical condition or organ system dysfunction which, in the investigator's opinion, could compromise the subject's safety or interfere with the absorption or metabolism of GS-9973

3) Active or symptomatic central nervous system (CNS) disease

   For study purposes a subject will NOT be considered as having active CNS disease if the subject has documentation of prior CNS disease and has received treatment (IT or radiation) and are:

   a) asymptomatic for the last 28 days prior to screening, and

   b) has documented at least 2 negative cerebrospinal fluid (CSF) cytology (which must include 1 lumbar puncture [LP] within the study screening window)

4) Uncontrolled intercurrent illness including, but not limited to, unstable angina pectoris or psychiatric illness/social situations that would limit compliance with study requirements. Subjects with active infection are permitted to enroll provided that the infection is documented to be under control and after discussion with study Sponsor

5) History of myelodysplastic syndrome or solid organ transplantation

6) History of a non-lymphoid malignancy except for the following:

   adequately treated local basal cell or squamous cell carcinoma of the skin, cervical carcinoma in situ, superficial bladder cancer, asymptomatic prostate cancer without known metastatic disease and with no requirement for therapy or requiring only hormonal therapy and with normal prostate specific antigen for > 1 year prior to the start of GS-9973, or any other cancer that has been in complete remission without treatment for ≥ 5 years prior to enrollment

7) Known hypersensitivity or intolerance to any of the active substances or excipients in the formulations for GS-9973

8) Evidence of uncontrolled systemic bacterial, fungal, or viral infection at the start of GS-9973 ***Note:*** *Subjects with localized fungal infections of skin or nails are eligible. Subjects may be receiving prophylactic antiviral, antifungal, or antibacterial regimens (eg, anti-pneumocystis prophylaxis at the discretion of the investigator per institutional guidelines. If azoles are used for antifungal prophylaxis, subjects must be monitored for possible DDI with VCR)*

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

10) Prior allogeneic bone marrow progenitor cell transplant within 100 days or on active systemic immunosuppression for graft versus host disease (GVHD) treatment or prophylaxis within 28 days prior to enrollment

11) Active (symptomatic or requiring current medical treatment within 28 days prior to the start of study treatment) for GVHD

12) Ongoing immunosuppressive therapy other than corticosteroids (corticosteroids being used for GVHD treatment are not permitted)
Note: *Subjects may use topical, enteric, inhaled, or systemic corticosteroids as therapy for manifestations of comorbid conditions*

13) Current therapy with proton pump inhibitors (PPI) must be avoided (as there is the potential to interfere with GS-9973 absorption).
Note: *H2 blockers and antacids will be allowed for the use during the study*

14) Pregnancy or breastfeeding

15) Ongoing active pneumonitis

16) Concurrent participation in an investigational drug trial with therapeutic intent defined as prior study therapy within 28 days prior to start of GS-9973 administration

17) Ongoing or recent treatment with an excluded medication, as defined in Section 5.3, Excluded Medication

5. INVESTIGATIONAL MEDICINAL PRODUCTS

5.1. Description and Handling of Entospletinib (ENTO [GS-9973])

5.1.1. Formulation

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

5.1.2. Source

GS-9973 will be supplied free of charge by Gilead Sciences, Inc, (GSI). Any questions or concerns regarding study treatment supply should be referred to your site monitor.

5.1.3. Packaging and Labeling

Study drug (Entospletinib [GS-9973] 100 mg and 200 mg tablets) are packaged in white, high-density polyethylene (HDPE) bottles. Each bottle contains 60 tablets, a silica gel desiccant and polyester packing material. Each bottle is enclosed with a white, continuous thread, child-resistant, polypropylene screw cap fitted with an induction-sealed, aluminum-faced liner.

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

5.1.4. Storage and Handling

Study drug (Entospletinib) should be stored at controlled room temperature of 25°C (77°F); excursions are permitted between 15°C and 30°C (59°F and 86°F). Storage conditions are specified on the label. Until dispensed to the subjects, all bottles of study drugs should be stored in a securely locked area, accessible only to authorized site personnel.

To ensure the stability and proper identification, study drug should not be stored in a container other than the container in which they were supplied. Keep the bottle tightly closed to protect from moisture.

Consideration should be given to handling, preparation, and disposal through measures that minimize drug contact with the body. Appropriate precautions should be followed to avoid direct eye contact or exposure when handling.

5.1.5. Study Drug Accountability

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

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

- Record the date received, quantity of GS-9973, and lot number
- Record the date, subject number, subject initials, the GS-9973 lot number dispensed
- Record the date, quantity of used and unused GS-9973 returned, along with the initials of the person recording the information

5.2. Treatment Plan

5.2.1. Pre-medication

No specific pre-medications or supporting medications are required in conjunction with GS-9973 administration. For VCR, dexamethasone, and CNS prophylaxis please follow the most recent version of the package insert and institutional guidelines when administrating.

5.2.2. Administration Instructions

GS-9973 should be taken under fasted conditions. Fasting is defined as no food or liquids other than water for 2 hours pre and 1 hour post-dose. Subjects should be instructed not to bite or chew the tablets. In case of breakage of the tablets in the oral cavity, additional water should be taken as a rinse.

5.2.3. Dosing Schedule

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

5.2.4. Dose Schedule Interruptions and Vomited Doses

Subjects who have a delay in administration of a dose of GS-9973 of < 6 hours should take the planned dose as soon as possible after the intended time of administration. For subjects who have a delay in administration of GS-9973 of ≥ 6 hours, the dose should not be taken. GS-9973 administration may continue but the missed dose should not be made up and the planned timing of subsequent GS-9973 dosing should not be altered.

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

5.2.5. Concomitant and Supportive Therapy

Subjects should receive full supportive care including transfusions of blood and blood products, antibiotics, antiemetics, allopurinol, etc., when appropriate.

No other direct anti-leukemia therapy is permitted.

Growth Factor (eg. G-CSF or GM-CSF) use in Cycle 1 is not permitted as it may impact the determination of DLT. Beyond cycle 1 the use of myeloid growth factors is permitted according to American Society of Clinical Oncology (ASCO) guidelines for use in ALL.

rEPO is not permitted at any time on the study.

Palliative radiation therapy may not be administered while the subject is on study unless discussed and approved by the Sponsor.

5.3. Excluded Medication

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

Subjects who initiate therapy with excluded medications will be discontinued from the trial. The following therapies are not permitted at any point during the trial:

- Any non-study anti-cancer chemotherapy or non-study immunotherapy (approved or investigational), except steroids used as anti-emetics
- Co-administration of strong CYP3A and CYP2C9 inducers, and moderate CYP2C9 inducers are prohibited in this study. Administration of these medications should also be avoided for 2 weeks prior to study drug administration. Examples of these medicines, and other medications that are prohibited in this study are provided in Table 5-1
- Caution should be exercised when co-administering drugs that are moderate or strong inhibitors of CYP2C9 (eg fluconazole, voriconazole or amiodarone) as they may increase Entospletinib exposure
- Proton Pump Inhibitors are prohibited in combination with Entospletinib. Use of a proton pump inhibitor should be avoided for 1 week prior to study drug administration and for the duration of treatment with study drug. H2 blockers and antacids will be allowed for use during the protocol.

Table 5-1. Examples of Contraindicated Medication Requiring GSI Medical Monitor Approval

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

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

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

HMG-CoA reductase inhibitor	Dose Adjustment Required
Atorvastatin	Maximum dose 20 mg QD
Rosuvastatin	Maximum dose 10 mg QD
Pravastatin	Maximum dose 40 mg QD
Simvastatin	Maximum dose 20 mg QD
Lovastatin	Maximum dose 20 mg QD
Fluvastatin	Maximum dose 20 mg BID or 40 mg QD
Pitavastatin	Maximum dose 1 mg QD

The management of subjects who are benefiting from the protocol treatment and who subsequently require treatment with the above medications should be discussed with the Gilead Medical Monitor.

- Granulocyte-colony stimulating factors (GCSF) are not permitted during Cycle 1 for all subjects

5.4. Study Drug Disposal

At the start of the study, the study monitor will evaluate each study center's study drug disposal procedures and provide appropriate instruction for return or destruction of unused study drug supplies. If the site has a process instruction (eg, Standard Operating Procedures [SOPs]) for on-site drug destruction which is reviewed by the study monitor, then the site should destroy used (empty bottles) and unused study drug supplies in accordance with the site's

(hospital/pharmacy) procedure. The destruction process should include records noting the identification and quantity of each unit destroyed, the method of destruction, and person who disposed of the drug. A copy of the site's SOP/process document will be obtained for central files at the pre-study or otherwise applicable monitoring visit. Upon study completion, a copy of the relevant Investigational Drug Accountability records must be filed at the site and provided for the sponsor files. If the site does not have acceptable procedures in place for drug destruction, arrangements will be made between the site and GSI (or Gilead Sciences' representative) for return of unused study drug supplies.

