



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.
199 E. Blaine Street
Seattle, WA 98102

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PROTOCOL SYNOPSIS

Gilead Sciences, Inc.
199 East Blaine
Seattle, WA 98102

Study Title:	An Extension Study to Investigate the Safety and Durability of Clinical Activity of Idelalisib (IDELA) 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:	<p>The primary objective of this study is as follows:</p> <ul style="list-style-type: none">• To investigate the long-term safety of idelalisib (IDELA) in patients with hematologic malignancies• To determine the duration of clinical benefit of IDELA in patients with hematologic malignancies
Study Design:	<p>This is a long-term safety extension study of IDELA in subjects with hematologic malignancies who complete other IDELA 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 IDELA study. Subjects will be withdrawn from the study if they develop progressive disease, unacceptable toxicity related to IDELA, or if they no longer derive clinical benefit in the opinion of the investigator.</p>
Number of Subjects Planned:	The number of subjects enrolled will be determined by the number of subjects completing a prior IDELA study with a clinical benefit and who wish to continue therapy with IDELA.
Target Population:	Subjects who complete a prior IDELA 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.

Diagnosis and Main Eligibility Criteria:	Subjects with hematologic malignancies completing a prior IDELA study (101-02, 101-07, 101-08, 101-10)
Study Procedures/ Frequency:	<p>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 Grade ≥ 3 AEs and all SAEs, and return of used drug supplies and dispensing of new drug supply.</p> <p>While on study, the subject will be followed for disease status according to standard of care. At each study visit 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 IDELA, the most recent prior response documented for the study will be recorded.</p> <p>All subjects with CLL will have the following laboratory tests at each visit: ALC, PLT, Hgb, ANC. All subjects with WM will have the following laboratory tests at each visit: IgM, serum M protein.</p> <p>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.</p>
Test Product, Dose, and Mode of Administration:	IDELA 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 IDELA 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 <ul style="list-style-type: none">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

Sample Size Calculation:

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
BID	twice per day
CAL-101	Former name for idelalisib
CFR	Code of Federal Regulations
CI	confidence interval
CLL	chronic lymphocytic leukemia
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
FL	Follicular lymphoma
GCP	Good Clinical Practice
GS-1101	Former name for idelalisib
Hgb	Hemoglobin
IDELA	idelalisib, formerly GS-1101, CAL-101
IMP	Investigational medicinal product
IgM	Immunoglobulin M
iNHL	Indolent non-Hodgkin lymphoma
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ITT	Intent to treat
IWCLL	International Workshop on Chronic Lymphocytic Leukemia
MCL	Mantle cell lymphoma
MTD	Maximum tolerated dose
NCCN	National Comprehensive Cancer Network

GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS (CONTINUED)

NOAEL	No observed adverse effect levels
ORR	Overall response rate
OS	Overall survival
PFS	Progression-free survival
PI3K	Phosphatidylinositol 3-kinase
PLT	Platelets
PR	Partial response
SAE	Serious adverse event
SD	Stable disease
SLL	Small lymphocytic lymphoma
SOP	Standard Operating Procedure
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 (IDELA, 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) p110 δ catalytic domain, which has been shown to be prominently expressed in cells of hematopoietic origin {23619}, {17690}. PI3K δ is critical for multiple signaling pathways that are hyperactive in B-cell malignancies. Inhibition of PI3K δ modulates B-cell receptor signaling as well as signaling through cytokine and chemokine receptors and integrin $\alpha\beta$ 1. 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 PI3K δ -dependent signaling, IDELA inhibits proliferation, survival, homing, motility, and retention, and promotes apoptosis in many B-cell malignancies.

An essential role of PI3K δ 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 PI3K δ resulted in the inhibition of Akt phosphorylation and cellular proliferation {21136}. Sustained activation of the PI3K δ 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 {19038}. The Sponsor has shown that PI3K δ is expressed in all primary CLL patient cells tested and treatment with IDELA 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 {21135}. 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 {21137}. 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 {21134} and Waldenström's macroglobulinemia (WM) {21146}. These data provide the rationale for targeting the PI3K δ signaling pathway with IDELA as a potential new treatment for hematologic malignancies. In addition, the relative lack of activity of IDELA against p110 α should minimize the potential for hyperglycemia relative to pan-PI3K inhibitors.

