CLINICAL STUDY PROTOCOL

Study Title:	An Extension Study to Investigate the Safety and Durability of Clinical Activity of Idelalisib in Subjects with Hematologic Malignancies	
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404	
IND Number:	101254	
EudraCT Number:	Not Applicable	
Clinical Trials.gov Identifier:	NTC01090414	
Indication:	Hematologic malignancies	
Protocol ID:	101-99	
Gilead Medical Monitor:	Name: Telephone:	PPD PPD
Gilead Clinical Program Manager:	Name: Telephone:	PPD PPD
Protocol Version/Date:	Original: Amendment 1: Amendment 2: Amendment 3: Amendment 4: Amendment 5:	22 January 2010 12 April 2010 28 October 2013 25 November 2014 25 March 2016 07 November 2016

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

PROTOCOL SYNOPSIS

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

Study Title:	An Extension Study to Investigate the Safety and Durability of Clinical Activity of Idelalisib in Subjects with Hematologic Malignancies
IND Number:	101254
EudraCT Number:	Not Applicable
Clinical Trials.gov Identifier:	NTC01090414
Study Centers Planned:	Approximately 19 centers in the United States
Objectives:	The primary objective of this study is as follows: • To investigate the long-term safety of idelalisib in patients with hematologic malignancies • To determine the duration of clinical benefit of idelalisib in patients with hematologic malignancies
Study Design:	This is a long-term safety extension study of idelalisib in subjects with hematologic malignancies who complete other idelalisib studies. Subjects will be followed according to the standard of care as appropriate for their type of cancer, and will be treated at the dosage level received upon completion of their prior idelalisib study. Subjects will be withdrawn from the study if they develop progressive disease, unacceptable toxicity related to idelalisib, or if they no longer derive clinical benefit in the opinion of the investigator.
Number of Subjects Planned:	The number of subjects enrolled will be determined by the number of subjects completing a prior idelalisib study with a clinical benefit and who wish to continue therapy with idelalisib.
Target Population:	Subjects who complete a prior idelalisib study (101-02, 101-07, 101-08, 101-10) and who are still deriving benefit
Duration of Treatment:	Treatment will continue for as long as the subject derives clinical benefit and the subject's benefit-risk profile is deemed positive by the investigator.

Diagnosis and Main Eligibility Criteria:	Subjects with hematologic malignancies completing a prior idelalisib study (101-02, 101-07, 101-08, 101-10)
Study Procedures/ Frequency:	While on study, the subject will return at regular intervals (approximately every 2-3 months) for evaluation of disease status, recording of all adverse events (AEs) and serious adverse events (SAEs), return of used drug supplies, and dispensing of new drug supply. PJP prophylaxis is required during treatment with idelalisib and for 2 to 6 months, based on clinical judgment, following treatment discontinuation. While on study, the subject will be followed for disease status according to standard of care. Subjects' disease status will be assessed and information will be collected to determine response to treatment. If no change in disease status is identified and subject is dispensed additional idelalisib, the most recent prior response documented for the study will be recorded. All subjects should have the following laboratory tests approximately every 2-3 months : Subjects with CLL will have ALC, PLT, Hgb, ANC; subjects with WM will also have IgM, serum M protein. All subjects will be monitored for CMV status approximately every 4 weeks, and for immunologic status approximately every 12 weeks. All subjects will have CT scan at least once every 12 months and at time of initial response (PR or CR after SD, or CR after PR) or progression. In addition, for initial CR a bone marrow evaluation is required.
Test Product, Dose, and Mode of Administration:	Idelalisib 100 mg, 150 mg, 200 mg BID, or 100 mg, 200 mg, or 300 mg once daily Oral
Reference Therapy, Dose, and Mode of Administration:	Not Applicable
Criteria for Evaluation:	Subjects who complete a prior idelalisib study (101-02, 101-07, 101-08, 101-10) and who are still deriving benefit
Safety:	Safety will be evaluated by assessing all Grade ≥ 3 AEs and all SAEs.

Efficacy:	**Primary Endpoint** • Overall response rate (ORR) – defined as the proportion of subjects who achieve CR, PR, or MR (for WM only) **Secondary Endpoints** • Duration of Response (DOR) – defined as the interval from the first documentation of CR, PR or MR (for WM) to the earlier of the first documentation of definitive disease progression or death from any cause • Progression-free survival (PFS) – defined as the interval from enrollment in the parent study to the earlier of the first documentation of definitive disease progression (excluding lymphocytosis alone) or death from any cause • Overall survival (OS) – defined as the interval from the start of study treatment in the parent study to death from any cause
Pharmacokinetics:	Not Applicable
Statistical Methods:	The intent-to-treat (ITT) analysis set will consist of all subjects receiving at least 1 dose of study treatment. This analysis set will be used for the efficacy and safety analyses. Subject characteristics and study results will be described and summarized. Overall response rate based on investigator's response will be calculated along with its 95% confidence intervals (CIs) based on exact binomial method. For the analyses of DOR and PFS, the Kaplan-Meier method will be used. For data summaries involving continuous variables, data tables will typically contain the following information: sample size, mean, standard deviation, standard error, median, minimum and maximum. For categorical variables, the following information will typically be presented: sample size, proportion, and 95% CIs based on exact binomial method. Safety will be assessed via Grade ≥ 3 adverse events (AEs). Summary of efficacy will be presented by integrating parent study with 101-99 extension study. All treatment emergent adverse events that are observed in the parent studies (101-02, 101-07, 101-08, and 101-10) and their extension study will be summarized <u>Sample Size Calculation:</u> Not applicable

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

AE	Adverse event
ALC	absolute lymphocyte count
ALT	alanine aminotransferase
AML	Acute myeloid leukemia
ANC	absolute neutrophil count
AST	aspartate aminotransferase
ATP	Adenosine triphosphate
AUC	area under the concentration-time curve
B	bendamustine
BID	twice per day
CAL-101	Former name for idelalisib
CFR	Code of Federal Regulations
CI	confidence interval
CLL	chronic lymphocytic leukemia
CMV	Cytomegalovirus
C_{max}	maximum concentration
CR	complete response
CRO	contract research organization
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
C_{trough}	trough concentration
CYP	cytochrome P450 enzyme
DLBCL	diffuse large B-cell lymphoma
DOR	duration of response
DSPH	Gilead Sciences Department of Safety and Public Health
E	everolimus
FL	Follicular lymphoma
GCP	Good Clinical Practice
GS-1101	Former name for idelalisib
Hgb	Hemoglobin
IEC	Independent Ethics Committee
IgM	Immunoglobulin M
IHC	immunohistochemistry
IMP	Investigational medicinal product
iNHL	Indolent non-Hodgkin lymphoma
IRB	Institutional Review Board
ITT	Intent to treat
IWCLL	International Workshop on Chronic Lymphocytic Leukemia
L	lenalidomide

MCL	Mantle cell lymphoma
MTD	Maximum tolerated dose
NCCN	National Comprehensive Cancer Network
NOAEL	No observed adverse effect levels
ORR	Overall response rate
OS	Overall survival
PFS	Progression-free survival
PI3K	Phosphatidylinositol 3-kinase
PJP	*Pneumocystis jirovecii* pneumonia
PLT	Platelets
PR	Partial response
R	rituximab
SAE	Serious adverse event
SD	Stable disease
SJS	Stevens-Johnson Syndrome
SLL	Small lymphocytic lymphoma
SOP	Standard Operating Procedure
TEAE	treatment-emergent adverse event
TEN	toxic epidermal necrolysis
TTR	Time to Response
WM	Waldenström's macroglobulinemia

1. INTRODUCTION

1.1. Background

1.1.1. General Information

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

Idelalisib (GS-1101; formerly CAL-101) is a targeted, highly selective competitive inhibitor of the adenosine triphosphate (ATP) binding site of the phosphatidylinositol 3-kinase (PI3K) p110δ catalytic domain, which has been shown to be prominently expressed in cells of hematopoietic origin {Okkenhaug et al 2003, Vanhaesebroeck et al 2005}. PI3Kδ is critical for multiple signaling pathways that are hyperactive in B-cell malignancies. Inhibition of PI3Kδ modulates B-cell receptor signaling as well as signaling through cytokine and chemokine receptors and integrinαβl. These signaling pathways act via downstream enzymes (most importantly the serine/threonine protein kinase, Akt) to regulate proliferation, apoptosis, motility, homing, and retention of malignant B-cells in lymphoid tissues and bone marrow compartments. By inhibiting PI3Kδ-dependent signaling, idelalisib inhibits proliferation, survival, homing, motility, and retention, and promotes apoptosis in many B-cell malignancies.