6. STUDY PROCEDURES

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

The investigator must document any deviation from protocol procedures and notify the sponsor or the Clinical Research Associate (CRA).

6.1. Subject Enrollment and Treatment Assignment

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

6.2. Subject Enrollment and Treatment Assignment

A subject will be considered enrolled once enrolled in IWRS. It is the responsibility of the investigator to ensure each subject is eligible for the study before enrollment.

6.2.1. Obtain Written Informed Consent

All subjects must personally sign and date the institutional review board / independent ethics committee (IRB/IEC) approved informed consent form before any study procedures are performed (Section 9.1.3)

6.2.2. Recording Medical History

A complete medical, surgical and smoking history will be obtained prior to enrollment.

6.2.3. Medication History

A history of smoking and medications taken within 30 days prior to screening and during the screening period will be obtained prior to enrollment.

6.2.4. Physical Examination

A complete physical examination will be performed at the screening visit and a modified exam at all other study visits. Physical examination will be performed to monitor for any changes and will include vital signs, weight and height. Weight should be collected with the subject standing without shoes. Physical examination findings during the screening period will be reported as medical history.

6.2.5. Vital Signs

Vital signs will include pulse, respiratory rate, systolic and diastolic blood pressure, oxygen saturation level, and body temperature. They should be collected per institutional guidelines.

6.2.6. Laboratory Assessments

All samples collected in this study for laboratory assessments will be sent to the central laboratory with the exception of urine pregnancy test which will be completed at the site. Screening laboratory samples should be obtained within 7 days prior to the first dose of study drug. If the samples were obtained more than 7 days prior to first dose of study drug, only the hematology and chemistry lab samples must be repeated. Local laboratory results may be used for eligibility evaluation while pending central laboratory results.

The central laboratory will be responsible for chemistry, CBC, coagulation, urinalysis, and serum pregnancy testing per Table 6-1. Any samples collected per the Study Procedure Table (Appendix 2) may be analyzed for any tests necessary to ensure subject safety. Specific instructions for processing, labeling, and shipping samples will be provided in a central laboratory manual. The date and time of sample collection will be reported to the central laboratory.

Table 6-1. Analytes

<table>
<tr><th>Serum Chemistry</th><th>Hematology</th><th>Other</th></tr>
<tr><td rowspan="5">Sodium
Potassium
Chloride
Lipase
Amylase
Bicarbonate
Creatinine
BUN
Phosphorus
LDH [a]
Uric acid [a]
Magnesium [a]
Total bilirubin
Indirect Bilirubin
Direct Bilirubin
ALT
AST
Alkaline phosphatase
CPK[b]</td><td>Hemoglobin
Hematocrit
Red Blood Cell (RBC) count
White Blood Cell (WBC) Count
Neutrophils
Lymphocytes
Monocytes
Eosinophils
Basophils
Platelets</td><td rowspan="5">Pharmacokinetic Sampling

Biomarker Sampling
• Syk and relevant down-stream signaling pathways
• mechanisms of resistance
PPD [redacted]
• PBMC
• Bone Marrow Aspirate
• Bone Marrow Biopsy</td></tr>
<tr><td>Urinalysis</td></tr>
<tr><td>Coagulation</td></tr>
<tr><td>Prothrombin Time
APTT
INR</td></tr>
<tr><td>Pregnancy Testing</td><td>Virology</td></tr>
<tr><td>Serum Qualitative β-HCG or FSH [a]
Urine pregnancy test</td><td>Hep B
Hep C
HIV</td></tr>
</table>

a Screening only
b At Screening, Day 1 of each cycle and End of Treatment

6.2.7. Bone Marrow Aspirate and Biopsy

Bone marrow aspirate/biopsy samples will be assessed by a local hematopathologist. Unstained slides should be made available to the sponsor for central review. Results from assessment of bone marrow aspirate/biopsy samples obtained as part of the subject's routine medical care may be used if the documentation is available.

6.2.8. Eastern Cooperative Oncology (ECOG) Performance Status

The ECOG performance status is an investigator assessment of the impact of the disease on the subject's activities of daily living. It is assessed on a 6-point scale as described in Appendix 6 {Oken 1982}.

6.3. Biomarker Testing

6.3.1. Biomarker Samples to Address the Study Objectives:

The following biological specimens will be collected in this study and will be used to evaluate the association of exploratory systemic and/or tissue specific biomarkers with study drug response including efficacy and/or adverse events, as well as to increase knowledge and understanding of the biology of related diseases. The specific analyses will include, but will not be limited to, the biomarkers and assays listed below. Because biomarker science is a rapidly evolving area of investigation, and adverse events in particular are difficult to predict, it is not possible to specify prospectively all tests that will be done on the specimens provided. The testing outlined below is based upon the current state of scientific knowledge. It may be modified during or after the end of the study to remove tests no longer indicated and/or to add new tests based upon the growing state of the art knowledge. Specimens will be collected from all subjects which may allow for individualized drug therapy for subjects in the future. Blood samples will be collected from all subjects at baseline and after treatment to assess changes in the Syk pathway, relevant downstream pathways and Syk associated pathways in blasts. The testing may include assessing phosphorylation of Syk and other downstream mediators, cytokines and chemokines. Specimens will be collected from all subjects. PPD

Blood and bone marrow samples will be collected to study:

- Mechanisms of resistance to GS-9973 by analysis of DNA and genes, and/or proteins that change between baseline and at disease progression. These studies will allow us to identify new and improved therapies for ALL

- Effects of GS-9973 on signaling and minimal residual disease to better understand the effects of GS-9973 on disease burden

6.3.2. Biomarker Samples for Optional Future Research

PPD

PPD

PPD

6.4. Pretreatment Assessments

6.4.1. Screening Visit

Subjects will be screened within 28 days of their first administration of study treatment to determine eligibility for participation in the study. The following will be performed and documented at screening:

- Obtain written informed consent
- Obtain medical history
- Obtain smoking status
- Complete physical examination including, vital signs, body weight, and height
- Obtain blood samples
- Bone marrow aspirate/biopsy (if not done within 28 days of the first dose of GS-9973)
- CT scan or PET-CT of affected site/s for subjects with EMD only and without measureable BM involvement
- Record any serious adverse events and all adverse events related to protocol mandated procedures occurring after signing of the consent form

Subjects meeting all of the inclusion criteria and none of the exclusion criteria will return to the clinic within 28 days of screening for enrollment into the study.

From the time of obtaining informed consent through the first administration of study drug (GS-9973), record all serious adverse events (SAEs), as well as any adverse events related to protocol-mandated procedures on the adverse events case report form (CRF/eCRF). All other untoward medical occurrences observed during the screening period, including exacerbation or changes in medical history are to be captured on the medical history CRF/eCRF. See Section 7.6 Adverse Events and Toxicity Management for additional details.

6.5. Treatment Assessments

Subjects who have met all eligibility criteria will come to the clinic to start the Lead-in phase of the study and to perform study required procedures prior to dosing. Review prior/ concomitant medications and record adverse events at each clinic visit.

For study purposes, the GS-9973 Lead-in is 7 days.

6.5.1. Lead-in Phase:

- Review prior/concomitant medication

- Record any adverse events
- Vital signs; including blood pressure, respiratory rate, pulse, temperature, oxygen saturation
- Performance status (ECOG)
- Modified physical exam including weight
- Smoking Status
- Laboratory assessments (Section 6.2.6):
  - Hematology
  - Chemistry
  - Coagulation
  - Pharmacokinetic sampling at pre-dose and 1.5 hours post-dose of GS-9973 (± 30 minutes)
  - Biomarker sampling (pre-dose)
  - Urine pregnancy test for females of child bearing potential
- Study drug dispensation

6.5.2. Cycle 1

After completing the 7 day Lead-in phase, the subjects will start Cycle 1 for 28 days.

6.5.2.1. Cycle 1: Day 1

- Review prior/concomitant medication
- Record any adverse events
- Obtain smoking status
- Vital signs; including blood pressure, respiratory rate, pulse, temperature, oxygen saturation level
- Performance status (ECOG)
- Modified physical exam including weight
- Laboratory assessments (Section 6.2.6.):
  - Hematology
  - Chemistry

- Coagulation
- Pharmacokinetic peripheral blood sampling at pre-dose and 1.5 hours post-dose of GS-9973 (± 30 minutes)
- Biomarker sampling

PPD

- Study drug dispensation
- VCR administration
- Urine pregnancy test for females of child bearing potential

6.5.2.2. Cycle 1: Day 8

- Review prior/concomitant medication
- Record any adverse events
- Vital signs; including blood pressure, respiratory rate, pulse, temperature, oxygen saturation level
- Performance status (ECOG)
- Modified physical exam
- Laboratory assessments (Section 6.2.6.):
  - Hematology
  - Chemistry
  - Coagulation
  - Pharmacokinetic peripheral blood sampling pre-dose and 1.5 hours post-dose of GS-9973 (± 30 minutes)
  - Biomarker sampling (pre-dose)
- VCR administration
- Dexamethasone dispensation
- Bone marrow aspirate/biopsy
- CT scan or PET-CT of affected site/s for subjects with EMD only and without measureable BM involvement (Patients with no BM involvement and only EMD will not require BM aspirate/biopsy on cycle 1 day 8).

