CLINICAL STUDY PROTOCOL

Study Title:	An Open Label, Roll Over Study to Provide Idelalisib to Subjects Previously Treated with the Investigational PI3Kδ Inhibitor, GS-9820
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404
IND Number: **EudraCT Number:** **Clinical Trials.gov Identifier:**	N/A 2015-005766-39
Indication:	Lymphoid Malignancies
Protocol ID:	GS-US-313-2120
Gilead Study Director or Clinical Program Manager:	Name: PPD Telephone: PPD Fax: PPD
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Protocol Version/Date:	Original: 05 January 2016

CONFIDENTIALITY STATEMENT

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PROTOCOL SYNOPSIS

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Study Title:	An Open Label, Roll Over Study to Provide Idelalisib to Subjects Previously Treated with the Investigational PI3Kδ Inhibitor, GS-9820
IND Number:	Not Applicable
EudraCT Number:	2015-005766-39
Clinical Trials.gov Identifier:	
Study Centers Planned:	2 centers in the Netherlands
Objectives:	The primary objective of this study is as follows: • To provide open-label idelalisib to subjects receiving GS-9820 in Study GS-US-315-0102 at the time of study closure who have had objective evidence of clinical benefit defined as at least stable disease on imaging assessed by an independent review committee (IRC) and no toxicities prior to enrollment in this study that would preclude initiating therapy with idelalisib. Idelalisib and GS-9820 are both in the class of agents that inhibit PI3Kδ and as such this exchange of class for class agent is warranted and acceptable.
Study Design:	This study is an open-label, rollover study to provide idelalisib to subjects receiving GS-9820 in Study GS-US-315-0102 at the time of study closure.
Number of Subjects Planned:	Approximately 6 subjects
Target Population:	Subjects receiving GS-9820 in Study GS-US-315-0102 at the time of study closure who have objective evidence of clinical benefit defined as at least stable disease on imaging assessed by the IRC at final response assessment prior to enrollment in this study.
Duration of Treatment:	Subjects will be treated until progressive disease or intolerable toxicity.

Diagnosis and Main Eligibility Criteria:

Inclusion Criteria

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

1) Receiving GS-9820 in Study GS-US-315-0102 with objective evidence of clinical benefit defined as at least stable disease on imaging assessed by the IRC at the time of Study GS-US-315-0102 closure
2) For female subjects of childbearing potential, willingness to use a protocol recommended method of contraception during heterosexual intercourse from the signing of informed consent throughout the study treatment period and up to 30 days from the last dose of idelalisib (see Appendix 2)
3) For male subjects of reproductive potential having intercourse with females of childbearing potential, willing to use a protocol recommended method of contraception during heterosexual intercourse and to refrain from sperm donation throughout the study treatment period and for 90 days following discontinuation of idelalisib (see Appendix 2)
4) Willingness to comply with scheduled visits, drug administration plan, imaging studies, laboratory tests, other study procedures, and study restrictions. ***Note: Psychological, social, familial, or geographical factors that might preclude adequate study participation should be considered***.
5) Evidence of a personally signed informed consent indicating that the subject is aware of the neoplastic nature of their disease and has been informed of the procedures to be followed, the experimental nature of the therapy, alternatives, potential benefits, possible side effects, potential risks and discomforts, and other pertinent aspects of study participation.

Exclusion Criteria

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

1) Known hypersensitivity or intolerance to any of the active substances or excipients in the formulation of idelalisib.
2) Toxicities that would preclude initiating therapy with idelalisib prior to enrollment (eg, history of drug-induced pneumonitis, ongoing inflammatory bowel disease)
3) Concurrent participation in another therapeutic clinical trial.
4) Pregnant or breastfeeding

Study Procedures/ Frequency:	All subjects will receive idelalisib 150 mg taken orally, twice per day (BID) continuously. Subjects will undergo disease assessments and receive medical care per institutional standards of care.
Test Product, Dose, and Mode of Administration:	Idelalisib: 150 mg taken orally BID starting on Day 1 and administered continuously thereafter.
Reference Therapy, Dose, and Mode of Administration:	None
Criteria for Evaluation:	
Safety:	Overall safety profile characterized by the type, frequency, severity, timing of onset, duration, and relationship to study therapy of ≥ Grade 3 adverse events (AEs), serious adverse events (SAEs), and deaths.
Efficacy:	Investigator response assessments
Statistical Methods:	Safety will be assessed by incidence of ≥ Grade 3 AEs, SAEs, and deaths. Efficacy will be evaluated by investigator response assessments. Both safety and efficacy will be assessed using data collected from subjects who received at least 1 dose of idelalisib. All analyses will be limited to descriptive summaries and listings.
Sample Size:	Up to 6 subjects