For further information on IDELA, 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 IDELA 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 PI3K δ inhibition.

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

1.1.3. Clinical Trials of Idelalisib (IDELA)

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 IDELA was administered in cohorts of subjects across a range of dose levels from 50 mg BID to 350 mg BID. IDELA 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 {12154}.

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 IDELA was studied. The multiple-dose C_{max} , C_{trough} , and AUC of IDELA 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 IDELA, 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 IDELA dosing, a high level of constitutive pAkt^{T308} was noted. Following 8 and 28 days of dosing with IDELA 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 IDELA 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 IDELA administration. IDELA 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 IDELA) 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” {22541}. 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. {24731}. 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 IDELA-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 IDELA given in combination with bendamustine or bendamustine-rituximab to subjects with recurrent iNHL (indolent non-Hodgkin lymphoma) or CLL {20228}, {20229}.

In this study, 28 subjects with CLL received IDELA with bendamustine alone (n=14) or with bendamustine/rituximab (n=14). Bendamustine doses were 70 or 90 mg/m² on Days 1 and 2 of each of 6 planned 4-week cycles. Rituximab was infused at a dose of 375 mg/m² on Day 1 of each of the 6 planned 4-week cycles. IDELA was first evaluated at a dose level of 100 mg/dose BID (n=4) and then at a dose level of 150 mg/dose BID (n=24) and was administered continuously for as long as individual subjects were safely benefiting from therapy. Subjects were evaluated in 4-week cycles; response and progression assessments were based on standard criteria {12154}.

Among the subjects with CLL, the median age was 65 and ranged to 86 years. Bulky tumors (≥ 1 lymph node ≥ 5 cm in diameter) were present in 64% of the subjects. The median number of prior therapies was 3 and ranged up to 9 prior treatments. The substantial majority (> 90%) had

received prior purine analogs, alkylating agents, and rituximab and 36% had received prior bendamustine. Approximately half of subjects had CLL that was refractory to the last prior therapy. At the time of data cut-off, therapy had been administered for a median of 6 cycles, ranging up to 17 cycles (ie, 68 weeks).

No IDELA-related dose-limiting toxicities were observed within the tested subject cohorts. Grade ≥ 3 neutropenia was observed in 11 (40%) subjects and only 1 (4%) subject had febrile neutropenia. Grade 3-4 non-myelosuppressive adverse events largely comprised background events resulting from pre-existing disease- or treatment-related conditions or from intercurrent illness. Among these subjects with CLL, 4 (15%) developed pneumonia. For subjects receiving IDELA together with bendamustine or bendamustine/rituximab, Grade 3-4 elevations in ALT/AST were observed in 3 (11%) subjects.

When IDELA was coadministered with bendamustine or bendamustine/rituximab, combination therapy showed a high level of antitumor activity. The ITT ORR was 11/14 (79%) for the IDELA plus bendamustine regimen and 12/14 (86%) among subjects receiving IDELA with bendamustine/rituximab. Concomitant administration of bendamustine appeared to largely eliminate the redistribution lymphocytosis that is associated with IDELA monotherapy. At the time of the data analysis, overall PFS through 48 weeks was $>80\%$ and a median PFS had not yet been observed.

1.1.3.3. Phase 2 Study of IDELA 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 IDELA 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: IDELA 150 mg BID orally on Days 1 through 28 of each 28-day cycle (Cycles 1 through 12) + rituximab 375 mg/m² IV weekly for 8 doses (Cycles 1 and 2). Treatment with IDELA 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 IDELA due to one or more AEs. Diarrhea, respiratory disorders, and rash were the most frequently reported AEs leading to discontinuation of IDELA 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%).

For additional or updated information, please refer to the current version of the IDELA 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 IDELA to continue IDELA 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 IDELA in subjects with hematologic malignancies
- To determine the duration of clinical benefit of IDELA 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 IDELA in subjects with hematologic malignancies who complete other IDELA 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 IDELA study. Subjects will be withdrawn from the study if they develop progressive disease, unacceptable toxicity related to IDELA, or if they no longer derive clinical benefit in the opinion of the investigator.