6.5.2.3. Cycle 1: Day 15

- Review prior/concomitant medication
- Record any adverse events
- Vital signs; including blood pressure, respiratory rate, pulse, temperature, oxygen saturation level
- Performance status (ECOG)
- Modified physical exam
- Laboratory assessments (Section 6.2.6.):
  - Hematology
  - Chemistry
  - Coagulation
- VCR administration

6.5.2.4. Cycle 1: Day 22

- Review prior/concomitant medication
- Record any adverse events
- Vital signs; including blood pressure, respiratory rate, pulse, temperature, oxygen saturation level
- Performance status (ECOG)
- Modified physical exam
- Laboratory assessments (Section 6.2.6.):
  - Hematology
  - Chemistry
  - Coagulation
- VCR administration
- Dexamethasone dispensation

6.5.2.5. Cycle 1: Day 28

- Review prior/concomitant medication

- Record any adverse events
- Vital signs; including blood pressure, respiratory rate, pulse, temperature, oxygen saturation level
- Performance status (ECOG)
- Modified physical exam including weight
- Laboratory assessments:
  - Hematology
  - Chemistry
  - Pharmacokinetic peripheral blood sampling at pre-dose and 1.5 hours post-dose of GS-9973 (± 30 minutes)
  - Biomarker sampling (pre-dose)
- CNS Prophylaxis (per institutional standard)
- Bone marrow aspirate/biopsy
- Cerebrospinal fluid (CSF) for PK analysis (prior to CNS prophylaxis administration)
- CT scan or PET-CT of affected site/s for subjects with EMD only and without measureable BM involvement (Patients with no BM involvement and only EMD will not require BM aspirate/biopsy on cycle 1 day 28)
- Study drug dispensation; if needed for cycle break coverage

6.5.3. Cycle 2

Subjects may continue to Cycle 2 within 7 days of completing Cycle 1.

6.5.3.1. Cycle 2: Day 1

- Review prior/concomitant medication
- Record any adverse events
- Obtain smoking status
- Vital signs; including blood pressure, respiratory rate, pulse, temperature, oxygen saturation level
- Performance status (ECOG)

- Modified physical exam including weight
- Laboratory assessments (Section 6.2.6.):
  - Hematology
  - Chemistry
  - Coagulation
- Urine pregnancy test for females of child bearing potential
- Study drug dispensation
- VCR administration
- Dexamethasone dispensation

6.5.3.2. Cycle 2: Day 8

- Review prior/concomitant medication
- Record any adverse events
- Vital signs; including blood pressure, respiratory rate, pulse, temperature, oxygen saturation level
- Performance status (ECOG)
- Modified physical exam
- Laboratory assessments (Section 6.2.6.):
  - Hematology
  - Chemistry
  - Coagulation
- VCR administration

6.5.3.3. Cycle 2: Day 15

- Review prior/concomitant medication
- Record any adverse events

- Vital signs; including blood pressure, respiratory rate, pulse, temperature, oxygen saturation level
- Performance status (ECOG)
- Modified physical exam
- Laboratory assessments (Section 6.2.6.):
  - Hematology
  - Chemistry
  - Coagulation
- VCR administration
- Dexamethasone dispensation

6.5.3.4. Cycle 2: Day 22

- Review prior/concomitant medication
- Record any adverse events
- Vital signs; including blood pressure, respiratory rate, pulse, temperature, oxygen saturation level
- Performance status (ECOG)
- Modified physical exam
- Laboratory assessments (Section 6.2.6.):
  - Hematology
  - Chemistry
  - Coagulation
- VCR administration

6.5.3.5. Cycle 2: Day 28

- Review prior/concomitant medication
- Record any adverse events

- Vital signs; including blood pressure, respiratory rate, pulse, temperature, oxygen saturation level
- Performance status (ECOG)
- Modified physical exam
- Laboratory assessments :
  - Hematology
  - Chemistry
  - Pharmacokinetic peripheral blood sampling at pre-dose and 1.5 hours post-dose of GS-9973 (± 30 minutes)
  - Biomarker sampling (pre-dose)
- Study drug dispensation, if needed for cycle break coverage
- CNS prophylaxis (per institutional standard)
- Bone marrow aspirate/biopsy
- Cerebral fluid (CSF) for PK analysis (prior to CNS prophylaxis administration)
- CT scan or PET-CT of affected site/s for subjects with EMD only and without measureable BM involvement, unless imaging was performed within 30 days of end of treatment (Patients with no BM involvement and only EMD will not require BM aspirate/biopsy on cycle 2 day 28).

6.6. Maintenance

Subjects who obtain clinical benefit in the opinion of the treating physician may continue GS-9973 at the assigned dose level during maintenance for up to 36 cycles. VCR will be administered on Day 1 of each 28-day cycle. Dexamethasone (20 mg total dose daily for 4 days, either 10 mg twice daily or 20 mg once daily) will be taken on Days 1-4 and 15-18 of each 28-day cycle.

Refer to Appendix 2 for procedures performed during maintenance. Study drug (GS-9973) will be dispensed at Day 1 of each cycle during maintenance.

Bone marrow evaluations and additional central nervous system (CNS) prophylaxis can be performed as clinically indicated per institutional standards in the maintenance.

6.7. End of Study Treatment Assessments

Subjects will be removed from study treatment when any of the criteria listed in Section 6.8 apply.

The following procedures will be conducted when a subject goes off study treatment and prior to initiating a new regimen.

If the subject chooses not to continue participation on the study, the procedures listed below are to be conducted within 14 days of the last dose of study treatment or prior to initiating a new therapy.

- Review prior/concomitant medication
- Record any adverse events
- Performance status (ECOG)
- Modified physical exam including weight
- Vital signs; including blood pressure, respiratory rate, pulse, temperature, oxygen saturation level
- Laboratory assessments (Section 6.2.6.):
  - Chemistry
  - Hematology
  - Coagulation
  - Biomarker sampling
- Obtain bone marrow aspirate/biopsy samples for disease assessment and Biomarker testing
- CT scan or PET-CT of affected site/s for subjects with EMD only and without measureable BM involvement unless imaging was performed within 30 days of end of treatment (Patients with no BM involvement and only EMD will not require BM aspirate/biopsy)

6.7.1. 30-Day Follow-up

After the last dose of study drug, subjects should be followed for any drug-related AEs and/or ongoing serious adverse events (SAEs) until those events have resolved or become stable, whichever occurs later. The site will contact the study subject regardless of AE/SAE status approximately 30 days after the subject's last dose of study drug to assess adverse events since the last study visit and review concomitant medications. Subject should be contacted by phone (or in person, if necessary) to assess the subject's condition and record any adverse events reported during the follow-up contact. Phone call or visit should be documented.

6.7.2. Long Term Follow-Up

Long term follow-up for survival will be conducted every 3 months (± 4 weeks) after the discontinuation of treatment visit until end of study. Information to be gathered includes ALL treatments, other malignancies, and survival which could be collected during a routine clinic visit, other contact with the subject, or via telephone. Gilead reserves the right to discontinue or shorten the duration of participation in the long term follow-up period at any time.

6.8. Criteria for Discontinuation of Study Treatment

Study medication must be discontinued in the following instances:

- Intercurrent illness that would, in the judgment of the investigator, affect assessments of clinical status to a significant degree. Following resolution of intercurrent illness, the subject may resume study dosing at the discretion of the investigator
- Unacceptable toxicity, or toxicity that, in the judgment of the investigator, compromises the ability to continue study-specific procedures or is considered not to be in the subject's best interest
- The investigator, in consultation with the Gilead Medical Monitor or designee, 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
- Subject request to discontinue for any reason. Any subject has the right to withdraw from the study at any time
- Subject noncompliance with study treatment 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 who becomes pregnant or begins breastfeeding should be withdrawn from study drug; refer to Appendix 5
- Discontinuation of the study at the request of GSI, a regulatory agency or an institutional review board or independent ethics committee (IRB/IEC)

6.9. End of Study

End of study will be defined as when all patients complete long term follow-up or discontinue their participation in the study due to death, withdrawal of consent or lost to follow up, or the time at which the Sponsor closes the study.

6.10. Post Study Care

Does not apply.

7. ADVERSE EVENTS AND TOXICITY MANAGEMENT

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

7.1.1. Adverse Events

An adverse event (AE) is any untoward medical occurrence in a clinical study subject administered a medicinal product, which does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and/or unintended sign, symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. AEs may also include pre- or post-treatment complications that occur as a result of protocol specified procedures, lack of efficacy, overdose, drug abuse/misuse reports, or occupational exposure. Preexisting events that increase in severity or change in nature during or as a consequence of participation in the clinical study will also be considered AEs.