An essential role of PI3Kδ signaling in the proliferation and survival of hematopoietic cancer cells has been demonstrated for several myeloid and B-cell malignancies. Blasts from patients with acute myeloid leukemia (AML) have high constitutive PI3K activity, and inhibition of PI3Kδ resulted in the inhibition of Akt phosphorylation and cellular proliferation {Sujobert et al 2005}. Sustained activation of the PI3Kδ pathway has been shown to have a pivotal role in the survival of B-cell chronic lymphocytic leukemia (CLL) cells co-cultured with primary or stromal cell lines {Cuni et al 2004}. The Sponsor has shown that PI3Kδ is expressed in all primary CLL patient cells tested and treatment with idelalisib in vitro led to a decrease in viability of most CLL patient cells tested. Constitutive activation of Akt has been demonstrated in aggressive blastoid variants of mantle cell lymphoma (MCL) as well as cell lines, and treatment of MCL cell lines with the pan-PI3K inhibitor LY294002 resulted in apoptosis {Rudelius et al 2006}. Constitutive activation of AKT has also been reported in diffuse large B-cell lymphoma (DLBCL) cell lines and in approximately 50% of DLBCL tissue samples {Uddin et al 2006}. Treatment with LY294002 resulted in apoptosis of some DLBCL cell lines. The PI3K/Akt pathway has also been implicated in survival of follicular lymphoma (FL) cells {Leseux et al 2006} and Waldenström's macroglobulinemia (WM) {Leleu et al 2007}. These data provide the rationale for targeting the PI3Kδ signaling pathway with idelalisib as a potential new treatment for hematologic malignancies. In addition, the relative lack of activity of idelalisib against p110α should minimize the potential for hyperglycemia relative to pan-PI3K inhibitors.

For further information on idelalisib, refer to the current version of the Investigator's Brochure.

1.1.2. Nonclinical Pharmacology and Toxicology

A comprehensive set of nonclinical safety and toxicology studies of idelalisib have been completed and have established no observed adverse effect levels (NOAELs) to support clinical studies. Lymphoid depletion in lymphoid tissues was observed in these nonclinical studies, which is consistent with the expected pharmacological activity of PI3Kδ inhibition.

Further details on the toxicology of idelalisib can be found in the idelalisib Investigator's Brochure.

1.1.3. Clinical Trials of Idelalisib

1.1.3.1. Phase 1 Monotherapy Study in Patients with Hematological Malignancies (Study 101-02)

Study 101-02 was a dose ranging study where idelalisib was administered in cohorts of subjects across a range of dose levels from 50 mg BID to 350 mg BID. Idelalisib administration was continued as long as individual subjects were safely benefitting from therapy. Subjects were evaluated in 4-week cycles; response and progression assessments were based on standard criteria {Hallek et al 2008}.

Study 101-02 has completed enrollment. A total of 191 subjects were enrolled to the study, 54 of whom had a diagnosis of CLL. In this cohort, the median age was 63 years (range 37-82). The disease was considered refractory in 70%, and subjects had a median of 5 prior regimens. Leukemia cells from 24% of the 54 CLL subjects had del(17p) and/or TP53 mutation and 91% had an unmutated immunoglobulin heavy chain variable region (IGHV). Pharmacokinetics of idelalisib was studied. The multiple-dose C_{max}, C_{trough}, and AUC of idelalisib increase in a less than dose proportional manner, with only modest increase in exposure observed at the dose level of 350 mg/dose BID (compared with 150 mg). To assess the pharmacodynamic effect of idelalisib, the phosphorylation status of Akt (a direct downstream target of PI3K) in CLL subject samples was investigated. Subject sample peripheral blood mononuclear cells (PBMC) were screened for levels of phospho-Akt (pAkt) by flow cytometry. At baseline prior to idelalisib dosing, a high level of constitutive $pAkt^{T308}$ was noted. Following 8 and 28 days of dosing with idelalisib BID, constitutive phosphorylation of Akt in cells from subjects with CLL was reduced to the background level observed in healthy volunteers. In the evaluation of the effect of idelalisib on cytokine production, plasma concentrations of CLL-derived chemokines, CCL3 and CCL4, and of the stroma-derived chemokine, CXCL13, were elevated at baseline and decreased significantly during idelalisib administration. Idelalisib treatment was associated with a peripheral lymphocytosis in the CLL subjects, with median ALC approximately doubling over the first 8 weeks of treatment, and then descending thereafter. This lymphocytosis is considered consistent with inhibition of chemokine signaling, with subsequent redistribution of lymphocytes from the lymph node to the blood compartment.

Study 101-02 was completed prior to a revision in the 2013 National Comprehensive Cancer Network (NCCN) guidelines for overall response rate (ORR) that no longer considers isolated lymphocytosis as a sign of progressive disease (PD). The revision to the standard response criteria was driven by the recent recognition that novel agents (including idelalisib) can mobilize

CLL cells from tissues into the peripheral blood by interfering with their homing and that this represents an expected pharmacologic action rather than an indication of disease progression. This effect is especially prominent with monotherapy. These guidelines were modified based on a publication by Cheson in 2012 recommending that "persistent lymphocytosis should not interfere with the time of designation of a partial response (PR), which should be based more on the other measurable aspects of the disease than on lymphocytosis" {Cheson et al 2012}. Based on data supplied by investigators in the database, and by applying the 2013 NCCN and Cheson 2012 criteria, the ORR in CLL subjects was 72.2% with 22% showing stable disease. {Brown et al 2013}. Amongst the 13 subjects with 17p deletion and/or TP53 mutation, the ORR was 53.8% based on investigator response, and amongst the 4 subjects with 17p deletion and/or TP53 mutation who received twice daily dosing at ≥150 mg BID, the ORR was 75%. The median Kaplan-Meier estimate of progression free survival in all CLL subjects is 17.1 months, and in 28 subjects who received twice daily dosing at ≥150 mg per dose, the estimated progression-free survival (PFS) is 29 months.

Adverse events (AEs) were usually mild to moderate and not clearly idelalisib-related. The most frequently reported AEs, all grades, in the 54 CLL subjects were fatigue (32%), diarrhea (30%), pyrexia (30%), cough (24%), back pain (22%), rash (22%), upper respiratory infection (URI) (22%), and pneumonia (20%). Elevation of alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) was observed in 28%. There was no clear dose effect for the occurrence of transaminase elevation.

Although no maximum tolerated dose (MTD) was identified over the dosing range of 50 to 350 mg BID, the pharmacokinetic, pharmacodynamic and efficacy results led to a determination that 150 mg BID would be the recommended Phase 2 dose, and this has been used in all subsequent studies.

1.1.3.2. Phase 1 Combination Study in Patients with Hematologic Malignancies (Study 101-07)

A separate Phase 1 trial (Study 101-07) has evaluated the safety and preliminary activity of idelalisib given in combination with an anti-CD20 monoclonal antibody (mAb), a chemotherapeutic agent, a mammalian target of rapamycin (mTOR) inhibitor, a proteasome inhibitor, an angiogenic agent, and/or an immunomodulatory agent in subjects with relapsed or refractory B cell CLL, indolent non-Hodgkin lymphoma (iNHL), or mantle cell lymphoma (MCL).

In subjects with relapsed/refractory CLL who had been heavily pretreated, high overall response rates (ORR of 80.9%) were achieved, including responses occurring after cessation of the combination drugs. Substantial improvements were achieved in all individual response criteria: lymph nodes (response rate of 80.9%, mean best percent change in area from baseline of −72.0), spleen (response rate of 57.6%), and liver (response rate of 60.0%). Rapid reductions in lymphadenopathy (median TTR of 1.9 months) and durable tumor control (median KM estimates of DOR and PFS were not reached) were observed. Improvements in hematologic parameters were noted in subjects with CLL who had abnormal hematologic parameters at baseline.

In subjects with relapsed/refractory iNHL who had been heavily pretreated, high overall response rates (ORR of 79.1%) were achieved, including responses occurring after cessation of the combination drugs. Idelalisib in combination with rituximab (R) and/or bendamustine (B) induced rapid reductions in lymphadenopathy (median TTR of 1.9 months) and durable tumor control (median KM estimates of DOR and PFS were not reached). Improvements in hematologic parameters were noted in subjects with iNHL who had abnormal hematologic parameters at baseline.