3.4. Study Treatments

The Sponsor will provide IDELA drug product to study sites.

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

- 100, 150, or 200 mg IDELA BID
- 100, 200, or 300 mg IDELA once daily

Subjects receive IDELA 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. 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 IDELA treatment for any reason (see Section 6.5)
- The subject experiences a toxicity that necessitates permanent discontinuation of IDELA treatment
- The subject has progressive disease or is no longer deriving clinical benefit
- 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 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 IDELA study with a clinical benefit who wish to continue therapy with IDELA.

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 IDELA 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 (IDELA)

5.2.1. Storage and Handling

IDELA, 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 IDELA 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

IDELA drug product is provided as plain-faced, modified oval tablets. The 100-mg tablets are orange film-coated, and the 150-mg tablets are pink film-coated.

5.2.3. Packaging and Labeling

IDELA 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 (IDELA)

IDELA 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 IDELA trial. Subjects should be instructed to take the doses with water. IDELA 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 IDELA 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. Dose reduction may be considered if severe toxicities occur that may be related to IDELA.

Recommendations for dose adjustment due to hematologic and non-hematologic toxicity follow; 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

Recommendations for 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. Recommendations for Modifications of Study Treatment

NCI CTCAE Grade	Recommendation
	Idelalisib
HEMATOLOGICAL ADVERSE EVENTS	
Neutropenia	
Grade ≤ 2 neutropenia	Maintain current dose level and schedule.
Grade ≤ 3 neutropenia	Maintain current idelalisib dose level and schedule.
Grade 4 neutropenia (or occurrence of neutropenic fever or infection)	Consider G-CSF support and continue idelalisib at initial or lower dose level at investigator discretion.
Thrombocytopenia	
Grade ≤ 3	Maintain current dose level and schedule.
Grade 4	Withhold for bruising or bleeding until Grade ≤ 3 . May resume idelalisib at initial or lower dose level at investigator discretion.
NON-HEMATOLOGICAL ADVERSE EVENTS	
Dermatological	
Grade ≤ 1	Maintain current dose level and schedule.
Grade 2	Maintain current dose level and schedule.
Grade ≥ 3	Withhold idelalisib until Grade ≤ 1 . May resume at lower dose level or discontinue idelalisib at investigator discretion.
Gastrointestinal Inflammation/Diarrhea	
Grade ≤ 1	Provide anti-diarrheal (eg, loperamide) and maintain current idelalisib dose level and schedule.
Grade 2	Provide anti-diarrheal (eg, loperamide). Consider addition of anti-inflammatory agent (eg, sulfasalazine, budesonide). Maintain current IDELA dose and schedule.
Grade 3	Provide anti-diarrheal (eg, loperamide). Withhold idelalisib until Grade ≤ 1 . Resume at lower dose level. Consider addition of anti-inflammatory agent (eg, sulfasalazine, budesonide).
Grade 4	Provide anti-diarrheal (eg, loperamide). Withhold idelalisib until Grade ≤ 1 . May resume at lower dose level or discontinue idelalisib at investigator discretion. Consider addition of anti-inflammatory agent (eg, sulfasalazine, budesonide).

NCI CTCAE Grade	Recommendation
	Idelalisib
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)	Maintain current dose level and schedule. Monitor ALT, AST, ALP, and bilirubin at least 1x per week.
Grade 3 (ALT/AST>5-20xULN) (Bilirubin>3-10xULN)	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)	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, resume idelalisib at lower dose level. If bilirubin abnormality was Grade 4, discontinue idelalisib.
Pneumonitis (dyspnea, cough, hypoxia and/or diffuse interstitial pattern or ground-glass opacities on chest CT and no obvious infectious cause)	
Grade ≤1	Maintain current dose level and schedule. Consider pneumocystis prophylaxis.
Grade 2	Withhold idelalisib until Grade ≤1, institute systemic corticosteroids, and consider pneumocystis treatment. May resume at lower dose level.
Grade ≥3	Withhold idelalisib until Grade ≤1, consider systemic corticosteroids and consider pneumocystis treatment. May resume at lower dose level or discontinue idelalisib at investigator discretion.
Other Nonhematological Adverse Events	
Grade ≤2	Maintain current dose level and schedule.
Grade ≥3	Withhold idelalisib until Grade ≤1. May resume idelalisib at initial or lower dose level or discontinue idelalisib at investigator discretion.