An AE does not include the following:

- Medical or surgical procedures such as surgery, endoscopy, tooth extraction, and transfusion. The condition that led to the procedure may be an adverse event and must be reported
- Preexisting diseases, conditions, or laboratory abnormalities present or detected before the screening visit that do not worsen
- Situations where an untoward medical occurrence has not occurred (e.g., hospitalization for elective surgery, social and/or convenience admissions)
- Overdose without clinical sequelae (see Section 7.7.1)
- Any medical condition or clinically significant laboratory abnormality with an onset date before the consent form is signed and not related to a protocol-associated procedure is not an AE. It is considered to be preexisting and should be documented on the medical history CRF

7.1.2. Serious Adverse Events

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

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

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

7.1.2.1. Protocol-Specific Serious Adverse Event Instructions

Disease Progression and Death Related to Disease Progression:

In order to maintain the integrity of the study, the following events that are assessed as unrelated to study drugs will not be considered SAEs:

- Progression of Acute Lymphoblastic Leukemia (ALL) being studied
- Death due to Acute Lymphoblastic Leukemia (ALL) being studied

Disease progression and death from disease progression should be reported as SAEs by the investigator only if it is assessed that the study drugs caused or contributed to the disease progression (i.e., by a means other than lack of effect). Unrelated disease progression should be captured on the eCRF.

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

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

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

For specific information on handling of clinical laboratory abnormalities in this study, please refer to Section 7.5.

7.2. Assessment of Adverse Events and Serious Adverse Events

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

7.2.1. Assessment of Causality for Study Drugs and Procedures

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

- **No**: Evidence exists that the adverse event has an etiology other than the study drug. For SAEs, an alternative causality must be provided (eg, preexisting condition, underlying disease, intercurrent illness, or concomitant medication).

- **Yes**: There is reasonable possibility that the event may have been caused by the investigational medicinal product (study drug GS-9973).

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

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

- **No:** Evidence exists that the adverse event has an etiology other than the study procedure

- **Yes:** The adverse event occurred as a result of protocol procedures, (eg., venipuncture)

7.2.2. Assessment of Severity

The severity of adverse events will be graded using the CTCAE, Version 4.03. For each episode, the highest severity grade attained should be reported.

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

Table 7-1. Grading of Adverse Event Severity

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

The distinction between the seriousness and the severity of an 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 7.3.

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

Requirements for collection prior to study drug initiation:

After informed consent, but prior to initiation of study medication, the following types of events should be reported on the case report form (CRF/eCRF): all SAEs and adverse events related to protocol-mandated procedures.

Adverse Events

Following initiation of study medication until 30 days after last administration of study medication AEs, regardless of cause or relationship, must be reported to the CRF/eCRF database as instructed.

All AEs should be followed up until resolution or until the adverse event is stable, if possible. Gilead Sciences may request that certain AEs be followed beyond the protocol defined follow up period.

Serious Adverse Events

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

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

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

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

Electronic Serious Adverse Event (eSAE) Reporting Process

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

- If for any reason it is not possible to record the SAE information electronically, ie, the eCRF database is not functioning, record the SAE on the paper serious adverse event reporting form and submit within 24 hours to: Email: PPD and Fax: PPD

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

- If an SAE has been reported via a paper form because the eCRF database has been locked, no further action is necessary. For fatal or life-threatening events, copies of hospital case reports, autopsy reports, and other documents are also to be submitted by e-mail or fax when requested and applicable. Transmission of such documents should occur without personal subject identification, maintaining the traceability of a document to the subject identifiers.

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

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

7.4. Gilead Reporting Requirements

Depending on relevant local legislation or regulations, including the applicable US FDA Code of Federal Regulations, the EU Clinical Trials Directive (2001/20/EC) and relevant updates, and other country-specific legislation or regulations, Gilead may be required to expedite to worldwide regulatory agencies reports of SAEs, serious adverse drug reactions (SADRs), or suspected unexpected serious adverse reactions (SUSARs). In accordance with the EU Clinical Trials Directive (2001/20/EC), Gilead or a specified designee will notify worldwide regulatory agencies and the relevant IEC in concerned Member States of applicable SUSARs as outlined in current regulations.

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

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

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

Laboratory abnormalities are usually not recorded as AEs or SAEs. However, laboratory abnormalities (eg, clinical chemistry, hematology, and urinalysis) that require medical or surgical intervention or lead to investigational medicinal product interruption or discontinuation must be recorded as an AE, as well as an SAE, if applicable. In addition, laboratory or other abnormal assessments (eg, electrocardiogram, X-rays, vital signs) that are associated with signs and/or symptoms must be recorded as an AE or SAE if they meet the definition of an AE or SAE as described in Section 7.1.1 and 7.1.2, respectively. If the laboratory abnormality is part of a syndrome, record the syndrome or diagnosis (ie, anemia) not the laboratory result (ie, decreased hemoglobin).

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

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

7.6. Toxicity Management

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

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

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

7.7. Special Situations Reports

7.7.1. Definitions of Special Situations

Special situation reports include all reports of medication error, abuse, misuse, overdose, reports of adverse events associated with product complaints, and pregnancy reports regardless of an associated AE.

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

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

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

An overdose is defined as an accidental or intentional administration of a quantity of a medicinal product given per administration or cumulatively which is above the maximum recommended dose as per protocol or in the product labelling (as it applies to the daily dose of the subject in question). In cases of a discrepancy in drug accountability, overdose will be established only when it is clear that the subject has taken the excess dose(s). Overdose cannot be established when the subject cannot account for the discrepancy except in cases in which the investigator has reason to suspect that the subject has taken the additional dose(s).

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

7.7.2. Instructions for Reporting Special Situations

7.7.2.1. Instructions for Reporting Pregnancies

The investigator should report pregnancies in female study subjects that are identified after initiation of study medication and throughout the study, including the post study drug follow-up period, to the or Gilead DSPH using the pregnancy report form within 24 hours of becoming aware of the pregnancy.

Refer to Section 9.1.6 and the CRF/eCRF completion guidelines for full instructions on the mechanism of pregnancy reporting.

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

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

A spontaneous abortion is always considered to be an SAE and will be reported within 24 hours (Section 7.3). Furthermore, any SAE occurring as an adverse pregnancy outcome post study must be reported to Gilead DSPH.

The subject should receive appropriate monitoring and care until the conclusion of the pregnancy. The outcome should be reported to Gilead DSPH using the pregnancy outcome report form. If the end of the pregnancy occurs after the study has been completed, the outcome should be reported directly to Gilead DSPH. Gilead DSPH contact information is as follows: Email: PPD and Fax: PPD

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

Refer to Appendix 5 for Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Requirements.

7.7.2.2. Reporting Other Special Situations

All other special situation reports must be reported on the special situations report form and forwarded to Gilead DSPH within 24 hours of the investigator becoming aware of the situation. These reports must consist of situations that involve study drug and/or Gilead concomitant medications, but do not apply to non-Gilead concomitant medications.

Special situations involving non-Gilead concomitant medications does not need to be reported on the special situations report form; however, for special situations that result in AEs due to a non-Gilead concomitant medication, the AE should be reported on the AE form.

Any inappropriate use of concomitant medications prohibited by this protocol should not be reported as “misuse,” but may be more appropriately documented as a protocol deviation.

Refer to Section 7.7 and the CRF/eCRF completion guidelines for full instructions on the mechanism of special situations reporting.

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

8. STATISTICAL CONSIDERATIONS

8.1. Analysis Objectives and Endpoints

8.1.1. Analysis Objectives

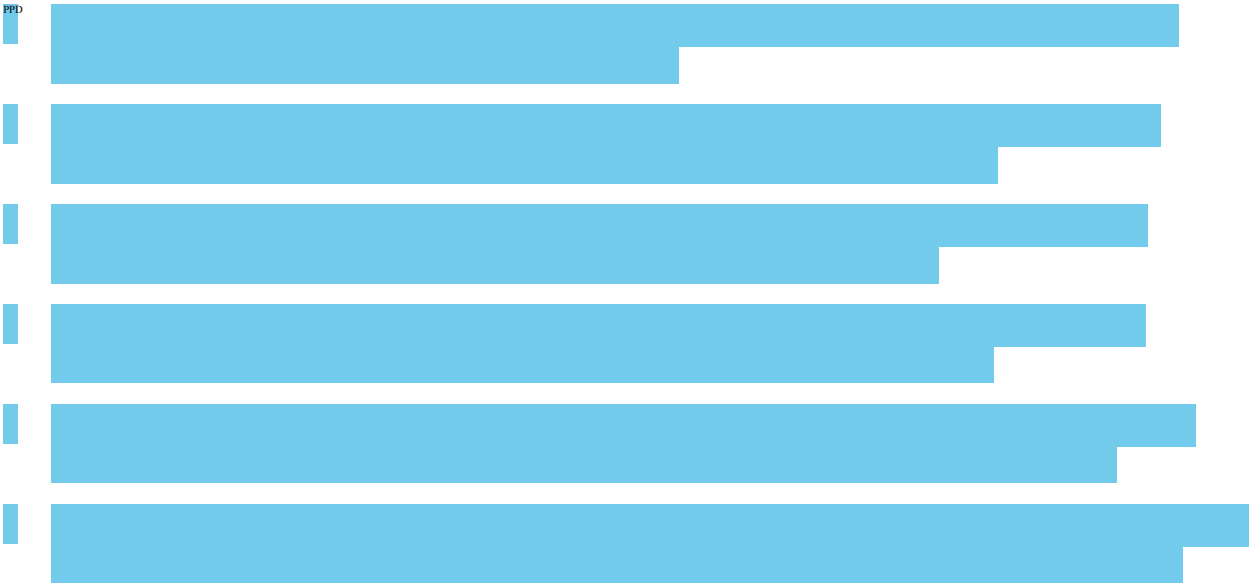
Primary objectives

- To evaluate safety of entospletinib (GS-9973) in combination with vincristine (VCR) and dexamethasone in adult subjects with previously treated relapsed or refractory B-cell lineage ALL