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
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AUC	area under the concentration versus time curve
β-HCG	beta human chorionic gonadotropin
BID	bis in die (twice daily)
CFR	Code of Federal Regulations
CLL	chronic lymphocytic leukemia
CRO	contract research organization
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DSPH	Drug Safety and Public Health
eCRF	electronic case report form
EOS	end of study
EU	European Union
FDA	Food and Drug Administration
FSH	follicle stimulating hormone
G-CSF	granulocyte colony-stimulating factor
GCP	good clinical practice
GM-CSF	granulocyte-macrophage colony-stimulating factors
HLT	High-Level Term
HMG-CoA	3-hydroxy-3-methyl-glutaryl-Coenzyme A
IB	investigator's brochure
ICH	International Conference on Harmonisation
iNHL	indolent non-Hodgkin lymphoma
IEC	independent ethics committee
IUD	intrauterine device
MCL	mantle cell lymphoma
NHL	non-Hodgkin lymphoma
PI3K	phosphatidylinositol 3-kinase
PDE5	phosphodiesterase-5
SAE	serious adverse event
SOC	system organ class
SOP	standard operating procedure
SADR	serious adverse drug reaction
SUSAR	suspected unexpected serious adverse reactions
ULN	upper limit of normal

1. INTRODUCTION

1.1. Background

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

The goal of therapy for these diseases is to induce tumor regression and delay tumor progression in order to control disease-related complications and potentially extend life. Patients who require treatment are commonly given chemotherapeutic and/or immunotherapeutic agents {Hoppe et al 2008}, {Jost 2007} {Eichhorst et al 2010}, {Friedberg 2011}, {Gribben et al 2011}, {Zelenetz et al 2011}. Among patients with iNHL, CLL, and MCL, front line combination therapies can be effective in providing durable remissions {Lenz et al 2005}, {Santoro et al 1987}, {Schulz et al 2007}, {Hallek et al 2010}, {Recher et al 2011}. In DLBCL and HL, such front-line regimens can be curative in the majority of patients {Santoro et al 1987}, {Kuruvilla 2009}, {Recher et al 2011}. However, most treated patients with iNHL, CLL, and MCL will eventually experience disease relapse. Some patients with DLBCL or HL will experience recurrent disease even with initial induction therapy and later salvage therapy. For any of these cancers, further sequential therapies are given in an attempt to control disease manifestations. Despite use of agents with differing mechanisms of action, progressive resistance to treatment develops. Patients with progressive disease have a poor prognosis; median survival for these groups of patients is generally ≤2 years {Keating et al 2002}, {Goy et al 2009}, {Hess et al 2009}, {Moskowitz et al 2009}, {Di Bella et al 2010}, {Wierda et al 2010}, {Friedberg 2011}. Novel mechanisms of action are needed to offer additional treatment options for patients with lymphoid malignancies who are experiencing progressive lymphadenopathy or symptoms due to disease progression.

1.2. Idelalisib

Idelalisib (Zydelig®) was first approved in the United States on July 23, 2014 for the treatment of relapsed CLL, follicular lymphoma (FL), and small lymphocytic lymphoma (SLL), followed by approval in the EU on September 18, 2014 (centrally authorized). To date, Zydelig is currently approved in 37 countries. Refer to local labeling for the approved indication statements.

Idelalisib is a potent competitive inhibitor of the adenosine triphosphate (ATP) binding site of the phosphatidylinositol 3 kinase (PI3K) p110δ catalytic domain, which has been shown to be prominently expressed in cells of hematopoietic origin {Okkenhaug et al 2003}, {Vanhaesebroeck et al 2005}. The effects of p110δ on lymphocyte activation/function, cellular proliferation, and protection from apoptosis provide the rationale for targeting this isoform as a therapy for hematologic malignancies.

Further details on the preclinical pharmacology, toxicology, metabolism and pharmacokinetics (PK) of idelalisib can be found in the idelalisib Investigator's Brochure (IB).

1.3. Rationale for This Study

Study GS-US-315-0102 is being conducted to evaluate the safety and efficacy of GS-9820, a second generation PI3Kδ inhibitor in subjects with iNHL, DLBCL, MCL, HL, or CLL. GS-9820 was anticipated to offer similar efficacy to idelalisib in lymphoid malignancies while offering a more favorable safety profile than idelalisib. The development of GS-9820 has been discontinued by Gilead Sciences due to demonstration of a similar safety profile to idelalisib. Manufacture of the investigational agent GS-9820 has been discontinued, and will no longer be available to the ongoing subjects in Study GS-US-315-0102.

This rollover study provides access to idelalisib for eligible subjects receiving GS-9820 in Study GS-US-315-0102 at the time of study closure who have had objective evidence of clinical benefit defined as at least stable disease on imaging assessed by the independent review committee (IRC) and no toxicities prior to enrollment in this study that would preclude initiating therapy with idelalisib. Subjects will be allowed to receive treatment on this study until unacceptable toxicity, progressive disease, study withdrawal, or death occurs.

1.4. Benefit/Risk Assessment for the Study

Subjects enrolled in this study have a serious life-threatening disease, with limited treatment options. Without treatment their disease will progress and ultimately be fatal. Transitioning subjects from GS-9820 to idelalisib, a similar agent in class that has shown proof of clinical activity and has received regulatory approval for the treatment of relapsed CLL and iNHL {Gilead Sciences Limited 2015}, is rational as described in Section 1.3 of this protocol; therefore, subjects enrolled in this study may derive clinical benefit defined as an improvement in disease control such as response to study treatment. The risks that may accompany study treatment are related to the identified and potential toxicities of treatment with idelalisib and are described in Section 5 of this protocol and in the ICF. The management of these toxicities is described in Table 5-2. Taken together, there is a positive benefit/risk for initiating study treatment with idelalisib in subjects previously treated with GS-9820.