In subjects with relapsed/refractory MCL who were heavily pretreated, high overall response rates (ORR of 57.5%) were achieved with idelalisib-based combination therapies, including responses occurring after completion of the combination drugs. Idelalisib in combination with bendamustine + rituximab (BR) induced rapid reductions in lymphadenopathy (median TTR of 1.9 months) and durable tumor control (median KM estimates of DOR and PFS were 9.3 and 11.1 months, respectively). Improvements in hematologic parameters were noted in subjects with MCL who had abnormal hematologic parameters at baseline.

Rapid control of B symptoms in symptomatic patients was also demonstrated in all cohorts.

With the exception of the idelalisib+rituximab+lenalidamide (idelalisib+RL) combination, idelalisib had a manageable safety profile when administered in combination therapy with agents used routinely in clinical practice. The safety data suggest that idelalisib may lead to an increased risk of hepatotoxicity when used in combination with R and L at the dose and schedule evaluated in this study. Excluding the idelalisib+RL combination, the absence of overlapping toxicities allowed the administration of idelalisib and combination therapies at the planned doses of each. Diarrhea, neutropenia, pyrexia, rash, and transaminase elevations were similar to what has been observed with idelalisib monotherapy. Idelalisib did not exacerbate the known safety profile of any of the combination drugs, except possibly for everolimus (E). Everolimus is a CYP3A substrate and, after the idelalisib+E treatment cohort completed, it was established that the primary idelalisib metabolite is a CYP3A inhibitor, which may account for the comparatively high incidence of SAEs (77.8%) and AEs leading to discontinuation of idelalisib (55.6%).

Overall, the AE profile was consistent with that expected for a heavily pretreated, relapsed/refractory hematologic cancer population receiving combination immunochemotherapy agents. The most frequently reported treatment-emergent AE (TEAE) was pyrexia (42.7% of all subjects). The most frequently reported Grade $\geq$ 3 TEAE was neutropenia (32.8% of all subjects). Grade $\geq$ 3 rash occurred in 5.0% of subjects, including subjects receiving bendamustine.

Early transaminase elevations that occurred were generally asymptomatic and transient. Overall, a Grade 3 or 4 ALT or AST elevation was reported for 30 subjects (12.4%); 29 subjects (12.0%) had a dose interruption due to a Grade 3 or 4 ALT or AST elevation. The overall median time to onset of Grade 3 or 4 ALT/AST elevation was 6.1 weeks and the overall time to resolution of the first Grade 3 or 4 ALT/AST elevation was 2.1 weeks.

There were no clinically meaningful changes in blood pressure, heart rate, or ECG results during the study.

1.1.3.3. Phase 2 Study of Idelalisib Plus Rituximab in Treatment Naïve Elderly Patients with Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma (Study 101-08)

The primary objective of this study was to evaluate the ORR of idelalisib when combined with rituximab in subjects ≥65 years with previously untreated CLL or small lymphocytic lymphoma (SLL). Enrollment is complete, and 64 subjects have been followed through at least 48 weeks. Eligible subjects received the following treatment regimen: idelalisib 150 mg BID orally on Days 1 through 28 of each 28-day cycle (Cycles 1 through 12) + rituximab 375 mg/m^2 IV weekly for 8 doses (Cycles 1 and 2). Treatment with idelalisib continued until disease progression, unacceptable toxicity, or completion of 12 cycles of therapy. Subjects were evaluated by the investigators for response after Cycles 2, 4, 6, 9, and 12 according to standard International Workshop on Chronic Lymphocytic Leukemia (IWCLL) 2008 criteria.

Of the 64 subjects enrolled in the study 62 (96.9%) completed Cycle 2 of the study, and 43 subjects (67.2%) completed the study (48 weeks).

At baseline, the subjects (N = 64) were predominantly male, white, with median age of 71 years. The majority of subjects (92.2%) were diagnosed with CLL; 7.8% of subjects were diagnosed with SLL.

The ORR for all subjects (N = 64) for Study 101-08, including subject participation in Study 101-99, was 96.9%; 12 subjects (18.8%) had a CR, and 50 subjects (78.1%) had a PR. Two subjects (3.1%) were not evaluable, and no subject had a best response of SD or PD on study. The ORR for subjects with the del(17p) and/or TP53 mutation or IgHV mutation was 100% and 95.7%, respectively. Of note, 3 of 9 subjects with del(17p)/TP53 mutation achieved CR, and the remainder PR. Among evaluable subjects, the lymph node response rate was 98.0%, the splenomegaly response rate was 96.4%, the hepatomegaly response rate was 100%, the ALC response rate was 100%, the platelet response rate was 94.1%, the hemoglobin response rate was 100%, and the ANC response rate was 100%.The Kaplan-Meier estimate of PFS at 24 months was 93%. The median time to response (TTR) was 1.9 months.

In this study in elderly subjects with previously untreated CLL or SLL, therapy was generally well tolerated. The most frequently reported AEs for subjects during either the parent study or extension Study 101-99 were diarrhea (55%), pyrexia (42 %), nausea (38%), rash (38%), chills (36%), cough (33%), fatigue (31.%), ALT increased (28%), AST increased (27%) and pneumonia (27%), dyspnea (23%), headache (23%), vomiting (20%), insomnia (20%), constipation (17%), pruritus (17%), arthralgia (17%), night sweats (16%), and colitis (16%). Eighteen subjects (28.1%) discontinued treatment with idelalisib due to one or more AEs. Diarrhea, respiratory disorders, and rash were the most frequently reported AEs leading to discontinuation of idelalisib therapy. Four subjects (6.3%) died during Study 101-08. The causes of death were pneumonitis, pneumonia and metastatic melanoma, drug induced pneumonitis and respiratory failure, and sepsis respiratory failure. An additional subject from 101-08 died during the extension Study 101-99 due to acute myocardial infarction. Thirty-seven subjects (48.4%) reported a Serious Adverse Event (SAE) during either the parent study or extension Study 101-99. The most commonly reported SAEs were diarrhea and pneumonia (10 subjects each, 15.6%) and colitis (7 subjects, 10.9%).

1.1.3.4. Single-agent Idelalisib for Previously Treated Low-grade Lymphoma: A Phase 1/2 Study of Safety, Efficacy, and Flow-cytometric Assessment of Tumor-cell Signaling Events (Study 101-10)

Study 101-10 was a Phase 1/2, open-label, single-arm, safety, efficacy, and flow-cytometric assessment of tumor cell signaling events study of idelalisib in subjects with previously treated low-grade iNHL. Eligible subjects were administered idelalisib 150 mg orally twice daily for 28 days (1 cycle) for up to 12 cycles. Subjects who experienced disease progression while receiving idelalisib ≤ 150 mg twice daily may have been eligible to receive an escalated-dose of idelalisib up to a maximum of 300 mg twice daily, per judgment of the investigator.

Idelalisib administration was continued until subjects developed progressive disease while receiving idelalisib at a dose of 300 mg twice daily, if they experienced unacceptable toxicity, or if in the opinion of the investigator they were no longer deriving clinical benefit

Study 101-10 has completed enrollment. All 18 subjects enrolled in the study received study drug. Five subjects (27.8%) completed the study and 13 subjects (72.2%) prematurely discontinued the study.

For additional or updated information, please refer to the current version of the idelalisib Investigator's Brochure.

1.2. Rationale for This Study

This extension study provides the opportunity for subjects with hematologic malignancies who have completed a prior study of idelalisib to continue idelalisib treatment for as long as they derive clinical benefit.