Secondary objectives

- To determine the recommended dose of GS-9973 in combination with VCR and dexamethasone in adult subjects with previously treated relapsed or refractory B-cell lineage ALL
- To evaluate the therapeutic response of GS-9973 in combination with VCR and dexamethasone in adult subjects with previously treated relapsed or refractory B-cell lineage ALL

The exploratory objectives of this study are:



8.1.2. Primary Endpoint

The primary endpoint is safety. Safety will be evaluated by:

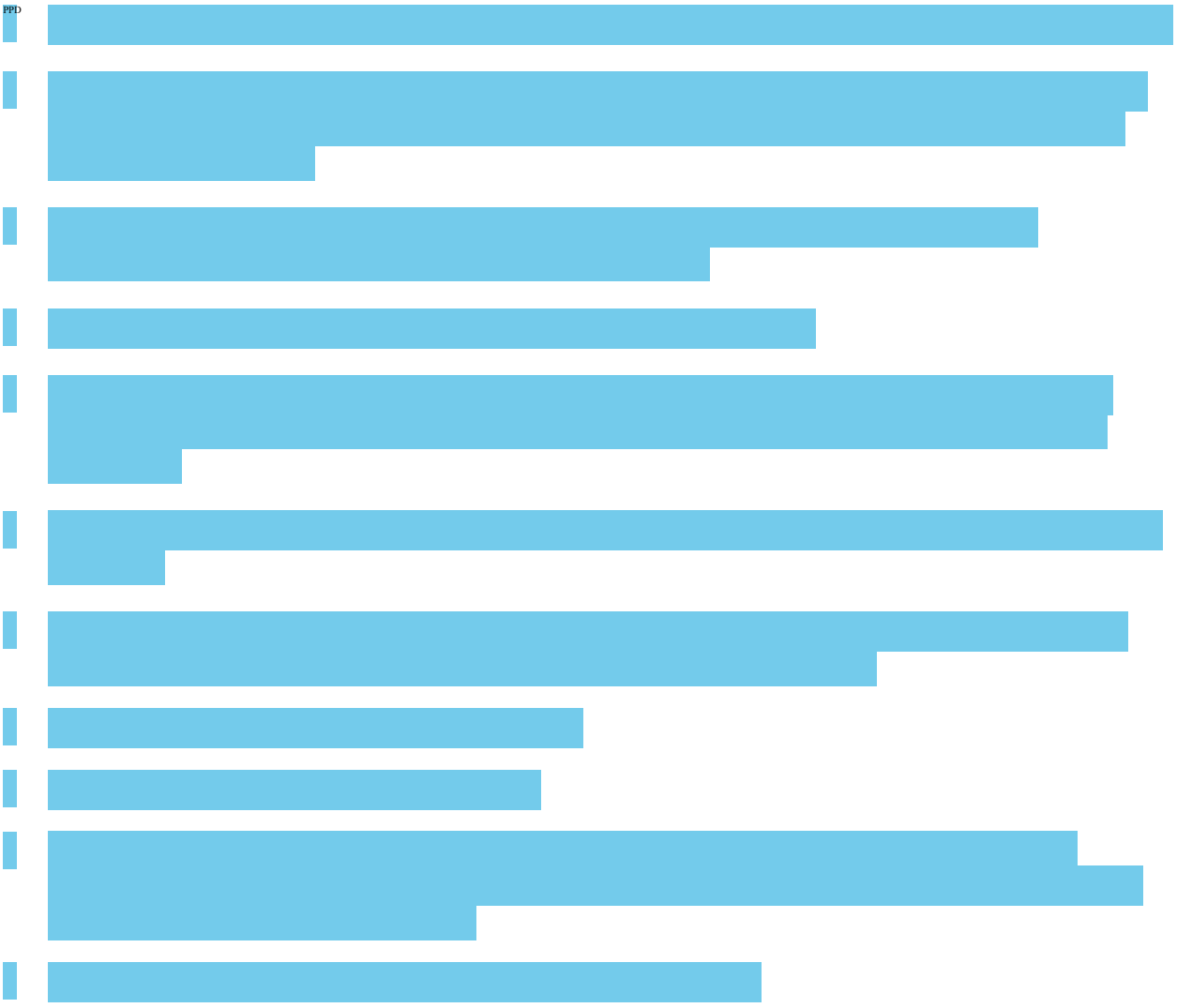
- Occurrence of adverse events and laboratory abnormalities defined as dose limiting toxicities (DLTs)

8.1.3. Secondary Endpoint

- Overall Remission (CR or CRi) rate at end of induction - defined as the proportion of subjects who achieve a complete remission (CR) or complete remission with incomplete hematologic recovery (CRi) at end of induction
- Complete remission (CR) rate at end of induction
- Partial response (PR) rate at end of induction - defined as the proportion of subjects who achieve a partial response of marrow (as defined in Appendix 4) or by imaging criteria for patients with extramedullary disease (NCCN guidelines version 2.2016) as the best response.
- Overall Response (CR, CRi, or PR) rate at end of induction - defined as the proportion of subjects who achieve a complete remission (CR), complete remission with incomplete hematologic recovery (CRi) or partial response (PR) at end of induction

8.1.4. Exploratory endpoints

PPD



8.2. Analysis Sets

8.2.1. All Enrolled Analysis Set

All Enrolled Analysis Set includes all subjects who received a study subject identification number in the study after screening.

8.2.2. Full Analysis Set

The Full Analysis Set (FAS) includes all subjects who receive at least 1 dose of study treatment. This analysis set will be used in the analyses of subject characteristics, exposure, safety, and efficacy. Subjects will be grouped by dose level and overall.

8.2.3. DLT Analysis Set

The DLT Analysis Set includes subjects in FAS with sufficient drug exposure (Section 3.3.1) or experience a DLT during the DLT assessment window. Subjects will be grouped by dose level and overall.

8.2.4. Pharmacokinetic Analysis Set

The Pharmacokinetic Analysis sets include subjects in FAS who have the necessary baseline and post-treatment measurements to provide interpretable results for the specific parameters of interest. This analysis set will be used in the analysis of GS-9973 plasma pharmacokinetic.

8.3. Data Handling Conventions

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 dose level, analysis set, and time point if applicable. As appropriate, changes from baseline to each subsequent time point will be described and summarized. Similarly, as appropriate, the best change from baseline during the study will also be described and summarized. Graphical techniques (eg, waterfall plots, Kaplan-Meier curves, line plots) may be used when such methods are appropriate and informative.

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

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

8.4. Demographic Data and Baseline Characteristics

A listing of all full-analysis subjects will be generated to describe site, subject number, first screening date, first treatment date, dose level, duration of study drug treatment, and the reason for discontinuing study treatment. Available information on subjects who were screened but not treated may be listed separately.

Subject demographic and baseline characteristics will be listed and summarized by dose level for the full analysis set.

8.5. Efficacy Analysis

The efficacy will be evaluated per the response criteria in NCCN guidelines on ALL (Appendix 4).

8.5.1. Primary Analysis

Categorical Endpoints

Overall remission rate and other response rate variables will be described. In the analyses of overall remission rate at induction completion, 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% exact CIs will be presented.

Time-to-Event Endpoints

RFS, EFS and OS will be analyzed using Kaplan-Meier (KM) methods. The KM estimate of the survival function will be computed and the results will be presented using KM curves. The median will be provided along with the corresponding 95% CI. Additionally, the 25% and 75% percentiles for these endpoints will also be provided. In addition, the estimated rate at 6 month, 12 month, 2 year and 3 year will be reported.