1.5. Compliance

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

2. OBJECTIVES

The primary objective of this study is:

- To provide idelalisib, a marketed PI3Kδ inhibitor, in lieu of GS-9820, an investigational second generation PI3Kδ inhibitor, to subjects receiving GS-9820 in Study GS-US-315-0102 at the time of study closure who have had objective evidence of clinical benefit defined as at least stable disease on imaging assessed by the IRC and no toxicities prior to enrollment in this study that would preclude initiating therapy with idelalisib. Idelalisib and GS-9820 are both in the class of agents that inhibit PI3Kδ and as such this exchange of class for class agent is warranted and acceptable.

3. STUDY DESIGN

3.1. Endpoints

There is no primary endpoint of this study.

3.2. Study Design

This study is an open-label, rollover study to provide idelalisib to subjects receiving GS-9820 in Study GS-US-315-0102 at the time of study closure.

3.3. Study Treatments

All subjects will receive idelalisib 150 mg taken orally, twice per day (BID) continuously.

3.4. Duration of Treatment

Treatment will continue until unacceptable toxicity, disease progression, study discontinuation (outlined below), or death occurs.

3.5. Discontinuation Criteria

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

- The subject withdraws consent to participate in the study
- The subject permanently discontinues idelalisib treatment for any reason
- The subject experiences a toxicity that necessitates permanent discontinuation of idelalisib treatment
- The subject has progressive disease
- The subject does not comply with the requirements of the protocol (eg initiation of a non-protocol anti-tumor treatment)
- Gilead, a regulatory agency, or an independent ethics committee (IEC) discontinues the study

The reason for withdrawal will be recorded in the eCRF.

3.6. Source Data

Electronic data (ie, diagnostic machines that transcribe data directly to a database, or data entered directly into an Electronic Medical Record system) is considered source data, provided the data is not recorded directly on the CRF/eCRF, and provided there is a clear audit trail in the electronic record(s). No data will be recorded directly on the CRF/eCRF, and any data recorded directly on the CRF/eCRF will not be considered source data.

3.7. Biomarker Testing

There will be no biomarker testing in this study.

4. SUBJECT POPULATION

4.1. Number of Subjects and Subject Selection

Approximately 6 subjects receiving GS-9820 in Study GS-US-315-0102 at the time of study closure are anticipated.

4.2. Inclusion Criteria

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

1) Receiving GS-9820 in Study GS-US-315-0102 with objective evidence of clinical benefit defined as at least stable disease on imaging assessed by the IRC at the time of Study GS-US-315-0102 closure

2) For female subjects of childbearing potential, willingness to use a protocol recommended method of contraception during heterosexual intercourse from the signing of informed consent throughout the study treatment period and up to 30 days from the last dose of idelalisib (see Appendix 2)

3) For male subjects of reproductive potential having intercourse with females of childbearing potential, willing to use a protocol recommended method of contraception during heterosexual intercourse and to refrain from sperm donation throughout the study treatment period and for 90 days following discontinuation of idelalisib (see Appendix 2)

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

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

4.3. Exclusion Criteria

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

1) Known hypersensitivity or intolerance to any of the active substances or excipients in the formulation of idelalisib.

2) Toxicities that would preclude initiating therapy with idelalisib prior to enrollment (eg history of drug-induced pneumonitis, ongoing inflammatory bowel disease)

3) Concurrent participation in another therapeutic clinical trial.

4) Pregnant or breastfeeding.

5. INVESTIGATIONAL MEDICINAL PRODUCTS

5.1. Randomization, Blinding and Treatment Codes

The study is open-label and non-randomized.

5.2. Description and Handling of Study Treatments

5.2.1. Formulation

Idelalisib 150 mg tablets are pink, oval-shaped and debossed with ''GSI'' on one side and ''150'' on the other. The 100 mg tablets are orange, oval-shaped and debossed with ''GSI'' on one side and ''100'' on the other. All tablets are film-coated, and include the following inactive excipients: PPD

5.2.2. Packaging and Labeling

Idelalisib tablets, 150 mg or 100 mg, are packaged in white, high density polyethylene (HDPE) bottles. Each bottle contains 60 tablets and polyester packing material. Each bottle is enclosed with a white, continuous thread, child-resistant polypropylene screw cap with an induction-sealed and aluminum-faced liner.

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

5.2.3. Storage and Handling

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

To ensure the stability and proper identification, study drug should not be stored in a container other than the container in which they were supplied. Consideration should be given to handling, preparation, and disposal through measures that minimize drug contact with the body. Appropriate precautions should be followed to avoid direct eye contact or exposure when handling.

5.2.4. Dosage and Administration of Idelalisib

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

Idelalisib will be taken twice daily. Idelalisib should be taken at approximately the same times each day. Ideally, doses should be taken at approximately 12 hour intervals as instructed (eg, at 7 AM and at 7 PM). While it is realized that variations in dosing schedule may occur in the outpatient setting, the prescribed regimen should be followed as closely as possible.

5.2.5. Dispensing

The clinic staff (eg, pharmacist or other qualified person) will be responsible for dispensing idelalisib. It is planned that idelalisib will be dispensed at 4-week intervals through the first 16 weeks of treatment, at 8-weeks, and at 12-week intervals thereafter. Sufficient idelalisib will be provided for each study period at the beginning of the period. Tablets should be dispensed in the original bottles provided.