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 also observed early in the IDELA program in Phase 1 studies (101-02 and 101-07) in subjects with hematologic malignancies. Transaminase elevations generally occurred within 4 to 12 weeks of drug initiation, and resolved spontaneously over a period of 2 to 4 weeks with drug being continued for Grade 1 and 2 elevations and drug withheld for Grade 3 or 4 elevations until resolution. These early observations have been repeated throughout the program and transaminase elevations are now well characterized as follows: they occur within the first 3 months of treatment; are generally asymptomatic and transient in nature;

Grade 1 or 2 elevations commonly resolve despite continued IDELA treatment; and Grade 3 or 4 elevations can be managed by temporarily withholding IDELA. Successful rechallenge after resolution at lower dose levels of IDELA has been achieved in the majority of subjects. There has been no evidence of impaired synthetic liver function.

Close monitoring of hepatic laboratory tests early during therapy is important to inform appropriate IDELA interruption and reinstatement in order to ensure that subjects who appear to be benefiting are able to continue with IDELA treatment.

5.6.2. Gastrointestinal Events

Cases of severe diarrhea (reported as Grade 3 or 4 diarrhea and/or colitis) have been reported in subjects with hematologic malignancies treated with IDELA for which the more common etiologies anticipated for the study population could not be readily identified. In the majority of such cases, subjects presented after several months of IDELA administration with several weeks of watery diarrhea unresponsive to antidiarrheals or to empiric treatment with antimicrobials. Resolution has been documented in almost all cases, and treatment regimens have included budesonide, mesalamine, systemic steroids, and supportive care, with some subjects receiving more than 1 treatment approach concomitantly. Resolution of the diarrhea occurred within approximately 1 month from the discontinuation of IDELA (regardless of treatment approach). In subjects with \geq Grade 3 diarrhea who were rechallenged with IDELA, recurrence of diarrhea has occurred in some but not all subjects.

For subjects who develop severe persistent diarrhea for which an underlying etiology cannot be identified (eg, infection), IDELA should be interrupted. Resumption of IDELA should be considered once diarrhea resolves if the subject is experiencing evidence of clinical benefit from therapy.

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. Upon recovery, rituximab may be resumed. IDELA may be resumed following resolution of a bowel obstruction, if appropriate for the clinical situation. IDELA should be discontinued in subjects who experience bowel perforation.

5.6.3. Rash

Rash has been observed throughout the development program for IDELA although the frequency of \geq Grade 3 and serious dermatological AEs has remained low. Subjects with \geq 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 steroids. The occurrence of \geq Grade 3 rash has been more frequent when IDELA was administered in combination with immunochemotherapy agents. Rechallenge with IDELA has resulted in recurrence of rash in some but not all subjects.

For subjects who develop a severe maculopapular rash for which an underlying etiology cannot be identified (eg, infection, co-suspect drug), IDELA should be interrupted. Resumption of IDELA should be considered once rash resolves if the subject is experiencing evidence of clinical benefit from therapy. Subjects should be monitored for the development of a severe cutaneous reaction (Steven Johnson syndrome, toxic epidermal necrolysis, etc) and should be discontinued from IDELA in the event of a severe cutaneous reaction.

5.6.4. Pneumonitis

Some subjects receiving IDELA alone or in combination have developed evidence of pneumonitis with no clinical evidence of infection, in some cases supported by biopsy or necropsy results. Some of these events have required mechanical ventilation and/or have been fatal.

For subjects with suspected pneumonitis (eg, onset of cough, dyspnea, hypoxia and/or a diffuse interstitial pattern or ground-glass opacities on chest imaging without obvious infectious etiology), IDELA should be interrupted and therapy with systemic corticosteroids should be instituted rapidly. Supportive care, including oxygen or mechanical ventilation, should be provided as necessary. Resumption of IDELA could be considered if the symptoms resolve and if the subject is appropriate for re-treatment. Reoccurrence of drug-related pneumonitis upon rechallenge should result in permanent discontinuation of IDELA.