Subjects with hematologic malignancies who complete one of the following studies are eligible for enrollment:

- Study 101-02: A Phase 1 Sequential Dose Escalation Study to Investigate the Safety, Pharmacokinetics, Pharmacodynamics, and Clinical Activity of Idelalisib in Subjects with Select, Relapsed or Refractory Hematologic Malignancies

- Study 101-07: A Phase 1 Study to Investigate the Safety and Clinical Activity of Idelalisib in Combination with Chemotherapeutic Agents and Anti-CD20 mAb in Subjects with Relapsed or Refractory Indolent B-cell Non-Hodgkin Lymphoma, Mantle Cell Lymphoma, or Chronic Lymphocytic Leukemia

- Study 101-08: A Phase 2 Single Arm Study to Investigate the Safety and Clinical Activity of Idelalisib in Combination with Rituximab in Elderly Subjects with Previously Untreated Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma

- Study 101-10: Single-Agent GS-1101 (CAL-101) for Previously Treated Low-Grade Lymphoma: A Phase 1/2 Study of Safety, Efficacy, and Flow-Cytometric Assessment of Tumor-Cell Signaling Events

1.3. Compliance

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

2. OBJECTIVES

The primary objectives of this study are:

- To investigate the long-term safety of idelalisib in subjects with hematologic malignancies
- To determine the duration of clinical benefit of idelalisib in subjects with hematologic malignancies

3. STUDY DESIGN

3.1. Primary Endpoint

The primary endpoint of this study is:

- Safety, assessed using Grade ≥3 adverse events according to the Common Terminology Criteria for Adverse Events (CTCAE) v4.03

3.2. Secondary Endpoints

The secondary endpoints of this study are:

- Duration of response (DOR) – defined as the interval from the first documentation of CR, PR or MR to the earlier of the first documentation of definitive disease progression or death from any cause

- Progression-free survival (PFS) – defined as the interval from enrollment to the earlier of the first documentation of definitive disease progression excluding lymphocytosis alone or death from any cause

- Overall survival (OS) – defined as the interval from the start of study treatment to death from any cause

- Time to response (TTR) – defined as the interval from first dose to the first documentation of CR or PR

3.3. Study Design

This is a long-term safety extension study of idelalisib in subjects with hematologic malignancies who complete other idelalisib studies. Subjects will be followed according to the standard of care as appropriate for their type of cancer, and will be treated at the dosage level received upon completion of their prior idelalisib study. Subjects will be withdrawn from the study if they develop progressive disease, unacceptable toxicity related to idelalisib, or if they no longer derive clinical benefit in the opinion of the investigator.

3.4. Study Treatments

The Sponsor will provide idelalisib drug product to study sites.

Subjects will be treated at the dose level they were receiving at completion of their prior idelalisib trial. Subjects receive idelalisib in the following doses:

- 100, 150, or 200 mg idelalisib BID

- 100, 200, or 300 mg idelalisib once daily

Subjects receive idelalisib in the following formulations:

- 100- or 150-mg tablets

3.5. Duration of Treatment

Treatment will continue for as long as the subject derives clinical benefit and the subject's risk-benefit profile is deemed positive by the investigator. See Protocol Section 3.6, Study Discontinuation Criteria, for specific discontinuation criteria.

3.6. Study Discontinuation Criteria

A subject may be withdrawn from the study under the following circumstances:

- The subject withdraws consent to participate in the study
- The subject permanently discontinues idelalisib treatment for any reason (See Section 6.6)
- The subject experiences a toxicity that necessitates permanent discontinuation of idelalisib treatment
- The subject has progressive disease or whose benefit-risk profile is no longer deemed positive by the investigator.
- The subject does not comply with the requirements of the protocol
- Gilead, a regulatory agency, or an institutional review board (IRB)/ independent ethics committee (IEC) discontinues the study

The reason for withdrawal will be recorded in the Case Report Form (CRF).

4. SUBJECT POPULATION

4.1. Number of Subjects and Subject Selection

A maximum of approximately 250 subjects is anticipated. The number of subjects enrolled will be determined by the number of subjects completing a prior idelalisib study with a clinical benefit who wish to continue therapy with idelalisib.

4.2. Inclusion Criteria

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

- Subjects with hematologic malignancies completing a prior idelalisib study (101-02, 101-07, 101-08, 101-10) with a clinical benefit are eligible.
- A negative urine pregnancy test is required for female subjects (unless surgically sterile or greater than one year post-menopausal).
- Male subjects and female subjects of childbearing potential who engage in heterosexual intercourse must agree to use protocol specified method(s) of contraception as described in Appendix 2.

4.3. Exclusion Criteria

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

- Subjects who are pregnant or nursing will be excluded.
- Subjects who are unwilling or unable to comply with the requirements of the protocol will be excluded.

5. INVESTIGATIONAL MEDICINAL PRODUCT

5.1. Randomization, Blinding and Treatment Codes

The study is unblinded.

5.2. Description and Handling of Idelalisib

5.2.1. Storage and Handling

Idelalisib, the investigational medicinal product (IMP), will be provided in sealed bottles. The bottles should be stored at room temperature (ie, 15-30 °C or 59-86 °F). While stability of idelalisib tablets stored at controlled room temperature has been confirmed, brief excursions to temperatures as low as 5 °C or as high as 40 °C (eg, during shipping) will not adversely affect the drug. Updated stability data will be provided to the sites, as appropriate.

5.2.2. Formulation

Idelalisib is provided as 100 mg and 150 mg tablets. Idelalisib 100 mg tablets are either oval-shaped, film-coated orange tablets, debossed with “GSI” on one side and “100” on the other, or plain-faced tablets. Idelalisib 150 mg tablets are either oval-shaped, film-coated pink tablets, debossed with “GSI” on one side and “150” on the other or plain faced tablets. In addition to the active ingredient, idelalisib tablets contain the following inactive ingredients: microcrystalline cellulose, hydroxypropyl cellulose, croscarmellose sodium, sodium starch glycolate, magnesium stearate, polyethylene glycol, talc, polyvinyl alcohol (PVA), titanium dioxide, FD&C Yellow #6/ Sunset Yellow FCF Aluminum Lake (100 mg tablets only), and red iron oxide (150 mg only).

5.2.3. Packaging and Labeling

Idelalisib tablets will be supplied in bottles. A label containing the following information will be affixed to the bottle:

- Sponsor name and address
- Description of contents of package, including dose strength
- Caution statement (includes “Keep out of Reach of Children” statement)
- Storage conditions
- Lot number

The expiry date will be provided in a separate communication and updated as appropriate

5.3. Dosage and Administration of Idelalisib

Idelalisib formulated drug product of 100 and 150 mg strengths has been manufactured for clinical trials and will be provided to the subject to be taken at home. Subjects will be treated at the dose level they were receiving at completion of their prior idelalisib trial. Subjects should be instructed to take the doses with water. Idelalisib may be taken with or without food. Missed doses should not be taken unless it is within 6 hours of the scheduled dosing and vomited doses should be retaken only if the tablet is visible in the vomitus.

5.4. Dose Adjustment

The idelalisib dose may be increased if the subject has worsening disease but does not meet criteria for progressive disease, up to a maximum dose level of 150 mg BID. Recommendations and requirements for dose adjustment or discontinuation due to hematologic and non-hematologic toxicity are provided in Table 5-1.

Required discontinuation and dose modification instructions provided in Table 5-1 must be followed. Recommended actions provided in Table 5-1 comprise guidelines; variations from these recommendations may be warranted based on an investigator's individual judgment in considering potential risks, benefits, and therapeutic alternatives available to each subject.

Any planned dose changes should be discussed with the Sponsor prior to implementation.

5.5. Idelalisib Interruption/Dose Modification/Discontinuation

Requirements and recommendations for discontinuation or modification of study treatment based on the type and severity of adverse events or laboratory abnormalities are provided in Table 5-1.

Table 5-1. Requirements and Recommendations for Discontinuation or Modifications of Study Treatment in Response to Adverse Events

NCI CTCAE Grade	Idelalisib
HEMATOLOGICAL ADVERSE EVENTS	
Neutropenia	
Grade ≤2	Maintain current dose level and schedule.
Grade 3	*Required:* Blood counts must be monitored at least weekly until neutropenia is ≤ Grade 2. *Recommended:* Maintain current dose level and schedule.
Grade 4 (or occurrence of neutropenic fever or infection)	*Required:* Interrupt idelalisib. Blood counts must be monitored at least weekly until neutropenia ≤ Grade 2 *Recommended:* Idelalisib may be resumed at lower dose when neutropenia is ≤ Grade 3. Neutropenia should be managed according to established clinical guidelines.
Thrombocytopenia	
Grade ≤3	Maintain current dose level and schedule.
Grade 4	*Required:* Withhold idelalisib for bruising or bleeding until Grade ≤3. *Recommended:* May resume idelalisib at initial or lower dose level at investigator discretion.