The clinic staff (eg, pharmacist or other qualified person) will write the subject number on each bottle that is dispensed. Immediately before dispensing, the clinic staff will write the bottle number for each dispensed bottle in the idelalisib administration record corresponding to the subject number.

5.2.6. Premedication

No specific pre-medications or supporting medications are required in conjunction with idelalisib administration.

5.2.7. Administration Instructions

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

Idelalisib may be taken with or without food. There are no known dietary restrictions related to idelalisib use.

5.2.8. Dosing Schedule

Idelalisib will be administered on a BID schedule. Idelalisib should be taken at approximately the same times each day.

5.2.9. Dose Levels

Idelalisib dose levels are shown in Table 5-1. The starting dose level will be 150 mg BID. The lower dose level (Dose Level -1) is provided in case a subject requires a dose modification.

Table 5-1. Idelalisib Dose Levels

Dose Level	Dosing Regimen
Starting	150 mg BID
-1	100 mg BID

Abbreviation: BID=twice per day

Consistent with Table 5-2, if a subject experiences an AE that is suspected to be related to idelalisib during the course of study, idelalisib administration may be held, as necessary, until the AE resolves or stabilizes to an acceptable degree (as defined in Table 5-2). Thereafter, idelalisib may be reinitiated at either the Starting Dose Level or at Dose Level -1 consistent with the instructions in Section 5.2.10. A further attempt at reinitiation of therapy at Dose Level -1 may be attempted if the investigator feels that a second rechallenge at that dose level is medically appropriate. If the subject cannot tolerate idelalisib after 2 rechallenges at Dose Level -1 for the same AE, then the subject should be discontinued from idelalisib treatment.

After an idelalisib dose reduction, the dose need not be re-escalated, even if there is minimal or no toxicity with the reduced dose. However, if the subject tolerates Dose Level -1 of idelalisib for ≥ 4 weeks, then the dose may be increased back to Starting Dose Level, at the discretion of the investigator. Such a re-escalation may be particularly warranted if further evaluation reveals that the AE that led to the dose reduction was not related to idelalisib.

5.2.10. Idelalisib Dose Adjustments

The dose adjustment recommendations in Table 5-2 are based on the Common Terminology Criteria for Adverse Events (CTCAE) grade of specific toxicities. However, exceptions are expected for subjects who initiate study treatment with low blood counts. Clinical judgment should apply, and in cases of uncertainty, the study medical monitor should be contacted.

The dose modification instructions focus on the types of events most commonly attributed to idelalisib. The recommendations provided in Table 5-2 comprise only guidelines; variations from these recommendations may be warranted based on an investigator's individual judgment in considering potential risks, benefits, and therapeutic alternatives available to each subject.

Table 5-2. Dose Adjustment Guidelines {Gilead Sciences Inc 2014}

Pneumonitis	**Any symptomatic pneumonitis**		
	Discontinue Zydelig in subjects with any severity of symptomatic pneumonitis		
ALT/AST	**>3-5 x ULN**	**>5-20 x ULN**	**>20 x ULN**
	Maintain idelalisib dose. Monitor at least weekly until <1 x ULN.	Withhold idelalisib. Monitor at least weekly until ALT/AST are <1 x ULN, then may resume idelalisib at 100 mg BID.	Discontinue idelalisib permanently.
Bilirubin	**>1.5-3 x ULN**	**>3-10 x ULN**	**>10 x ULN**
	Maintain idelalisib dose. Monitor at least weekly until <1 x ULN.	Withhold idelalisib. Monitor at least weekly until bilirubin is <1 x ULN, then may resume idelalisib at 100 mg BID.	Discontinue idelalisib permanently.
Diarrhea	**Moderate diarrhea**	**Severe diarrhea or hospitalization**	**Life-threatening diarrhea**
	Maintain idelalisib dose. Monitor at least weekly until resolved.	Withhold idelalisib. Monitor at least weekly until resolved, then may resume idelalisib at 100 mg BID.	Discontinue idelalisib permanently.
Neutropenia	**ANC 1.0 to <1.5 Gi/L**	**ANC 0.5 to <1.0 Gi/L**	**ANC <0.5 Gi/L**
	Maintain idelalisib dose.	Maintain idelalisib dose. Monitor ANC at least weekly.	Interrupt idelalisib. Monitor ANC at least weekly until ANC ≥0.5 Gi/L, then may resume idelalisib at 100 mg BID.
Thrombocytopenia	**Platelets 50 to <75 Gi/L**	**Platelets 25 to <50 Gi/L**	**Platelets <25 Gi/L**
	Maintain idelalisib dose.	Maintain idelalisib dose. Monitor platelet counts at least weekly.	Interrupt idelalisib. Monitor platelet count at least weekly. May resume idelalisib at 100 mg BID when platelets ≥25 Gi/L.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BID, twice daily; ULN, upper limit of normal

5.3. Prior and Concomitant Medications

If considered necessary for the subject's well-being, drugs for concomitant medical conditions or for symptom management may be given at the discretion of the investigator.

Any concomitant medications prescribed as a therapeutic intervention for or resulting in an AE or SAE during the course of the study and the reason for use should be recorded on the eCRFs.