5.7. Prior and Concomitant Medications

Concomitant treatment as deemed medically necessary by the investigator is allowed. 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 IDELA. Subjects are not allowed to participate concurrently in any other therapeutic clinical study.

5.7.1. Drugs that Alter CYP3A4-Dependent Metabolism

IDELA 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 IDELA resulted in an ~80% increase in IDELA plasma exposures (AUC) {20361}, which is not considered to be clinically relevant and suggests that IDELA is a weak CYP3A substrate. Preliminary data indicate that when co-administered with rifampin, a highly potent inducer of CYP3A, IDELA exposures are ~75% lower. Co-administration of potent inducers of CYP3A with IDELA 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 IDELA, GS-563117, is a reversible and time dependent inhibitor of CYP3A; accordingly, co-administration of IDELA with midazolam, a probe CYP3A substrate, resulted in ~5-fold increase in midazolam systemic exposure (AUC), indicating that IDELA is a strong inhibitor of CYP3A. Co-administration of CYP3A substrates with IDELA 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 IDELA.

5.8. Accountability for Idelalisib (IDELA)

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

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

- Record the date received and quantity of IDELA
- Record the date, subject number, subject initials, and lot number, of the IDELA dispensed
- Record the date, quantity of unused IDELA and used supplies 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 (IDELA) 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 IDELA supplies. If the site has an appropriate Standard Operating Procedure (SOP) for drug destruction, the site may destroy unused IDELA and used drug supplies performed in accordance with the site's (hospital/pharmacy) SOP. Where possible, IDELA will be destroyed at the site. If drug is destroyed on site, the Investigator will maintain accurate records for all IDELA 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 IDELA 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 IDELA study protocol number
- Clinical response status at completion of prior IDELA study
- Dose of IDELA at completion of prior IDELA study
- Date of Last Subject Visit on prior IDELA study (may be the same date as enrollment to this study)
- Recording of Grade ≥ 3 AEs and all SAEs

The subject will be dispensed a supply of IDELA.

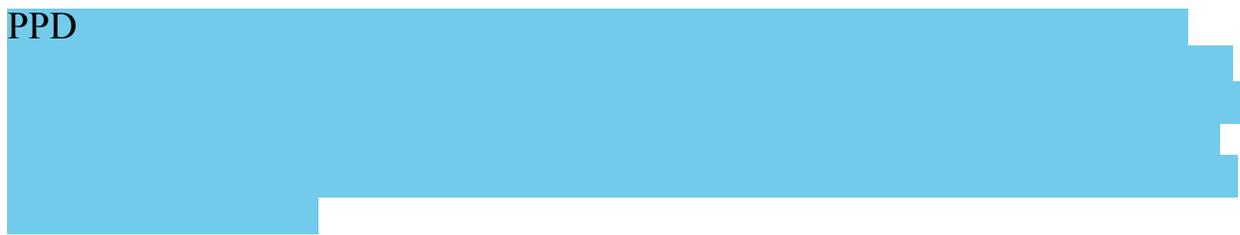
6.2. Study Assessments

From the time of obtaining informed consent through the first administration of investigational medicinal product, record all SAEs, as well as any non-serious Grade ≥ 3 AEs 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 Grade ≥ 3 AEs and all SAEs
- Return of used drug supplies and dispensing of new IDELA supply

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6.3. Clinical Evaluation

While on study, the subject will be followed for disease status according to standard of care. At each study visit the subject's disease status will be assessed and information will be collected to determine response to treatment. If no change in disease status is identified and the subject is dispensed additional IDELA, the most recent prior response documented for the study will be recorded.

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

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. 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 6.5). If this is not possible or acceptable to the subject or investigator, the subject may be withdrawn from the study.

6.5. Criteria for Discontinuation of Study Treatment

Study medication may be discontinued in the following instances:

- Intercurrent illness that would, in the judgment of the investigator, affect assessments of clinical status to a significant degree. Following resolution of intercurrent illness, the subject may resume study dosing at the discretion of the investigator.
- Unacceptable toxicity or toxicity that, in the judgment of the investigator, compromises the ability to continue study-specific procedures or is considered to not be in the subject's best interest
- 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

6.6. End of Study

Subjects will be withdrawn from this study if they develop progressive disease, unacceptable toxicity related to IDELA, 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 Grade ≥ 3 AEs and all SAEs
- CT scan to document progression
- Laboratory assessments
- Recording of the reason for withdrawal

Deaths occurring within 30 days following the last dose of IDELA, 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. It is considered to be pre-existing and should be documented on the medical history CRF.