NCI CTCAE Grade	Idelalisib
NON-HEMATOLOGICAL ADVERSE EVENTS	
Rash	
Grade ≤ 2	Maintain current dose level and schedule.
Grade ≥3	*Required:* Withhold idelalisib until Grade ≤1. *Recommended:* May resume idelalisib at lower dose level or discontinue at investigator discretion.
Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis	
Any Grade	*Required:* Discontinue idelalisib. Interrupt coadministered medications potentially associated with SJS or TEN. Institute treatment per institutional standards.
Bowel perforation	
Any Grade	*Required:* Discontinue idelalisib.
Diarrhea or Colitis	
Any Grade (in addition see below for response to specific CTCAE grades)	*Required:* Obtain history of onset and duration of diarrhea, including description of number of stools and stool composition (eg, watery, bloody, nocturnal), travel history, dietary changes and a medication review to identify possible diarrheogenic agents. Perform physical examination including assessment for fever, dizziness, abdominal pain/cramping, and weakness (ie, evaluate for sepsis, bowel obstruction, dehydration) *Recommended:* Provide anti-diarrheal and ensure good hydration status. Differentiate between small-bowel and large-bowel diarrhea on a clinical basis (Section 5.6.2.2).
Grade ≤1	*Recommended:* Provide anti-diarrheal agent (eg, loperamide) and maintain current idelalisib dose level and schedule.
Grade ≤ 2 (unless clinical diagnosis is established from medical history and physical examination)	*Required:* Stool culture for routine pathogens (Salmonella, Shigella, Campylobacter species), testing for Clostridium difficile toxin, Rotavirus, Cytomegalovirus (CMV), and Adenovirus. Stool for Ova and Parasites (Cryptosporidium parvum, Isospora belli, Enterocytozoon bieneusi, Septata intestinalis, Strongyloides, Microsporidia, Entamoeba histolytica, Cyclospora), Giardia antigen
Grade ≥ 3 diarrhea or colitis, or persistent Grade 2 diarrhea or colitis without clear etiology	*Required:* Withhold idelalisib. Consider anti-diarrheal (eg, loperamide) and/or addition of anti-inflammatory agent (eg, sulfasalazine, budesonide). *Recommended:* Endoscopy with biopsy is strongly recommended to assess by immunohistochemistry (IHC) and PCR for CMV, Adenovirus. PPD [redacted] At Grade ≤1, may resume idelalisib at lower dose level or discontinue at investigator discretion.
Hepatic Adverse Events (elevations in ALT, AST, or bilirubin)	
Grade ≤1 (ALT/AST≤3xULN) (Bilirubin≤1.5xULN)	Maintain current dose level and schedule.
Grade ≤ 2 (ALT/AST≤ 3-5xULN) (Bilirubin>1.5-≤3xULN)	*Recommended:* Maintain current dose level and schedule. Monitor ALT, AST, ALP, and bilirubin at least 1x per week until all abnormalities are Grade ≤1.
Grade 3 (ALT/AST>5-20 xULN) (Bilirubin>3-10xULN)	*Recommended:* Withhold idelalisib. Monitor ALT, AST, ALP, and bilirubin at least 1x per week until all abnormalities are Grade ≤1. If bilirubin abnormality was Grade <3, resume idelalisib at same dose level. If bilirubin abnormality was Grade ≥3, resume at lower dose level.
Grade 4 (ALT/AST>20xULN) (Bilirubin>10xULN)	*Required:* Withhold idelalisib. Monitor ALT, AST, ALP, and bilirubin at least 1x per week until all abnormalities are Grade ≤1. • If bilirubin abnormality was Grade 4, discontinue idelalisib. *Recommended:* If bilirubin abnormality was Grade <4, resume idelalisib at lower dose level.

NCI CTCAE Grade	Idelalisib
Pneumonitis (new onset or worsening of baseline dyspnea, cough, or hypoxia without obvious infectious cause	
Grade 1 (asymptomatic)	*Required:* Withhold idelalisib until resolution to baseline. May resume at lower dose level or discontinue at investigator discretion.
Grade ≥ 2	*Required:* Discontinue idelalisib permanently in subjects with any severity of symptomatic pneumonitis and institute therapy as clinically appropriate.
***Pneumocystis jirovecii* pneumonia (PJP)**	
Any Grade	*Required:* Discontinue idelalisib.
CMV infection/reactivation[a]	
Any Grade	*Required:* Interrupt idelalisib upon unequivocal clinical or laboratory evidence of CMV infection. Treat according to established clinical guidelines. If the benefits of resuming idelalisib outweigh the risks, consideration should be given to administering preemptive CMV therapy.
Other Nonhematological Adverse Events	
Grade ≤2	Maintain current dose level and schedule.
Grade ≥3	*Recommended:* Withhold idelalisib until Grade ≤1. May resume idelalisib at initial or lower dose level or discontinue idelalisib at investigator discretion.

a CMV should be diagnosed using clinical or laboratory criteria per established institutional standard
Abbreviations: ALP=alkaline phosphatase, ALT=alanine aminotransferase, AST= aspartate aminotransferase, CTCAE=Common Terminology Criteria for Adverse Events, G-CSF=granulocyte colony-stimulating factor, NCI=National Cancer Institute, ULN=upper limit of normal

5.6. Warnings and Precautions

5.6.1. Transaminase Elevations

Consistent with observations in a dog toxicology study, reversible asymptomatic ALT/AST increases were observed early in the idelalisib program in phase 1 studies (101-02 and 101-07) in subjects with hematologic malignancies. Transaminase elevations generally occurred within 4 to 12 weeks of drug initiation, and resolved spontaneously over a period of 2 to 4 weeks with drug being continued for Grade 1 and 2 elevations and drug withheld for Grade 3 or 4 elevations until resolution. These early observations are consistent with the ongoing experience with idelalisib treatment and transaminase elevations are now well characterized as most frequently asymptomatic, transient and occurring within the first 3 months of treatment.

Grade 1 or 2 elevations commonly resolve despite continued idelalisib treatment and Grade 3 or 4 elevations can be managed by temporarily withholding idelalisib. Successful rechallenge after resolution at either the same or lower dose level of idelalisib has been achieved in the majority of subjects. There has been no evidence of impaired synthetic function. Close monitoring of hepatic laboratory tests during therapy is important to allow for appropriate idelalisib interruption and reinstitution so that subjects may continue with study drug treatment.

In selected subjects who experience more complicated hepatic adverse events, further workup may be warranted particularly in subjects who first experience a serum ALT/AST elevation ≥12 weeks from the start of study drug therapy, who have an elevation in serum bilirubin concentration or coagulation parameters, or who have other characteristics that suggest an atypical change in transaminase values. Hepatic adverse events that require additional workup should be discussed with the Gilead Sciences Medical Monitor.

5.6.2. Gastrointestinal Events

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

Cholangitis manifest as hyperbilirubinemia out of proportion to serum transaminase elevations has been observed. While disease-related factors, neutropenia, toxicity from prior therapies, effects of ongoing supportive care, or pre-existing cholelithiasis may have initiated such events, it is possible that idelalisib played a contributory role. In such subjects, rechallenge with idelalisib has been possible and has not been associated with other severe adverse events. Subjects who have developed evidence of enteritis during idelalisib therapy have been successfully treated with antidiarrheals (eg, loperamide) and with enteric steroidal (eg, budesonide) or non-steroidal (eg sulfasalazine [Azulfidine®]) anti-inflammatory agents and have been able to continue or resume idelalisib.

For study subjects who develop severe abdominal pain the possibility of a bowel obstruction or perforation should be considered. Appropriate clinical and radiographic examination should be performed and supportive care or surgical intervention should be considered.

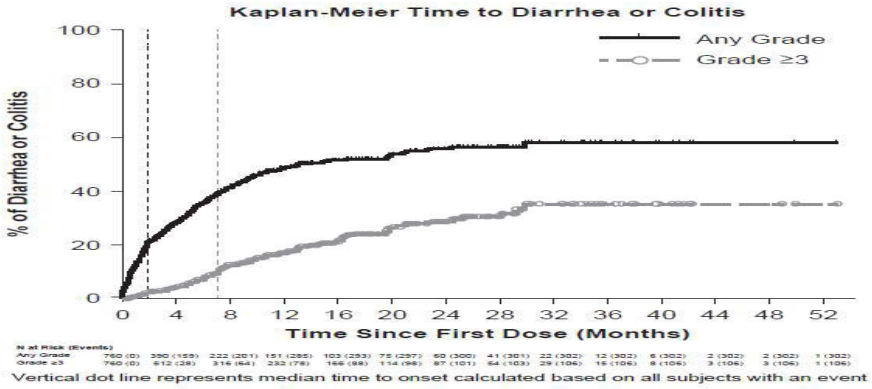
For subjects who develop persistent diarrhea, causes related to concomitant medications or gastrointestinal infections such as Clostridium difficile (particularly for patients recently treated with broad spectrum antibiotics), Shigella, Campylobacter, Yersinia and CMV should be considered and treated if appropriate. Depending upon the clinical circumstances, endoscopy and biopsy, with bacterial and viral IHC staining should be considered. In the event that an infectious cause is not identified, an antimotility agent (eg, loperamide) may lessen symptoms and intervention with enteric steroidal (eg, budesonide) or non-steroidal (eg, sulfasalazine) anti-inflammatory agents should be considered. In such subjects, rechallenge with idelalisib at a lower dose level has resulted in recurrence of symptoms in some but not all subjects and has not been associated with other severe adverse events.