5.3.1. Anticancer or Experimental Therapies Other than Investigational Treatments

Except for corticosteroids, no other anticancer therapies (including chemotherapy, radiation, antibody therapy, immunotherapy, or other experimental therapies) of any kind are permitted. Subjects are not allowed to participate concurrently in any other therapeutic clinical study.

5.3.2. Antibiotics

Except in a subject who has a contra-indication, investigators should consider initiation of antibiotic prophylaxis against pneumocystis infection (eg, with trimethoprim-sulfamethoxazole, dapsone, aerosolized pentamidine, or atovaquone) beginning prior to idelalisib administration. Investigator discretion and local practices or guidelines may be followed.

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

5.3.3. Antidiarrheals

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

5.3.4. Corticosteroids

Subjects may receive topical, inhaled, enteric, or systemic corticosteroids while on study.

5.3.5. Granulocyte Colony-Stimulating Factors and Erythropoietin

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

G-CSF (filgrastim, PEG-filgrastim, lenograstim) may be administered in response to Grade 4 neutropenia or neutropenic complications; (see Table 5-2).

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

5.3.6. Drugs that Alter CYP3A-Dependent Metabolism

Idelalisib is metabolized to its major metabolite PPD via aldehyde oxidase and cytochrome P450 3A (CYP3A). Idelalisib also undergoes minor metabolism by UDP glucoronosyltransferase 1-4 (UGT1A4). The AUC of idelalisib was increased 1.8 fold when

idelalisib was coadministered with a strong CYP3A inhibitor. Therefore, if subjects are taking concomitant strong CYP3A inhibitors, the subject should be monitored closely for signs of idelalisib toxicity and the dose modifications for adverse reactions should be followed in the event of toxicity (see Table 5-2).

Additionally, idelalisib exposures are approximately 75% lower when coadministered with rifampin, a highly potent inducer of CYP3A. Therefore, avoid coadministration of strong inducers of CYP3A (rifampin, carbamazepine, phenytoin, and St. John's wort) with idelalisib.

5.3.7. Drugs that undergo CYP3A-Dependent Metabolism

The major metabolite of idelalisib, PPD is a reversible and time dependent inhibitor of CYP3A; accordingly, coadministration of idelalisib with midazolam, a probe CYP3A substrate, resulted in a ~5-fold increase in midazolam systemic exposure (AUC). Coadministration of drugs that are narrow therapeutic index CYP3A substrates with idelalisib may result in an increase in their systemic exposures (eg, antiarrhythmics, calcium channel blockers, benzodiazepines, certain HMG-CoA reductase inhibitors, phosphodiesterase-5 [PDE5] inhibitors, warfarin). Avoid coadministration of drugs that are narrow therapeutic index CYP3A substrates (eg, alfentanil, cyclosporine, sirolimus, tacrolimus, cisapride, pimozide, fentanyl, quinidine, ergotamine, dihydroergotamine, astemizole, terfenadine) with idelalisib.

5.3.8. Immunization

Because of its actions to inhibit PI3Kδ-dependent B-cell function, high doses of idelalisib can impair primary or secondary responses to immunization in animals.

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

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

5.3.9. Ultraviolet Exposure

While nonclinical findings suggest the hypothetical potential for phototoxicity in humans, available clinical data do not reveal a photosafety concern. Although specific clinical correlates for these nonclinical data are not available, investigators and study subjects should be observant for the possibility that study participants may have exaggerated sunburn reactions (eg, burning, erythema, exudation, vesicles, blistering, edema) involving areas of skin exposed to ultraviolet light.

5.3.10. Surgery

There are no known effects of idelalisib on coagulation or wound healing. Pending receipt of additional information and considering the subject's current platelet counts, idelalisib may be continued in the peri-procedural period in subjects who require surgery or invasive procedures.

5.4. Accountability for Idelalisib

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

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

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

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

5.4.1. Overdose Precautions

In Phase 1 studies, an MTD for idelalisib was not reached when administering the drug continuously at dose levels of 350 mg/dose BID (700 mg per day) {Coutre et al 2011}, {Kahl et al 2011}. However, in this protocol, an overdose is defined as administration of more than the prescribed daily dose (ie, >300 mg in a single day).

The Gilead Sciences medical monitor should be contacted if an idelalisib overdose occurs. Cases of idelalisib overdose will result in specific reporting requirements.

5.4.2. Inadvertent Exposure and Spill Precautions

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

5.4.3. Investigational Medicinal Product Return or Disposal

Subjects will be instructed to return any unused idelalisib in the original container at post treatment study visits. Returned medication will be reconciled by the investigator in order to monitor the subject's compliance with the medication regimen. When possible, all idelalisib returned by the subject should be retained for review by the study site monitor prior to return to Gilead Sciences or destruction.

5.5. Discontinuation from Study

Subject study participation may be ended due to any of the follow reasons:

- Withdrawal of consent
- Objective evidence of disease progression.
- Unacceptable toxicity or unable to tolerate a second rechallenge for the same AE.
- Any subject who becomes pregnant or begins breastfeeding.
- Initiation of non-protocol specfied anticancer therapy.
- Noncompliance with idelalisib administration, study procedures, or study requirements.
- The investigator may discontinue idelalisib, if it is not in the subject's best interest to continue.
- Any subject who is lost to follow-up.
- Death
- Discontinuation of study by the Sponsor, a regulatory agency, or an EC

6. STUDY PROCEDURES

The study procedures to be conducted for each subject enrolled in the study are presented in tabular form in Table 6-1 and described in the text that follows.