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) of Grade ≥ 3 that require medical or surgical intervention or lead to IDELA 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 Grade ≥ 3 or SAE if they meet the definition of an AE or SAE as described in Sections 7.1.1 and 7.1.2. If the laboratory abnormality is part of a syndrome, record the syndrome or diagnosis (eg, anemia), not the laboratory result (ie, decreased hemoglobin).

7.2. Assessment of Adverse Events and Serious Adverse Events

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

7.2.1. Assessment of Causality for Study Drugs and Procedures

The investigator or qualified subinvestigator is responsible for assessing the relationship to IDELA 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. Only AEs \geq Grade 3 will be recorded.

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 Grade \geq 3 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.

- All Grade \geq 3 AEs and SAEs will be recorded in the CRF/eCRF database within the timelines outlined in the CRF/eCRF completion guideline.
- At the time of study start, SAEs will be reported using a paper serious adverse event reporting form. During the study conduct, sites may transition to an electronic SAE (eSAE) system. Gilead will notify sites in writing and provide training and account information prior to implementing an eSAE system.

Serious Adverse Event Paper Reporting Process

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

Electronic Serious Adverse Event (eSAE) Reporting Process

- Site personnel record all SAE data in the eCRF database and from there transmit the SAE information to 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:
E-mail:

PPD
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- 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 IDELA 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 IDELA, 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 IDELA 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 IDELA (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 IDELA 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 IDELA, 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. Only Grade 3 or higher AEs and all serious adverse events (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 IDELA will be generated from the IDELA 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. All Grade ≥ 3 AEs 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 (IDELA or rituximab) 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, and AEs of Grade ≥ 3 will be recorded. 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 3 (severe), Grade 4 (life-threatening), or Grade 5 (fatal). The relationship of the adverse event to IDELA 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:

- IDELA-related adverse events
- Adverse events that are Grade ≥ 3 in severity
- Adverse events leading to IDELA discontinuation

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.

For studies conducted under a United States Investigational New Drug application (IND) add:

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.

10. REFERENCES

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11. APPENDICES

- Appendix 1. Investigator Signature Page
- Appendix 2. Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Recommendations

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 (IDELA) in Subjects with Hematologic Malignancies

101-99, Amendment 3, Version 4.0, 25 November 2014

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

PPD

Name (Printed)
Medical Monitor

PPD

12/1/14
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 Recommendations

1) Pregnancy and Contraception Requirements for Males and Females of Childbearing Potential

Idelalisib (IDELA) is contraindicated in pregnancy as animal studies in rats and rabbits have shown that IDELA is teratogenic. Pregnancy must be excluded before the start of IDELA treatment and prevented thereafter by reliable contraceptive methods. Pregnancy tests will be performed at the start of study treatment, and subjects will be required to use contraception throughout the treatment period. Please refer to the latest version of the investigator's brochure for additional information.

2) Definition of Female of Childbearing Potential

For the purposes of this study, a female subject of childbearing potential is a nonmenopausal female who has not had a hysterectomy, bilateral oophorectomy or bilateral tubal ligation, or medically documented ovarian failure. This definition includes a pubertal female who has not yet started menstruating. A woman who has had a tubal sterilization is considered to be of childbearing potential.

A female subject may be considered menopausal in either of the following conditions:

- Surgical menopause: Appropriate medical documentation of prior complete bilateral oophorectomy (ie, surgical removal of the ovaries and occurring at the age at which the procedure was performed)
- Spontaneous menopause: Permanent cessation of previously occurring menses as a result of ovarian failure (no period for at least one year after menopause) with documentation of hormonal deficiency by a certified health care provider. The worldwide mean age of spontaneous menopause is 49.24 (standard deviation 1.73) years
- A hormonal deficiency should be properly documented in the case of suspected spontaneous menopause as follows:
 - If age ≥ 54 years and with the absence of normal menses: serum follicle stimulating hormone (FSH) level elevated to within the postmenopausal range based on the laboratory reference range where the hormonal assay is performed
 - If age < 54 years and with the absence of normal menses: negative serum or urine human chorionic gonadotropin (hCG) with concurrently elevated serum FSH level in the postmenopausal range, depressed estradiol (E2) level in the postmenopausal range, and absent serum progesterone level, based on the laboratory reference ranges where the hormonal assays are performed