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

See CTCAE Version 4.03 for definitions of colitis and diarrhea.

Among idelalisib-treated patients who reported diarrhea or colitis, the median time to onset of any grade diarrhea or colitis was 1.9 months (range, 0.0–29.8), of Grade 1 or 2 was 1.5 months (range, 0.0–15.2) and of Grade 3 or 4 was 7.1 months (range, 0.5–29.8). Kaplan–Meier curves of time to onset of diarrhea or colitis are shown for all idelalisib-treated patients in Figure 5-1 {Coutre et al 2015}.

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



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

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

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

- Small bowel diarrhea is characterized by large volume diarrhea (more than 1 per day), possible associated dehydration, weight loss, and paraumbilical pain. Consider an endoscopic small-bowel biopsy and evaluate other etiologies such as celiac disease.
- Large-bowel diarrhea may present with lower pelvic pain, tenesmus, generally smaller stool volumes with gross blood frequently found in the stool. Consider a colonoscopic evaluation and biopsy.

5.6.3. Dermatological Events

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

For subjects who develop a Grade ≥ 3 rash for which another underlying etiology cannot be identified (e.g., infection, co-suspect drug), idelalisib must be withheld until the rash is Grade ≤ 1, at which point idelalisib may be discontinued or resumed at a lower dose, at investigator discretion.

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

rituximab) and/or other concomitant medications known to be associated with SJS or TEN (e.g., allopurinol). If SJS or TEN is suspected, idelalisib must be discontinued, all coadministered medications associated with SJS or TEN should be interrupted and the subject treated accordingly.

Subjects should be monitored for the development of SJS, TEN, or other severe cutaneous reactions and idelalisib treatment should be discontinued if such events occur.

5.6.4. Pulmonary Events

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

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

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

For subjects with suspected Grade 1 pneumonitis, withhold idelalisib until resolution to baseline. Upon resolution to baseline, idelalisib may be resumed at lower dose level or discontinued at investigator discretion. For subjects with suspected Grade ≥ 2 pneumonitis (eg, new onset or worsening of baseline cough, dyspnea, hypoxia and/or a diffuse interstitial pattern or ground-glass opacities on chest imaging without obvious infectious etiology), idelalisib must be discontinued permanently and therapy initiated as clinically appropriate.

5.6.5. Hematological and Immunological Events

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

Treatment-emergent Grade 3 or 4 neutropenia events including those accompanied by fever or infection have occurred in subjects treated with idelalisib. All subjects must have their blood counts monitored at least every 2 weeks for the first 6 months of idelalisib treatment. At any time during the study, subjects who develop Grade 3 neutropenia must have blood counts monitored at least weekly until neutropenia is Grade ≤ 2. For subjects who develop Grade 4 neutropenia, idelalisib must be interrupted and blood counts monitored at least weekly until neutropenia is Grade ≤ 2 idelalisib may be resumed at a lower dose level once neutropenia is Grade ≤ 3. Neutropenia should be managed according to established clinical guidelines.

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

5.6.6. Infectious Events

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

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

CMV surveillance for active disease (quantitative PCR or PP65 antigen) must be conducted approximately every 4 weeks throughout the course of idelalisib treatment. CMV viral load testing should be performed from the same specimen type whenever possible and caution should be exercised when comparing CMV viral load results across different testing centers. If unequivocal clinical or laboratory evidence of CMV infection is present, the subject must interrupt idelalisib treatment and undergo effective antiviral treatment according to established clinical guidelines. If the benefits of resuming idelalisib are judged to outweigh the risks, consideration should be given to administering pre-emptive CMV therapy.

In high-risk subjects (history of recurrent infection, allogeneic transplant, treatment with alemtuzumab, hypogammaglobulinemia) other infection prophylaxis should be considered per consensus guidelines. Administration of intravenous immunoglobulin is permitted per standard institutional practice {Raanani et al 2009}. For subjects who develop an infection, appropriate medical therapy should be instituted in a timely manner.

5.6.7. Secondary Malignancies

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

5.6.8. Ultraviolet Exposure

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

5.6.9. Pregnancy, Lactation, and Reproduction

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

Given the potential the risks to a fetus or infant as a result of exposure to idelalisib, women of reproductive potential entering this study must have a negative serum pregnancy test at baseline and must not be breastfeeding. Males and females of childbearing potential should abstain from sexual intercourse or use an effective form of contraception (see Appendix 2). If a female study participant becomes pregnant or decides to breastfeed during the course of the study, all study therapy must be discontinued.

5.6.10. *Pneumocystis jirovecii* Pneumonia Prophylaxis

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

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

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

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

5.6.11. Further Safety Information

Further safety information regarding the study drug may be found in the investigator brochure for idelalisib.

5.7. Prior and Concomitant Medications

Concomitant treatment as deemed medically necessary by the investigator is allowed. Prophylaxis against PJP is required during idelalsib treatment and for 2 to 6 months following idelalisib treatment discontinuation (see Section5.6.6). No other anticancer therapies (including chemotherapy, radiation, antibody therapy, immunotherapy, or other experimental therapies) of any kind are permitted while the subject is receiving study treatment with idelalisib. Subjects are not allowed to participate concurrently in any other therapeutic clinical study.

5.7.1. Drugs that Alter CYP3A4-Dependent Metabolism

Idelalisib is metabolized primarily via aldehyde oxidase and in part by CYP3A. A clinical drug-drug interaction study indicated that administration of a potent CYP3A inhibitor together with idelalisib resulted in an ~80% increase in idelalisib plasma exposures (AUC) {Webb et al 2010}, which is not considered to be clinically relevant and suggests that idelalisib is a weak CYP3A substrate. Preliminary data indicate that when co-administered with rifampin, a highly potent inducer of CYP3A, idelalisib exposures are ~75% lower. Co-administration of potent inducers of CYP3A with idelalisib should be avoided; a list of strong inducers is provided in Table 5-2:

Table 5-2. Known Potent Inducers of CYP3A

Effect on CYP3A	Drug Class	Medications
Strong CYP3A Inducers	Antimycobacterial	Rifampin
	Anticonvulsants	carbamazepine, phenytoin
	Foods/herbs	St. John's wort

Abbreviation: CYP=cytochrome P450 enzyme

5.7.2. Drugs that Undergo CYP3A-Dependent Metabolism

The major metabolite of idelalisib, GS-563117, is a reversible and time dependent inhibitor of CYP3A; accordingly, co-administration of idelalisib with midazolam, a probe CYP3A substrate, resulted in ~5-fold increase in midazolam systemic exposure (AUC), indicating that idelalisib is a strong inhibitor of CYP3A. Co-administration of CYP3A substrates with idelalisib may result in an increase in their systemic exposures (eg, antiarrhythmics, calcium channel blockers, benzodiazepines, certain HMG-CoA reductase inhibitors, phosphodiesterase-5 [PDE5] inhibitors, Warfarin). Avoid co-administration of drugs that highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events, including narrow therapeutic index CYP3A substrates (eg, alfentanil, cyclosporine, sirolimus, tacrolimus, cisapride, pimozide, fentanyl, quinidine, ergotamine, dihydroergotamine, astemizole, terfenadine) with idelalisib.

5.8. Accountability for Idelalisib

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

Idelalisib accountability records will be provided to each study site to:

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

All study drug records must be maintained at the site and copies must be submitted to Gilead Sciences at the end of the study.

5.8.1. Idelalisib Return or Disposal

The study monitor will evaluate each site's study drug disposal procedures and provide appropriate instruction for return or destruction of unused idelalisib supplies. If the site has an appropriate Standard Operating Procedure (SOP) for drug destruction, the site may destroy unused idelalisib and used drug supplies performed in accordance with the site's (hospital/pharmacy) SOP. Where possible, idelalisib will be destroyed at the site. If drug is destroyed on site, the Investigator will maintain accurate records for all idelalisib destroyed. See Protocol Section 9.1.7, Investigational Medicinal Product Accountability and Return, for additional information.