The investigator must document any deviation from protocol procedures and notify the sponsor or contract research organization (CRO).

6.1. Subject Enrollment

6.1.1. Subject Recruitment

This study will enroll subjects receiving GS-9820 in Study GS-US-315-0102 at the time of study closure who have had objective evidence of clinical benefit defined as at least stable disease on imaging assessed by the IRC and no toxicities prior to enrollment in this study that would preclude initiating therapy with idelalisib. The study sponsor will post a description of the study on the ClinicalTrials.gov website.

6.1.2. Subject Compensation for Participation

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

6.1.3. Screening Visit

The investigator must inform each prospective subject of the nature of the study, explain the potential risks, and obtain written informed consent from the subject and/or a legal guardian prior to performing any study-related screening procedures.

From the time of obtaining informed consent through the first administration of investigational medicinal product, record all serious adverse events (SAEs), as well as any adverse events related to protocol-mandated procedures on the adverse events case report form (CRF/eCRF). All other untoward medical occurrences observed during the screening period, including exacerbation or changes in medical history are to be captured on the medical history CRF/eCRF. See Section 7 Adverse Events and Toxicity Management for additional details.

6.2. Treatment 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 all grade AEs on the AE case report form (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 Adverse Events and Toxicity Management (Section 7) for additional details.

While on study, the subject will return at regular intervals for the following procedures:

- Evaluation of disease status per standard of care
- Laboratory lab tests (ALT/AST/total bilirubin)
- Recording of all grade AEs and all SAEs
- Return of used drug supplies and dispensing of new idelalisib supply

The specific study procedures to be conducted for each subject enrolled in the study are presented in Table 7-1 and are described in the sections that follow.

6.2.1. 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. If no change in disease status is identified and the subject is dispensed additional idelalisib, the most recent prior response documented for the study will be recorded.

6.3. End of Study

Subjects will be withdrawn from this study if they develop progressive disease, unacceptable toxicity related to idelalisib, withdraw consent, are noncompliant, or are lost to follow up or die. In this event, the following procedures should be performed:

- Return of used and unused drug supply
- Recording of all Grade AEs and all SAEs
- Investigator Response Assessment
- Recording of the reason for withdrawal
- Deaths occurring within 30 days following the last dose of idelalisib, even if occurring after the End of Study Visit, will be captured.

Table 6-1. Schedule of Study Procedures

Period	Screen	Treatment							
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8+**	
Week	**-4**	**0**	**4**	**8**	**12**	**16**	**24**		
Study Day	**Within -28 days**	**1**	**28**	**52**	**84**	**112**	**168**	**Q12 weeks**	**End of study**
Visit Window			**±2**	**±2**	**±2**	**±2**	**±2**	**±7**	
Informed consent	X								
Serum β-HCG[a]	X								
ALT/AST/total bilirubin	X	X	X	X	X	X	X	X	X
Urine pregnancy test[a]		X	X	X	X	X	X	X	X
Assess adverse events and SAEs		X	X	X	X	X	X	X	X
Record concomitant medications[b]		X	X	X	X	X	X	X	X
Idelalisib dispensing/accounting		X	X	X	X	X	X	X	X
Investigator response assessment[c]	X		X	X	X	X	X	X	X

a For women of child bearing potential; Serum β-HCG to be collected to be collected at screening, urine pregnancy test to be collected at visits from first dose of idelalisib to EOS
b Concomitant medications only collected if it is related to an AE
c Record investigator response assessment if obtained per standard of care
Abbreviations: β-HCG=beta human chorionic gonadotropin, ALT=alanine aminotransferase, AST=aspartate aminotransferase

7. ADVERSE EVENTS AND TOXICITY MANAGEMENT

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

7.1.1. Adverse Events

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

An AE does not include the following:

- Lymphocytosis
- Laboratory abnormalities not requiring clinical intervention or further investigation. Such abnormalities will be captured as part of overall laboratory monitoring.
- 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
- 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) that require medical or surgical intervention or lead to idelalisib interruption, modification, or discontinuation must be recorded as an AE, as well as an SAE, if applicable. In addition, laboratory or other abnormal assessments (eg, electrocardiogram, x-rays, vital signs) that are associated with signs and/or symptoms must be recorded as an AE or SAE if they meet the definition of an AE or SAE as described in Sections 7.1.1 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 sub-investigator 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 Idelalisib and Procedures

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

- **No**: Evidence exists that the adverse event has an etiology other than idelalisib. 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 using the CTCAE, Version 4.03 and available at: http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

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

Table 7-1. Grading of Adverse Event Severity

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

The distinction between the seriousness and the severity of an adverse event should be noted. Severe is a measure of intensity; thus, a severe reaction is not necessarily a serious reaction. For example, a headache may be severe in intensity, but would not be classified as serious unless it met one of the criteria for serious events listed in Section 7.1.2.

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

All SAEs, regardless of cause or relationship, that occur after the subject first consents to participate in the study (ie, signing the informed consent) and throughout the duration of the study, including the protocol-required post treatment follow-up period, must be reported to the

eCRF database and Gilead Drug Safety and Public Health (DSPH) or designee 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 30 days after last administration of idelalisib must be reported to the 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 idelalisib, regardless of causality, should also be reported.