The following censoring rules will be applied:

RFS: For a subject who is not known to have relapsed or died by the end of the study follow-up or data cutoff, RFS is censored on the date of the last available disease assessment of the subject.

EFS: For subjects with none of the events defined in EFS before the end of the study follow-up or data cutoff, EFS is censored at the date of the last available disease assessment of the subject.

OS: For a subject who is not known to have died by the end of study follow-up or data cutoff, OS is censored on the date the subject is last known to be alive.

Analysis of remission duration will be analyzed using cumulative incidence by considering death without relapse as competing risks. The estimate of the cumulative incidence of relapse (CIR) will be reported with the associated 95% CI. For a subject with no report of relapse by the end of the study follow-up or data cutoff date, observation is censored on the date of the last available assessment of the subject.

Continuous Endpoints

Continuous endpoints (e.g. TTR and TTC) will be summarized using descriptive statistics.

8.6. Safety Analysis

All safety data collected on or after the date that study treatment was first dosed up to 30 days after the date of last dose of study treatment will be summarized by dose level.

8.6.1. Extent of Exposure

Descriptive information will be provided by dose level regarding the number of doses of study treatment prescribed, the total number of doses taken, duration of treatment, and the number and timing of prescribed dose reductions and interruptions.

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

8.6.2. 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 onset in the period from the first dose of study treatment to 30 days after the permanent discontinuation of study treatment or that leads to permanent discontinuation 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_5x7.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 treatment will be categorized as related or unrelated.

Treatment-emergent adverse events will be summarized. 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. The summary will be presented in decreasing frequency of System Organ Class and Preferred Term of the ‘Total’ column. Within the same frequency, the AEs are ordered in the alphabetical order of System Organ Class and Preferred Term.

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

- Study-drug-related adverse events
- Adverse events that are Grade ≥ 3 in severity
- Adverse events leading to study treatment interruption and/or dose modification
- Adverse events leading to study treatment discontinuation
- Serious adverse events
- DLT will be listed and summarized; DLT rate will be presented by dose level and the corresponding 90% CIs will be presented

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

Shift tables for hematology and serum chemistry 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]).

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

8.7. Pharmacokinetic Analysis

Concentrations of each agent of the treatment in plasma will be determined using a validated bioanalytical assay. Plasma concentrations will be displayed as individual concentration vs. time using scheduled sampling times. Concentrations will be listed by subject and summarized using descriptive statistics (eg, n, arithmetic mean, geometric mean, % coefficient of variation [CV], StD, median, Q1, Q3, min, and max). Mean (±StD) plasma concentration-time curves will be plotted in both semi-logarithmic and linear formats.

8.8. Biomarker Analysis

Changes in biomarkers will be evaluated descriptively. Data explorations may be performed to evaluate potential associations between subject characteristics and outcome measures. Explorations may also be performed to assess the potential associations between different outcomes measures (eg, relationships between biomarkers and clinical endpoints of response).

8.9. Sample Size

Assuming that 4 planned dose levels are tested for escalation and 3, 3, 6 and 6 subjects are tested at each dose level, respectively (18 subjects for Dose Escalation), and assuming 10% subjects are unevaluable during Dose Escalation, 20 subjects will be enrolled during Dose Escalation.

A total of 3 to 6 subjects will be treated at each of the proposed dose levels. Based on the 3+3 dose-escalation scheme, Table 8-1 shows the probability of escalating to the next dose level or proceeding to the next stage, based on the true rate of DLT at the current dose level.

Table 8-1. Probability of Dose Escalation (N=3+3)

True Incidence of DLT	Probability of Escalating
10%	0.91
20%	0.71
30%	0.49
40%	0.31
50%	0.17
60%	0.08

Thus, if the true underlying proportion of DLT is low (eg, ≤ 10% at the current dose level, there is a high probability (≥ 0.91) of dose escalation to the next dose level. Conversely, if the true underlying proportion of DLT is high (eg, ≥ 60%) at the current dose level, there is a low probability (≤ 0.08) of escalation to the next dose level.

The trial employs the standard NCI definition of MTD (starting dose associated with DLT in < 33.3% of subjects during the DLT assessment window).

8.10. Timing of Analyses

8.10.1. Interim Analyses

No formal interim analyses are planned in this study. The GSI study team and the investigators will collectively discuss study conduct and accumulating safety and other data.

8.10.2. Final Analysis

Final study reporting is expected to occur after all subjects have discontinued study.

9. RESPONSIBILITIES

9.1. Investigator Responsibilities

9.1.1. Good Clinical Practice

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

The investigator will ensure adherence to the basic principles of Good Clinical Practice, as outlined in 21 CFR 312, subpart D, "Responsibilities of Sponsors and Investigators," 21 CFR, part 50, 1998, and 21 CFR, part 56, 1998.

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

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

The investigator (or sponsor as appropriate according to local regulations) will submit this protocol, informed consent form, and any accompanying material to be provided to the subject (such as advertisements, subject information sheets, or descriptions of the study used to obtain informed consent) to an IRB/IEC. The investigator will not begin any study subject activities until approval from the Sponsor been documented and provided as a letter to the investigator.

Before implementation, the investigator will submit to and receive documented approval from the IRB/IEC any modifications made to the protocol or any accompanying material to be provided to the subject after initial IRB/IEC approval, with the exception of those necessary to reduce immediate risk to study subjects.

9.1.3. Informed Consent

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

and dated by the subject or the subject's legally authorized representative and the person conducting the consent discussion, and also by an impartial witness if required by local requirements. PPD

9.1.4. Confidentiality

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

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

9.1.5. Study Files and Retention of Records

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

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

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

- Subject identification (name, date of birth, gender);
- Documentation that subject meets eligibility criteria, ie, history, physical examination, and confirmation of diagnosis (to support inclusion and exclusion criteria);
- Documentation of the reason(s) a consented subject is not enrolled
- Participation in study (including study number);

- Study discussed and date of informed consent;
- Dates of all visits;
- Documentation that protocol specific procedures were performed;
- Results of efficacy parameters, as required by the protocol;
- Start and end date (including dose regimen) of study drug, including dates of dispensing and return;
- Record of all adverse events and other safety parameters (start and end date, and including causality and severity);
- Concomitant medication (including start and end date, dose if relevant; dose changes);
- Date of study completion and reason for early discontinuation, if it occurs.

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

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

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

9.1.6. Case Report Forms

For each subject consented, an eCRF will be completed by an authorized study staff member whose training for this function is documented according to study procedures. eCRF should be completed on the day of the subject visit to enable the sponsor to perform central monitoring of safety data. The Eligibility Criteria eCRF should be completed only after all data related to eligibility have been received. Subsequent to data entry, a study monitor will perform source data verification within the EDC system. Original entries as well as any changes to data fields will be stored in the audit trail of the system. Prior to database lock (or any interim time points as described in the clinical data management plan), the investigator will use his/her log in credentials to confirm that the forms have been reviewed, and that the entries accurately reflect

the information in the source documents. The eCRF capture the data required per the protocol schedule of events and procedures. System-generated or manual queries will be issued to the investigative site staff as data discrepancies are identified by the monitor or internal Gilead staff, who routinely review the data for completeness, correctness, and consistency. The site coordinator is responsible for responding to the queries in a timely manner, within the system, either by confirming the data as correct or updating the original entry, and providing the reason for the update (e.g. data entry error). At the conclusion of the trial, Gilead will provide the site with a read-only archive copy of the data entered by that site. This archive must be stored in accordance with the records retention requirements outlined in Section 9.1.5.

9.1.7. Investigational Medicinal Product Accountability and Return

Used and unused study drug supplies should be destroyed on site if the site has an appropriate standard operating procedure (SOP) for drug destruction as determined by Gilead. The site may destroy used (empty or partially empty) and unused study drug supplies in accordance with that site's approved SOP. A copy of the site's approved SOP will be obtained for central files.

The study monitor will evaluate each study center's study drug disposal procedures and provide appropriate instruction for destruction of unused study drug supplies on site. The investigator must maintain accurate records for all study drug destroyed at the site. Records must show the identification and quantity of each unit destroyed, the method of destruction, and the person who disposed of the study drug. Upon study completion, copies of the study drug accountability records must be filed at the site. Another copy will be returned to Gilead.

If destruction of study drug on site is not possible, the study drug is to be returned to the shipping facility for eventual destruction. The monitor will provide further instructions for the return.

The study monitor will review study drug supplies and associated records at study monitoring visits.

9.1.8. Inspections

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

9.1.9. Protocol Compliance

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

9.2. Sponsor Responsibilities

9.2.1. Protocol Modifications

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

9.2.2. Study Report and Publications

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

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

the results of the study in their entirety have been publicly disclosed by or with the consent of Gilead in an abstract, manuscript, or presentation form or the study has been completed at all study sites for at least 2 years

The investigator will submit to Gilead any proposed publication or presentation along with the respective scientific journal or presentation forum at least 30 days before submission of the publication or presentation.