5.9. Treatment Compliance

Subject compliance with dosing will be calculated based on return of unused idelalisib by subjects. The number of tablets dispensed, days of therapy, and number of tablets returned will be recorded.

6. STUDY PROCEDURES

The investigator must document any deviation from protocol procedures and notify the Sponsor or Sponsor's representative.

6.1. Subject Enrollment and Treatment Assignment

Subjects will sign the informed consent document prior to undergoing any study procedures.

The following information will be collected:

- Demographics
- Hematologic malignancy diagnosis
- Prior idelalisib study protocol number
- Clinical response status at completion of prior idelalisib study
- Dose of idelalisib at completion of prior idelalisib study
- Date of Last Subject Visit on prior idelalisib study (may be the same date as enrollment to this study)
- Recording of all AEs and SAEs

The subject will be dispensed a supply of idelalisib and prescribed an antibiotic for PJP prophylaxis.

6.2. Study Assessments

From the time of obtaining informed consent through the first administration of investigational medicinal product, record all AEs and SAEs on the AE case report form (CRF/eCRF). All other untoward medical occurrences observed during the screening period, including exacerbation or changes in pre-existing conditions are considered medical history (not collected for this study). See Section 7 Adverse Events and Toxicity Management for additional details.

While on study, the subject will return at regular intervals (approximately every 2-3 months) for the following procedures:

- Evaluation of disease status per standard of care
- Recording of all AEs and SAEs, including the following assessments for diarrhea / colitis:
  - Obtain history of onset and duration of diarrhea, including description of number of stools and stool composition (eg, watery, bloody, nocturnal), travel history, dietary changes and a medication review to identify possible diarrheogenic agents
  - Perform physical examination including assessment for fever, dizziness, abdominal pain/cramping, and weakness (ie, evaluate for sepsis, bowel obstruction, dehydration)
- Return of used drug supplies and dispensing of new idelalisib supply

PPD

6.3. Clinical Evaluation

While on study, the subject will be followed for disease status according to standard of care. At regular intervals (approximately every 2-3 months) the subject's disease status will be assessed (disease assessment visits) and information will be collected to determine response to treatment. If no change in disease status is identified and the subject is dispensed additional idelalisib, the most recent prior response documented for the study will be recorded.

All subjects will have CT scan at least once every 12 months and at time of initial response (PR or CR after SD, or CR after PR) or progression. In addition, for initial CR a bone marrow evaluation is required.

6.4. Laboratory Evaluation During the Study

All subjects should have the following laboratory tests at disease assessment visits: ALC, PLT, Hgb, ANC. All subjects with WM should also have the following laboratory tests at disease assessment visits: IgM, serum M protein.

All subjects will be monitored for CMV status via quantitative PCR or PP65 antigen approximately every 4 weeks during idelalisib therapy.

6.4.1. Evaluation for Gastrointestinal Events/Colitis

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

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

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

PPD

6.4.2. Immune Monitoring

The following laboratory assessments will be conducted every 12 weeks during idelalisib treatment:

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

6.5. Assessments for Premature Discontinuation from Study

If a subject discontinues study dosing (for example, as a result of an AE), every attempt should be made to keep the subject in the study and continue to perform the required study-related follow-up and procedures (see Section 6.7). If this is not possible or acceptable to the subject or investigator, the subject may be withdrawn from the study.

6.6. Criteria for Discontinuation of Study Treatment

Study medication may be discontinued in the following instances:

- Unacceptable toxicity or toxicity that, in the judgment of the investigator, compromises the ability to continue study-specific procedures or is considered to not be in the subject's best interest
- Toxicity for which the protocol specifies discontinuation of idelalisib
- Subject request to discontinue for any reason
- Subject noncompliance
- Pregnancy during the study; refer to Appendix 2
- Discontinuation of the study at the request of Gilead, a regulatory agency or an IRB/IEC

6.7. End of Study Assessments

Subjects will be withdrawn from this study if they develop progressive disease, unacceptable toxicity related to idelalisib, or if they no longer derive clinical benefit in the opinion of the investigator. The following procedures should be performed:

- Return of used and unused drug supply
- Recording of all AEs and SAEs
- CT scan to document progression

- Laboratory assessments

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

  — Lymphocyte subset panel using flow cytometry (immunophenotyping)

  — Quantitative immunoglobulins: IgG, IgM, IgA

  — Serum CH50 level

- Recording of the reason for withdrawal

Deaths occurring within 30 days following the last dose of idelalisib, even if occurring after the End of Study Visit, will be captured.

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 pharmaceutical 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.
- Pre-existing diseases, conditions, or laboratory abnormalities present or detected before the screening visit that do not worsen
- Situations where an untoward medical occurrence has not occurred (eg, hospitalization for elective surgery, social and/or convenience admissions)
- Overdose without clinical sequelae (see Section 7.5.1)
- 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.

7.1.2. Serious Adverse Events

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

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

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

7.1.3. 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 idelalisib 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 7.1.1and 7.1.2. If the laboratory abnormality is part of a syndrome, record the syndrome or diagnosis (eg, anemia), not the laboratory result (ie, decreased hemoglobin).

7.2. Assessment of Adverse Events and Serious Adverse Events

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

7.2.1. Assessment of Causality for Study Drugs and Procedures

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

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

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

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

- **No:** Evidence exists that the adverse event has an etiology other than the study procedure.
- **Yes:** The adverse event occurred as a result of protocol procedures, (eg, venipuncture)

7.2.2. Assessment of Severity

The severity of AEs will be graded according to CTCAE v4.03, available at:

http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

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

Table 7-1. Grading of Adverse Event Severity

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

The distinction between the seriousness and the severity of an AE should be noted. Severe is a measure of intensity; thus, a severe reaction is not necessarily a serious reaction. For example, a headache may be severe in intensity, but would not be classified as serious unless it met one of the criteria for serious events listed in Section7.1.2.

7.2.3. Assessment of the Outcome of Adverse Events

- ***Resolved:*** The subject has fully recovered from the event with no residual effects observable.
- ***Stabilized:*** Effects of the event are constant. The likelihood of these effects changing (improving or worsening) is low.
- ***Ongoing:*** Effects of the event are still present and changing. The event is not considered stabilized or resolved.

Death is an outcome of an event and not an event per se (sudden death or death of unexplainable causes can be reported but follow-up will be required until cause of death is determined).

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

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

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

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

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

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

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

<u>Serious Adverse Event Paper Reporting Process</u>

- All SAEs will be recorded on the serious adverse event report form and submitted by faxing the report form within 24 hours of the investigator’s knowledge of the event to the attention of INC Research Drug Safety.

<u>Electronic Serious Adverse Event (eSAE) Reporting Process</u>

- Site personnel record all SAE data in the eCRF database and from there transmit the SAE information to INC Research Drug Safety within 24 hours of the investigator’s knowledge of the event. Detailed instructions can be found in the eCRF completion guidelines.
- If for any reason it is not possible to record the SAE information electronically, ie, the eCRF database is not functioning, record the SAE on the paper serious adverse event reporting form and submit within 24 hours as described above.

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

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

INC Research Drug Safety: Fax: PPD
E-mail: PPD

- 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. The investigator should notify the IRB or IEC of SUSAR reports as soon as is practical, where this is required by local regulatory agencies, and in accordance with the local institutional policy.

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

To maintain the integrity of the study, disease progression and death related to disease progression should not be reported to Gilead Sciences as adverse events unless it is assessed that idelalisib caused or contributed to the disease progression or death related to disease progression (ie, by a means other than lack of effect).

All events of disease progression and death related to disease progression, regardless of relationship to idelalisib, will be reported in the eCRFs and, as appropriate, in the final clinical study report and in any relevant aggregate safety reports.

Disease progression information from this study will be reviewed on an ongoing basis.

7.5. Special Situations Reports

7.5.1. Definitions of Special Situations

Special situation reports include all reports of medication error, abuse, misuse, overdose, lack of effect reports and pregnancy reports regardless of an associated AE. Also includes reports of adverse reactions in infants following exposure from breastfeeding, and reports of adverse reactions associated with product complaints and reports arising from occupational exposure.

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

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

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

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

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

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

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

7.5.2. Instructions for Reporting Special Situations

7.5.2.1. Instructions for Reporting Pregnancies

The investigator should report all pregnancies that are identified after the subject first consents to participate in the study (ie, signs the informed consent) and throughout the study, including the post idelalisib follow-up period, to INC Drug Safety using the pregnancy report form within 24 hours of becoming aware of the pregnancy. Refer to Section 7.3 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 as described in Sections 7.1.1 and 7.1.2. Furthermore, any SAE occurring as an adverse pregnancy outcome post study must be reported to INC Drug Safety.