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

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

All AEs and SAEs will be recorded in the eCRF database within the timelines outlined in the eCRF completion guidelines.

7.3.1. Serious Adverse Event (eSAE) Reporting Process

Site personnel record the SAE on the paper serious adverse event reporting form and submit via fax to Gilead DSPH within 24 hours.

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

For fatal or life-threatening events, copies of hospital case reports, autopsy reports, and other documents are also to be submitted by e-mail or fax when requested and applicable. Transmission of such documents should occur without personal subject identification, maintaining the traceability of a document to the subject identifiers.

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

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

7.4. Gilead Reporting Requirements

Depending on relevant local legislation or regulations, including the applicable US FDA Code of Federal Regulations, the EU Clinical Trials Directive (2001/20/EC) and relevant updates, and other country-specific legislation or regulations, Gilead may be required to expedite to

worldwide regulatory agencies reports of SAEs, serious adverse drug reactions (SADRs), or suspected unexpected serious adverse reactions (SUSARs). In accordance with the EU Clinical Trials Directive (2001/20/EC), Gilead or a specified designee will notify worldwide regulatory agencies and the relevant IEC in concerned Member States of applicable SUSARs as outlined in current regulations.

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

All investigators will receive a safety letter notifying them of relevant SUSAR reports associated with idelalisib. The investigator should notify the 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 and Other Anticipated Medical Events in the Study Population

Given the endpoints of the study and in order to maintain the integrity of the study, the following events that are assessed as unrelated to idelalisib will not be considered SAEs:

- Progression of lymphoid malignancy
- Death related to progression of lymphoid malignancy
- Disease progression and death from disease progression should be reported as SAEs by the investigator only if it is assessed that the idelalisib caused or contributed to the disease progression (ie, by a means other than lack of effect). Unrelated disease progression should be captured on the eCRF.

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

7.4.2. Toxicity Management

See Table 5-2 for more information related to recommended dose modifications associated with toxicities. Please refer to the current idelalisib IB for information related to toxicity management.

7.5. Special Situations Reports

7.5.1. Definitions of Special Situations

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

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

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

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

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

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

7.5.2. Instructions for Reporting Special Situations

7.5.2.1. Instructions for Reporting Pregnancies

The investigator should report pregnancies in female study subjects that are identified after initiation of study medication and throughout the study to the Gilead DSPH using the pregnancy report form within 24 hours of becoming aware of the pregnancy.

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 Gilead DSPH.

The subject should receive appropriate monitoring and care until the conclusion of the pregnancy. The outcome should be reported to Gilead DSPH using the pregnancy outcome report form. If the end of the pregnancy occurs after the study has been completed, the outcome should be reported directly to Gilead DSPH. Gilead DSPH contact information is as follows: Email: Safety_FC@gilead.com and Fax: +1 (650) 522-5477.

Pregnancies of female partners of male study subjects exposed to idelalisib must also be reported and relevant information should be submitted to Gilead DSPH using the pregnancy and pregnancy outcome forms within 24 hours. Monitoring of the subject should continue until the conclusion of the pregnancy. If the end of the pregnancy occurs after the study has been completed, the outcome should be reported directly to Gilead DSPH, fax number +1 650 522-5477 or email Safety_FC@gilead.com.

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

7.5.2.2. Reporting Other Special Situations

All other special situation reports (excluding pregnancy) must be reported on the special situations report form and forwarded to Gilead DSPH within 24 hours of the investigator becoming aware of the situation. These reports must consist of situations that involve idelalisib, but do not apply to concomitant medications. Except for situations that result in AEs, special situations involving concomitant medication will not be reported. Any inappropriate use of concomitant medications prohibited by this protocol should not be reported as "misuse," but may be more appropriately documented as a protocol deviation.

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

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

8. STATISTICAL CONSIDERATIONS

8.1. Analysis Objectives

As noted in Section 2, the primary objective is to provide idelalisib to subjects receiving GS-9820 in Study GS-US-315-0102 at the time of study closure who have had objective evidence of clinical benefit defined as at least stable disease on imaging assessed by the IRC and no toxicities prior to enrollment in this study that would preclude initiating therapy with idelalisib.

8.2. Safety Endpoints

Safety will be assessed with endpoints including incidence of ≥ Grade 3 AEs, SAEs, and deaths.

8.3. Analysis Sets

Both safety and efficacy will be assessed using data collected from subjects who received at least 1 dose of idelalisib.

8.4. Analysis Methods

All the analyses will be limited to descriptive summaries and listings. Categorical variables will be summarized with the number and percentage of subjects in each category. Continuous variables will be summarized by presenting n, mean, standard deviation, median, Q1, Q3, minimum and maximum.

8.5. Adverse Events

Clinical and laboratory adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). System Organ Class (SOC), High-Level Group Term (HLGT), High-Level Term (HLT), Preferred Term (PT), and Lower-Level Term (LLT) will be attached to the clinical database.

9. RESPONSIBILITIES

9.1. Investigator Responsibilities

9.1.1. Good Clinical Practice

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

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

The investigator and all applicable sub-investigators 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 sub-investigator's) participation in the study. The investigator and sub-investigator 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. 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 IEC. The investigator will not begin any study subject activities until approval from the 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 IEC any modifications made to the protocol or any accompanying material to be provided to the subject after initial 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 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 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. NOTE: The investigator must keep a screening log showing codes, names, and addresses for all subjects screened and for all subjects enrolled in the trial. Subject data will be processed in accordance with all applicable regulations.