No such communication, presentation, or publication will include Gilead's confidential information (see Section 9.1.4).

The investigator will comply with Gilead's request to delete references to its confidential information (other than the study results) in any paper or presentation and agrees to withhold publication or presentation for an additional 60 days in order to obtain patent protection if deemed necessary.

9.3. Joint Investigator/Sponsor Responsibilities

9.3.1. Payment Reporting

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

9.3.2. Access to Information for Monitoring

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

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

9.3.3. Access to Information for Auditing or Inspections

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

9.3.4. Study Discontinuation

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

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11. APPENDICES

Appendix 1. Investigator Signature Page

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

STUDY ACKNOWLEDGEMENT

A Phase 1b/2, Open-Label, Dose Escalation and Expansion Study Evaluating the Safety and Efficacy of Entospletinib (GS-9973) with Vincristine and Dexamethasone in Adult Subjects with Relapsed or Refractory Acute Lymphoblastic Leukemia (ALL)

GS-US-339-1560, Amendment 5, 13April 2018

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

PPD

Name (Printed)
Author

PPD

Signature

13 APR 2018

Date

INVESTIGATOR STATEMENT

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

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

Principal Investigator Name (Printed)

Signature

Date

Site Number

Appendix 2. Study Procedures Table

Study Phase	Screening (-28 days)	GS-9973 Lead-in*	Cycle 1					Cycle 2					Maintenance**					End of Treatment	30 Day Follow-Up
Cycle Day	**Screening**	**-7**	**1**	**8**	**15**	**22**	**28**	**1**	**8**	**15**	**22**	**28**	**1**	**8**	**15**	**22**	**28**		
Study Day		**1**	**8**	**15**	**22**	**29**	**35**												
Study Assessments																			
Informed Consent	X																		
General and Safety Assessments																			
Physical Exam and weight[a]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital Signs[b]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AE/Concomitant Meds[c]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Medical History	X																		
HBV, HCV, and HIV Virology	X																		
Smoking status	X	X	X					X					X						
Disease Assessments																			
ECOG	X	X	X					X					X					X	
Laboratory Assessments																			
Bone marrow aspirate and biopsy[d]	X			X			X					X						X	
Hematology[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Serum Chemistry & Liver Function Testing	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Urinalysis	X		X					X					X					X	
Urine or Serum Pregnancy Test or FSH[f]	X	X	X					X					X					X	
Pharmacokinetic Sampling[g]		X	X	X			X					X							
CSF (for PK sampling)[h]							X					X							

PPD

Study Phase	Screening (-28 days)	GS-9973 Lead-in*	Cycle 1					Cycle 2					Maintenance**					End of Treatment	30 Day Follow-Up
Imaging																			
CT or PET[k] (Investigator's discretion, for EMD subjects only)	X			X			X					X							
Investigational Product and Auxiliary																			
GS-9973[l]		X	X				X	X				X	X				X		
IV Vincristine[m]			X	X	X	X		X	X	X	X		X						
Dexamethasone[n]				X		X		X		X			X		X				
CNS Prophylaxis per institutional standard[o]							X					X							

* For Dose Escalation only

** During Maintenance Cycle 1, all visits are required. Starting from Maintenance Cycle 2, Day 1 is required and Day 8/15/22/28 visits are per the Investigator's discretion.

a Complete physical examination will be performed at Screening which includes height. A modified physical examination capturing changes from prior exams will be performed at other visits.

b Vital signs (including blood pressure, respiratory rate, pulse, oxygen saturation by pulse oximetry and temperature) should be taken after the subject has been sitting for at least 5 minutes.

c Following consent, adverse events will be assessed pre-and post-dose during each clinic visit, and 30 (±7) days following completion of the subject's last dose of study drug. Subjects should be contacted by phone (or in person, if necessary) 30 days (±7 days) after the subject's last dose of study drug to assess AEs. Subjects should be asked specifically if there are any AEs since stopping the study.

d Bone marrow aspirate/biopsy will be taken during Screening; Cycle 1 on Day 8 and Day 28; Cycle 2 on Day 28. PPD

e CBC with differential including PT/INR and PTT.

f For female subjects of childbearing potential, serum testing performed at screening only. Urine pregnancy test will be performed at Lead-in on Day -7 of (escalation) or during Cycle 1 on Day 1 (expansion). Pregnancy tests will be performed on a Day 1 of each cycle thereafter.

g Pharmacokinetic peripheral blood samples will be obtained pre-dose during Lead-in on Day -7; Cycle 1 on Day 1, 8, 28 and Cycle 2 on Day 28. PK blood samples will also be collected 1.5 hours post-dose of GS-9973 (±30 minutes) during Lead-in on Day -7; Cycle 1 on Days 1, 8, 28 and Cycle 2 on Day 28. CNS prophylaxis administration is independent of PK time point.

h CSF samples will be collected for pharmacokinetic analysis during Cycles 1 and Cycle 2 on Day 28 (prior to CNS prophylaxis administration).

PPD

k Subjects with EMD only, with no BM involvement will not require BM aspirate/biopsy

l Treatment with GS-9973 will be continuous. GS-9973 should be dispensed on Day 28 to include cycle break drug coverage, if necessary.

m Vincristine will be administered during Cycles 1 and Cycle 2 on Days 1, 8, 15, 22 and during Maintenance on Day 1 of each cycle.

n Dexamethasone (20 mg BID; dosed for 4 days) will be dispensed during Cycle 1 on Day 8 and Day 22 and during Cycle 2 on Day 1 and Day 15. During Maintenance, dexamethasone (20 mg QD or 10 mg BID; dosed for 4 days) will be dispensed on Day 1 and Day 15 of each cycle.

o CNS prophylaxis per institutional standard during Cycle 1 and Cycle 2 on Day 28 (± 3 days).

Appendix 3. Management of Clinical and Laboratory Adverse Events

Dosing Delays/Dose Modifications for AEs Attributed to GS-9973 (beyond Cycle 1)				
Adverse Event	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Dermatological	Maintain current dose level and schedule.	Maintain current dose level and schedule.	Withhold dosing until ≤ Grade 1 or return to baseline. Resume dosing at current dose level. If re-challenge at current dose level results in recurrence, may resume dosing at same or lower dose level at investigator discretion.	Withhold dosing until Grade ≤1 or return to baseline. May resume at lower dose level or discontinue dosing at investigator discretion.
Gastrointestinal Inflammation-Diarrhea	Provide anti-diarrheal (e.g., loperamide) and maintain current dose level and schedule	Provide anti-diarrheal (e.g., loperamide). Withhold dosing until Grade <1. Resume dosing at current dose level. If re-challenge results in recurrence, may resume at initial or lower dose level at investigator discretion. Consider addition of anti-inflammatory (e.g., sulfasalazine, budesonide).	Provide anti-diarrheal (e.g., loperamide). Withhold dosing until Grade ≤1 or return to baseline. Resume at lower dose level. Consider addition of anti-inflammatory (e.g., sulfasalazine, budesonide).	Provide anti-diarrheal (e.g., loperamide). Withhold dosing until Grade ≤1 or return to baseline. May resume at lower dose level or discontinue dosing at investigator discretion. Consider addition of anti-inflammatory (e.g., sulfasalazine, budesonide).
Hepatic (elevations in ALT, AST, or bilirubin)	ALT/AST<3xULN) (Direct Bilirubin<1.5xULN)	(ALT/AST>3-5xULN) (Direct Bilirubin>1.5-<3xULN)	Withhold dosing. Monitor ALT, AST, ALP, and direct bilirubin at least 1x per week until all abnormalities are Grade ≤1 or return to baseline.	Withhold dosing. Monitor ALT, AST, ALP, and direct bilirubin at least 1x per week until all abnormalities are Grade ≤1 or return to baseline.
	Maintain current dose level and schedule	Maintain current dose level and schedule	If direct bilirubin was Grade <3, resume dosing at same dose level. If direct bilirubin was Grade >3, resume at lower dose level.	If direct bilirubin was Grade <4, resume dosing at lower dose level. If direct bilirubin was Grade 4, discontinue dosing.