3) Contraceptive Requirements

Female subjects of childbearing potential who engage in intercourse must agree to utilize protocol specified methods of contraception from the screening visit throughout the study period and for 30 days following the last dose of IDELA. Male subjects of reproductive potential having intercourse with females of childbearing potential, must agree to utilize protocol specified methods of contraception from the start of IDELA therapy throughout the study period and for 90 days following the last dose of IDELA. Female study subjects who are not heterosexually active must provide periodic confirmation of continued abstinence from heterosexual intercourse and regular pregnancy testing while taking IDELA. The investigator will counsel subjects on the protocol specified method(s) for avoiding pregnancy in case the subject chooses to engage in heterosexual intercourse.

Protocol specified contraceptive methods are as follows: (1) a combination of one hormonal method and one barrier method; (2) two barrier methods where one method is the male condom; or (3) use of an intrauterine device (IUD) or tubal sterilization; see [Appendix Table 1](#) below. Acceptable hormonal methods include injectable progesterone, progesterone implants, combination oral contraceptives, transdermal contraceptive patch, and vaginal ring. Acceptable barrier methods include diaphragm with spermicide, cervical cap with spermicide, and the male condom. Female subjects must use either a hormonal method or a barrier method if the partner has a vasectomy. If a subject has undergone tubal sterilization or has had a Copper T 380A IUD or LNG 20 IUD inserted, no other contraception is needed.

If tubal sterilization is via the Essure procedure, verification of tubal blockage by hysterosalpingogram (HSP) must be performed approximately 3 months after microinsertion. Prior to verification, Essure is not considered a reliable form of contraception and the contraception methods described below must be used. Female subjects who utilize hormonal contraceptives as one of their birth control methods must have used the same method for at least 3 months before study dosing.

Female subjects of childbearing potential must have a negative serum pregnancy test at screening and a negative urine pregnancy test at baseline (Day 1) prior to receiving the first dose of IDELA. Lactating females must discontinue nursing before IMP administration.

Appendix Table 1. Protocol Specified Contraceptive Methods

Methods to Use by Themselves	Combination Methods	
	Hormone Methods (choose one and use with a barrier method)	Barrier Methods (use both OR choose one and use with a hormone method)
Intrauterine Devices (IUDs) <ul style="list-style-type: none"> • Copper T 380A IUD • LNG 20 IUD Tubal Sterilization	Estrogen and Progesterone <ul style="list-style-type: none"> • Oral contraceptives • Transdermal patch • Vaginal ring Progesterone <ul style="list-style-type: none"> • Injection • Implant 	<ul style="list-style-type: none"> • Diaphragm with spermicide OR • Cervical cap with spermicide <ul style="list-style-type: none"> • Male condom (with spermicide)
Hysterectomy	Partner's vasectomy must be used with a hormone or barrier method.	

The investigator will counsel all subjects on the most effective method(s) for avoiding pregnancy during the study.

4) Additional Requirements for Male Subjects

Male subjects must agree to use condoms during heterosexual intercourse and avoid sperm donation while enrolled in the study and for at least 90 days after administration of the last dose of IDELA.

Use of condoms, with or without spermicide, has been proven to decrease the risk of transmission of HIV and other sexually transmitted diseases. The use of spermicide is not recommended if the subject or subject's partner is infected with HIV.

5) Procedures to be Followed in the Event of Pregnancy

Female subjects will be instructed to notify the investigator if they become pregnant at any time during the study or within 30 days of last dose of IDELA. Subjects who become pregnant or who suspect that they are pregnant during the study must report the information to the investigator and discontinue IDELA immediately. Male subjects whose partner has become pregnant or suspects she is pregnant during the study or within 90 days of last dose of IDELA must report the information to the investigator immediately.

Instructions for reporting pregnancy, partner pregnancy, and pregnancy outcome are outlined in Section 7.5.2.1.