The investigator agrees that all information received from Gilead, including but not limited to the investigator brochure, this protocol, CRF/eCRF, idelalisib, 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, 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);
  - — Birth dates will be collected as per local regulatory requirements, as needed
- 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 idelalisib, including dates of dispensing and return;
- Record of all adverse events and other safety parameters (start and end date, and including causality and severity);
- Concomitant medication (including start and end date, dose if relevant; dose changes);
- Date of study completion and reason for early discontinuation, if it occurs.

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

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

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

9.1.6. Case Report Forms

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

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

9.1.7. Drug Accountability and Return

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

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

The study monitor will review idelalisib 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 appropriately qualified personnel from Gilead Sciences or its representatives, to 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 IEC in accordance with local requirements and receive documented IEC approval before modifications can be implemented.

9.2.2. Communications with Regulatory Authorities

Gilead Sciences, working either directly or through designees, will assume responsibility for regulatory interactions with relevant regulatory authorities. Gilead Sciences will maintain an IND for idelalisib in support of the study in the United States and will maintain similar regulatory applications with other regulatory authorities, as required for conduct of the study. In fulfilling this responsibility, Gilead Sciences (or a designee) will collect, assemble, and communicate all required regulatory documents (eg, Form FDA 1572, investigator financial disclosure forms, protocol and protocol amendments, investigator brochures, informed consent documents, annual reports) as required by regulation. Gilead Sciences (or a designee) will also assume responsibility for adverse event reporting to regulatory authorities as described in Section 7.4.

9.2.3. 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. Payment Reporting

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

9.3.2. Access to Information for Monitoring

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

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

9.3.3. Access to Information for Auditing or Inspections

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

9.3.4. Study Discontinuation

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

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11. APPENDICES

Appendix 1. Investigator Signature Page

GILEAD SCIENCES, INC.
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STUDY ACKNOWLEDGEMENT

An Open Label, Roll Over Study to Provide Idelalisib to Subjects Previously Treated with the Investigational PI3Kδ Inhibitor, GS-9820

Original Protocol GS-US-313-2120, 05 January 2016

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

PPD

Lyndah Dreiling, MD

Gilead Medical Monitor

Jan 6, 2016

Date

INVESTIGATOR STATEMENT

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

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

Principal Investigator Name (Printed)

Signature

Date

Site Number

Appendix 2. Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Requirements

1) Definitions

a) Definition of Childbearing Potential

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

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

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

b) Definition of Male Fertility

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

2) Contraception Requirements for Female Subjects

a) Study Drug Effects on Pregnancy and Hormonal Contraception

Idelalisib has insufficient data to exclude the possibility of a clinically relevant interaction with hormonal contraception that results in reduced contraception efficacy. Therefore, contraceptive steroids are not recommended as a contraceptive method either solely or as a part of a contraceptive regimen. Data from clinical pharmacokinetic interaction studies of idelalisib have demonstrated no adverse effect on fertility or embryo-fetal development. However, there is no clinical data of idelalisib in pregnant women. Please refer to the latest version of the investigator's brochure for additional information.

b) Contraception Requirements for Female Subjects of Childbearing Potential

The inclusion of female subjects of childbearing potential requires using at least an acceptable effective contraceptive measure. They must also not rely on hormone-containing contraceptives as a form of birth control during the study. They must have a negative serum pregnancy test at Screening and a negative pregnancy test on the Baseline/Day 1 visit prior to randomization. At minimum, a pregnancy test will be performed at the end of relevant systemic exposure. In the

event of a delayed menstrual period (over one month between menstruations), a pregnancy test must be performed to rule out pregnancy. This is even true for women of childbearing potential with infrequent or irregular periods. They must also agree to one of the following from Screening until 30 days after the end of relevant systemic exposure.

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

Or

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

- Intrauterine device (IUD) with a failure rate of <1% per year
- Tubal sterilization
- Ensure micro-insert system (provided confirmation of success 3 months after procedure)
- Vasectomy in the male partner (provided that the partner is the sole sexual partner and had confirmation of surgical success 3 months after procedure)
- Barrier methods (one female barrier and one male barrier must be used in combination)
    - Female barriers: Diaphragm with spermicide or Cervical cap with spermicide
    - Male barriers: Male condom (with or without spermicide)

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

3) Contraception Requirements for Male Subjects

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

It is theoretically possible that a relevant systemic concentration may be achieved in a female partner from exposure of the male subject's seminal fluid. Therefore, male subjects with female partners of childbearing potential must use condoms during treatment until the end of relevant systemic exposure.

4) Unacceptable Birth Control Methods

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

5) Procedures to be Followed in the Event of Pregnancy

Subjects will be instructed to notify the investigator if they become pregnant at any time during the study, or if they become pregnant within 30 days of last idelalisib dose. Subjects who become pregnant or who suspect that they are pregnant during the study must report the information to the investigator and discontinue idelalisib immediately. Subjects whose partner has become pregnant or suspects she is pregnant during the study must report the information to the investigator. Instructions for reporting pregnancy, partner pregnancy, and pregnancy outcome are outlined in Section 7.5.2.1.