Dosing Delays/Dose Modifications for AEs Attributed to GS-9973 (beyond Cycle 1)				
Adverse Event	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Pneumonitis (dyspnea, cough, hypoxia and/or diffuse interstitial pattern or ground-glass opacities on chest CT and no obvious infectious cause)	Maintain current dose level and schedule. Consider Pneumocystis therapy	Withhold dosing until Grade <1. Consider systemic corticosteroids and Pneumocystis treatment. May resume at initial or lower dose level at investigator discretion.	Withhold dosing until Grade ≤ 1 or return to baseline. May resume dosing at initial or lower dose level or discontinue dosing at investigator discretion.	Withhold dosing until Grade ≤1 or return to baseline. May resume dosing at initial or lower dose level or discontinue dosing at investigator discretion.
Other Study Drug Related, Non hematological Adverse Events	Maintain current dose level and schedule	Maintain current dose level and schedule	Withhold dosing until Grade ≤ 1 or return to baseline. May resume dosing at initial or lower dose level or discontinue dosing at investigator discretion	Withhold dosing until Grade ≤1 or return to baseline. May resume dosing at initial or lower dose level or discontinue dosing at investigator discretion

Dosing Delays/Dose Modifications for Non-hematologic AEs Attributed to VCR (beyond Cycle 1)			
Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Maintain current dose level and schedule	Consider withholding dose until AE resolves to Grade ≤ 1 or baseline. May resume dosing at same dose level (or dose-reduced by 50%)	Withhold dosing until AE resolves to Grade ≤ 1 or baseline. May resume dosing at same dose level or dose-reduced by 50%.	Withhold dosing until AE resolves to Grade ≤ 1 or baseline. May resume dosing at 50% dose-reduction or discontinue per investigator discretion. For unacceptable neuropathy, consider permanent discontinuation.

Dosing Delays/Dose Modifications for Non-hematologic AEs Attributed to dexamethasone (beyond Cycle 1)			
Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Maintain current dose level and schedule	Consider withholding dose until AE resolves to Grade ≤ 1 or baseline. May resume at same dose level/frequency (or dose-reduced by 50%)	Consider withholding dosing until AE resolves to Grade ≤ 1 or baseline. May resume dosing at same dose level/frequency or dose-reduced by 50%.	Withhold dosing until AE resolves to Grade ≤ 1 or baseline. May resume dosing at 50% dose-reduction or discontinue per investigator discretion. For unacceptable myopathy, consider permanent discontinuation.

Appendix 4. Response assessment in ALL

Assessment of clinical response will be made according to NCCN guidelines on ALL Version 2. 2016 with the exception of Partial Remission, Overall Response Rate, Refractory Disease, and Relapsed Disease. The major criteria for judging response will include physical examination and examination of blood and bone marrow. All laboratory studies that are abnormal prior to study will be repeated to document the degree of maximal response.

Response criteria for blood and bone marrow

Complete Remission (CR)

CR requires all of the following:

- No circulating blasts or extramedullary disease (no lymphadenopathy, splenomegaly, skin/gum infiltration/testicular mass/CNS involvement
- Trilineage hematopoiesis (TLH) and < 5% blasts in bone marrow aspirate.
- Absolute Neutrophil Count (ANC) > 1,000/uL.
- Platelets > 100,000/uL.

CR with incomplete blood count recovery (CRi)

CRi meets all criteria for CR except platelet count and/or ANC:

- Platelets ≤ 100, 000/ uL and/or ANC is ≤ 1,000/uL

Overall response rate (ORR=CR+CRi+PR)

Partial Remission (PR)

Note: PR is not defined per NCCN guidelines but defined in this protocol. PR requires all of the following: Meets all criteria for CR except for BM blasts:

- bone marrow may contain ≥ 5% but less than 25% blast morphology

Refractory disease: Failure to achieve CR, CRi or PR at the end of induction

Progressive disease (PD): increase of at least 25% in the absolute number of circulating or bone marrow blasts or development of extramedullary disease

Relapsed disease: reappearance of blasts in the blood or bone marrow (> 5%) or in any extramedullary site after a CR / CRi/PR.

Response criteria for mediastinal/extramedullary disease:

CR: Complete resolution of mediastinal enlargement or extramedullary mass/es by CT. For patients with a previous positive PET scan, a post-treatment residual mass of any size is considered as CRE as long as it is PET negative.

PR: > 50% decrease in the SPD of the mediastinal enlargement or extramedullary mass/es from baseline. For patients with a previous positive PET scan, post-treatment PET must be positive in at least one previously involved site.

PD: > 25% increase in the SPD of the mediastinal enlargement or extramedullary mass/es from nadir or development new mediastinal/extramedullary mass/es. For patients with a previous positive PET scan, post-treatment PET must be positive in at least one previously involved site.

No Response (NR): failure to quantify for CR, PR or PD

Relapse: Recurrence of mediastinal enlargement after achieving CR. For patients with a previous positive PET scan, post-treatment PET must be positive in at least one previously involved site.

Appendix 5. Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Requirements

1) Definitions

a. Definition of Childbearing Potential

For the purposes of this study, a female born subject is considered of childbearing potential following the initiation of puberty (Tanner stage 2) until becoming post-menopausal, unless permanently sterile or with medically documented ovarian failure. Women are considered to be in a postmenopausal state when they are ≥ 54 years of age with cessation of previously occurring menses for ≥ 12 months without an alternative cause. In addition, women of any age with amenorrhea of ≥ 12 months may also be considered postmenopausal if their follicle stimulating hormone (FSH) level is in the postmenopausal range and they are not using hormonal contraception or hormonal replacement therapy. Permanent sterilization includes hysterectomy, bilateral oophorectomy, or bilateral salpingectomy in a female subject of any age.

b. Definition of Male Fertility

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

2) Contraceptive Requirements for Female Subjects

a. Study Drug Effects on Pregnancy and Hormonal Contraception

GS-9973 is contraindicated in pregnancy as there is a strong suspicion of human teratogenicity/fetotoxicity in early pregnancy based on non-clinical data. In addition, GS-9973 has insufficient data to exclude the possibility of a clinically relevant interaction with hormonal contraception that results in reduced contraception efficacy; therefore, contraceptive steroids are not recommended as a contraceptive method either solely or as a part of a contraceptive regimen. Please refer to the latest version of the investigator's brochure for additional information.

b. Contraception Requirements for Female Subjects of Childbearing Potential

The inclusion of female subjects of childbearing potential requires the use of highly effective contraceptive measures. They must also not rely on hormone-containing contraceptives as a form of birth control during the study. They must have a negative serum pregnancy test at screening and a negative pregnancy test on the Baseline visit (lead-in). Pregnancy tests will be performed on a monthly basis thereafter. Female subjects must agree to one of the following methods to avoid pregnancy from Screening until 30 days from the last dose of GS-9973.

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

Or

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

Female subjects must also refrain from egg donation and in vitro fertilization during treatment and until at least 30 days from the last dose of GS-9973.

3) Contraception Requirements for Male Subjects

It is theoretically possible that a relevant systemic concentration may be achieved in a female partner from exposure of the male subject's seminal fluid. Therefore, male subjects with female partners of childbearing potential must use condoms during treatment and until 90 days from the last dose of GS-9973. Additional contraception recommendations should also be considered if the female partner is not pregnant.

Male subjects must also refrain from sperm donation during treatment and until at least 90 days from the last dose of GS-9973.

4) Unacceptable Birth Control methods

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

5) Procedures to be Followed in the Event of Pregnancy

Subjects will be instructed to notify the investigator if they become pregnant at any time during the study, or if they become pregnant within 30 days from the last dose of GS-9973. Subjects who become pregnant or who suspect that they are pregnant during the study must report the information to the investigator and discontinue study drug immediately. Subjects whose partner has become pregnant or suspects she is pregnant during the study must report the information to the investigator.

Appendix 6. ECOG status

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

{Oken 1982}

Appendix 7. NCCN Guidelines (version 2.2016)

Response assessment

Response Criteria for Blood and Bone Marrow:

- **Complete Response (CR):**
  - No circulating blasts or extramedullary disease
  - No Lymphadenopathy, splenomegaly, skin/gum infiltration/testicular mass/CNS involvement
  - Trilineage hematopoiesis (TLH) and <5% blasts
  - Absolute neutrophil count (ANC) >1000/microL
  - Platelets >100,000/micro/L
  - No recurrence for 4 weeks
- **Complete Response with incomplete blood count recovery (CRi):**
  - Meets all criteria for CR except platelet count and/or ANC
- **Overall response rate (ORR = CR + CRi)**
- **Refractory disease**
  - Failure to achieve CR at the end of induction
- **Progressive disease (PD)**
  - Increase of at least 25% in the absolute number of circulating or bone marrow blasts or development of extramedullary disease
- **Relapsed disease**
  - Reappearance of blasts in the blood or bone marrow (>5%) or in any extramedullary site after a CR

Response Criteria for Mediastinal Disease

- CT of chest with IV contrast and PET imaging should be performed to assess response
- CR: Complete resolution of mediastinal enlargement by CT. For patients with a previous positive PET scan, a post-treatment residual mass of any size is considered a CR as long as it is PET negative
- PR: >50% decrease in the sum of the product of the greatest perpendicular diameters (SPD) of the mediastinal enlargement. For patients with a previous positive PET scan, post-treatment PET must be positive in at least one previously involved site
- PD: >25% increase in the SPD of the mediastinal enlargement. For patients with a previous positive PET scan, post-treatment PET must be positive in at least one previously involved site
- No Response (NR): failure to qualify for PR or PD
- Relapse: recurrence of mediastinal enlargement after achieving CR. For patients with a previous positive PET scan, post-treatment PET must be positive in at least one previously involved site