The subject should receive appropriate monitoring and care until the conclusion of the pregnancy. The outcome should be reported INC Drug Safety 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

Refer to Appendix 2 for Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Recommendations.

7.5.2.2. Reporting Other Special Situations

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

Refer to Section 7.3 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. Determination of Sample Size

The sample size for this study depends on the number of eligible subjects from prior studies treated with idelalisib (101-02, 101-07, 101-08 and 101-10). No formal sample size calculation is conducted.

8.2. Statistical and Analytical Plans

8.2.1. General Considerations

The baseline value used in each analysis will be the last value before or on the date of first dosing in the parent study. 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.

Summary of efficacy will be presented by integrating parent study with this extension study for 101-02, 101-07, 101-08, and 101-10 respectively

8.2.1.1. Handling of Missing Data

Analyses will be based upon observed data without imputation.

8.2.2. Analysis Populations

8.2.2.1. Intent-to-Treat Analysis Set

The intent-to-treat (ITT) analysis set will consist of all subjects receiving at least 1 dose of study treatment. This analysis set will be used for the efficacy and safety analysis.

The dose of idelalisib should be the same as the dose that was administered at the end of the parent study.

8.2.3. Subject Disposition

The number and percentage of subjects who received idelalisib, completed parent study, entered study 101-99 and discontinued from study 101-99 will be summarized. Summary for the reasons of the discontinuation from the study treatment will be provided separately for each individual study with 101-99.

8.2.4. Subject Characteristics

Demographics and baseline characteristics information will be captured from parent study. Summary will be provided separately for each individual study with 101-99, but will only include subjects who rolled over to 101-99.

8.2.5. Efficacy Analyses

Parent studies will be integrated with 101-99 for efficacy analysis. The data will be summarized separately for 101-02, 101-07, 101-08 and 101-10 with 101-99 based on subject disease and dose categorization as in parent study. The analysis will be performed including all subjects in the parent study regardless of their rolling over to 101-99 or not.

8.2.5.1. Primary Efficacy Analysis

Overall response rate based on investigator's response will be calculated along with its 95% confidence intervals (CIs) based on exact method. In the analyses of ORR, subjects who do not have sufficient baseline or on-study tumor assessment to characterize response will be counted in the denominator

8.2.5.2. Secondary Efficacy Analyses

For the analyses of DOR, PFS and OS, the Kaplan-Meier method will be used. For categorical variables, the following information will typically be presented: sample size, proportion, and 95% CIs based on exact binomial method.

For the DOR and PFS analyses, subjects who withdraw from the study or are lost to follow-up without disease progression or death will be censored on the date of the last visit that lack of disease progression was objectively documented. Subjects who start a new antitumor treatment other than study treatment before disease progression will be censored on the last visit that lack of disease progression was objectively documented before the start of new antitumor treatment. Subjects who have CLL progression or die after ≥ 2 consecutive missing tumor assessments will be censored at the last time prior to the missing assessments that lack of definitive CLL progression was objectively documented. For subjects without any adequate post-baseline disease assessment, PFS will be censored on the date of first study dose.

8.2.6. Pharmacokinetic and Pharmacodynamic Analyses

Not applicable.

8.2.7. Safety Analyses

The primary safety endpoint for this study will be the incidence of adverse events. All AEs and SAEs encountered by enrolled subjects during the clinical trial from the time the informed consent for 101-99 is signed through the end of study visit are required to be recorded on the AE CRF page(s). Summary will be provided by including all AEs recorded.

8.2.7.1. Extent of Exposure

A subject's extent of exposure to idelalisib will be generated from the idelalisib administration data. Exposure data will be summarized.

8.2.7.2. Adverse Events

All adverse events that are observed in the parent studies (101-02, 101-07, 101-08, and 101-10) and their extension study will be summarized. The focus of adverse event summarization will be on treatment-emergent adverse events. A treatment-emergent adverse event is defined as an adverse event that occurs or worsens in the period from the first dose of study treatment to 30 days after the last dose of study treatment. Adverse events occurring from the first dose administered on the parent study and throughout subjects' participation in this extension study will be included.

Adverse events will be classified using Medical Dictionary for Regulatory Activities (MedDRA) with descriptions by System Organ Class (SOC), High-Level Group Term, High-Level Term (HLT), Preferred Term, and Lower-Level Term. The severity of adverse events will be graded by the investigator according to the CTCAE, Version 4.03, whenever possible. If a CTCAE criterion does not exist for a specific type of 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) (see Table 7-1). The relationship of the adverse event to idelalisib will be categorized as related or unrelated.

Summaries (number and percentage of subjects) of treatment-emergent adverse events (by SOC, HLT, and preferred term) will be provided. A subject who reports multiple treatment-emergent adverse events within the same preferred term (or HLT or SOC) is counted only once for that preferred term (or HLT or SOC) using the worst severity grade. Adverse event descriptions will be presented by decreasing frequency for a given SOC, HLT and preferred term.

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

- idelalisib-related adverse events
- Adverse events that are Grade ≥3 in severity
- Adverse events leading to idelalisib discontinuation
- By-subject listings will be provided for all AEs collected in 101-99.

8.2.7.3. Serious Adverse Events

SAEs will be listed and summarized in a similar manner to AEs as described in Section 8.2.7.2.

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. For studies conducted in the EU, add: 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 IRB/IEC has been documented and provided as a letter to the investigator.

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

9.1.3. Informed Consent

The investigator is responsible for obtaining written informed consent from each individual participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study and before undertaking any study-related procedures. The

investigator must use the most current IRB- or IEC-approved consent form for documenting written informed consent. Each informed consent (or assent as applicable) will be appropriately signed and dated by the subject or the subject's legally authorized representative and the person conducting the consent discussion, and also by an impartial witness if required by IRB or IEC or local requirements.

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 submitted to the Sponsor, or IRB.

The investigator agrees that all information received from Gilead, including but not limited to the Investigator's Brochure, this protocol, CRF/eCRF, the IMP, 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 IMP, 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. 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 (eg data entry error). At the conclusion of the trial, Gilead will provide the site with a read-only archive copy of the data entered by that site. This archive must be stored in accordance with the records retention requirements outlined in Section 9.1.5.

9.1.7. Investigational Medicinal Product Accountability and Return

The study monitor will evaluate each study center's IMP disposal procedures and provide appropriate instruction for destruction of unused IMP supplies. If the site has an appropriate standard operating procedure (SOP) for drug destruction as determined by Gilead SOP, the site may destroy used (empty or partially empty) and unused IMP supplies in accordance with that site's approved SOP. A copy of the site's approved SOP will be obtained for central files.

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

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

9.1.8. Inspections

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

9.1.9. Protocol Compliance

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

9.2. Sponsor Responsibilities

9.2.1. Protocol Modifications

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

9.3.2. 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.

9.3.3. Study Discontinuation

Both the sponsor and the investigator reserve the right to terminate the study at any time. Should this be necessary, both parties will arrange discontinuation procedures and notify the appropriate regulatory authority(ies), IRBs, and IECs. In terminating the study, Gilead 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.
199 E. BLAINE STREET
SEATTLE, WA 98102

STUDY ACKNOWLEDGEMENT

An Extension Study to Investigate the Safety and Durability of Clinical Activity of Idelalisib in Subjects with Hematologic Malignancies

101-99, Amendment 5, Version 6.0, 07 November 2016

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

PPD

PPD

Name (Printed)
Medical Monitor

07 Nov 2016

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. 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 fertile after the initiation of puberty unless permanently sterile by bilateral orchidectomy or medical documentation.

2) Contraception Requirements for Female Subjects

a. Study Drug Effects on Pregnancy and Hormonal Contraception

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

b. Contraception Requirements for Female Subjects of Childbearing Potential

The inclusion of female subjects of childbearing potential requires the use of highly effective contraceptive measures. 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/Day 1 visit prior to randomization. Pregnancy tests will be performed at monthly intervals thereafter. Female subjects must agree to one of the following from Screening until 30 days following the end of relevant systemic exposure.

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

Or

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

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

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

3) Contraception Requirements for Male Subjects

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

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

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 for females or 90 days for female partners of male subjects of last study drug dose. 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. Instructions for reporting pregnancy, partner pregnancy, and pregnancy outcome are outlined in Section 7.5.2.1.