NON-INTERVENTIONAL POST-AUTHORIZATION SAFETY STUDY PROTOCOL

Study Title	Non-interventional study to assess the safety profile of idelalisib in patients with refractory follicular lymphoma (FL)
Protocol ID	GS-EU-313-4172
Protocol Version/Date:	Original V1.0: 30 Nov 2016 Version 1.1: 13 June 2017
EU PAS Register No	
Clinical Trials.gov Identifier	
Active Substance	idelalisib
Medicinal Product	Zydelig®
Product Reference	EU/1/14/938/001 and EU/1/14/938/002
Procedure Number	
Joint PASS	No
Research Question and Objectives	To assess the safety profile of idelalisib monotherapy in patients with refractory FL
Countries of Study	Europe and Australia
Gilead Study Director/ Author/Contact Person:	Name: Heribert Ramroth Telephone: +44 (0) 208 587 2560
Marketing Authorization Holder	Gilead Sciences International Ltd. Granta Park Cambridge CB21 6GT United Kingdom
Gilead Qualified Person Responsible for Pharmacovigilance:	Name: Dr. Anne-Ruth van Troostenburg de Bruyn Telephone: +44 (0) 1223 897500

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2. GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

ADR	Adverse drug reaction
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine transaminase
AST	Aspartate transaminase
CHMP	Committee for Medicinal Products for Human Use
CMV	Cytomegalovirus
CRF	Case Report Form
(e)CRF	(Electronic) case report form
DSPH	Drug Safety & Public Health
EAP	Early Access Program
EC	European Commission
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
EU	European Union
FL	Follicular Lymphoma
GGT	Gamma-glutamyl transpeptidase
GPP	Good Pharmacoepidemiology Practices (guidelines for)
GSI	Gilead Sciences, Inc.
GVP	Good Pharmacovigilance Practices (guidelines for)
HOI	Health Outcomes of Interest
HREC	Human Research Ethics Committees
IDL	idelalisib
IEC	Independent ethics committee
LDH	Lactate Dehydrogenase
MAR	Missing at random
MCAR	Missing completely at random
MST	Medical Search Term
OS	Overall Survival
PAS	Post-Authorization Study
PASS	Post-Authorization Safety Study
PJP	Pneumocystis jirovecii pneumonia
PML	Progressive Multifocal Leukoencephalopathy
QPPV	Qualified person responsible for pharmacovigilance
SADR	serious adverse drug reaction
SAE	serious adverse event
SmPC	Summary of Product Characteristics

SSR	Special situation report
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
TMF	Trial Master File
US, USA	United States, United States of America
Analytical dataset	The minimum set of data required to perform the statistical analyses leading to the results of the primary objective(s) of the study
Bias	Systemic error in the design, conduct or analysis of a study that results in a mistaken estimate
Cohort	Group of people characterized by a common experience (e.g., occurrence of a specified disease, exposure to a given medication)
Confounder	Extraneous factor that accounts for a difference in disease frequency between the exposure groups; associated factors serving as surrogates for these factors are also commonly called confounders
End of data collection	The date from which the analytical dataset is completely available
Exposure	A variable whose effect is of interest and is being studied
Odds	The ratio of the probability that an event will happen to the probability that it will not happen
Outcome	An event (such as disease occurrence or death) that is studied in relation to exposure
Rate	A measure of event occurrence, calculated by dividing the total number of events by the total amount of person-time within an exposure category
Risk	The proportion of a fixed cohort in which an outcome occurs during a specified period of time
Start of data collection	Date from which information on the first study subject is first recorded in the study dataset

3. RESPONSIBLE PARTIES

Table Responsible Parties

Responsibility	Name, Title, Qualifications, Affiliation, Address	Contact Information
Marketing Authorization Holder (MAH)	Gilead Sciences International Ltd. Cambridge, CB21 6GT United Kingdom	Phone: +44 (0) 1223 824613 Email: Celine.Cuegniet@gilead.com
Study Director	Heribert Ramroth Associate Director, Drug Safety and Public Health (DSPH) Epidemiology Gilead Sciences Europe Ltd. 2 Roundwood Avenue Stockley Park, Uxbridge, Middlesex UB11 1AF United Kingdom	Phone: +44 (0) 208 587 2560 Email: Heribert.Ramroth@gilead.com
EU QPPV	Anne-Ruth van Troostenburg de Bruyn Senior Director, DSPH Gilead Sciences International Ltd. Flowers Building, Granta Park Cambridge, Cambridgeshire CB21 6GT United Kingdom	Phone: +44 (0) 1223 824641 Email: Anna.vanTroostenburg@gilead.com
Clinical Operations	Christophe De Belder Clinical Operations Europe, Late Phase Gilead Sciences Europe Ltd. 2 Roundwood Avenue Stockley Park, Uxbridge, Middlesex UB11 1AF United Kingdom	Phone: +44 (0) 208 587 2552 Email: Christophe.DeBelder@gilead.com
Medical Monitor	Chuck Smith, MD, PhD Associate Director, DSPH Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404 USA	Phone: +1 (650) 522-5194 Email: Chuck.Smith@gilead.com

Responsibility	Name, Title, Qualifications, Affiliation, Address	Contact Information
Pharmacovigilance	DSPH Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404 USA	Phone: +1 800 445 3235 Fax: +1 (650) 522 5477 Email: safety_fc@gilead.com

4. PROTOCOL SYNOPSIS/ABSTRACT

Gilead Sciences International Ltd.
Flowers Building, Granta Park
Cambridge, CB21 6GT
United Kingdom

Study Title:	Non-interventional study to assess the safety profile of idelalisib in patients with refractory follicular lymphoma (FL)
Rationale and Background:	The Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion on the Pharmacovigilance Risk Assessment Committee (PRAC) recommendations following their review under Article 20 of the new safety findings for idelalisib. As a condition of the CHMP recommendations, additional safety information concerning the use of idelalisib to treat patients with refractory FL was requested.
Research Question and Objectives:	The objective of this study is to assess the overall safety profile of idelalisib monotherapy in patients with refractory FL. Serious Adverse Events (SAEs) will be collected and according rates will be estimated. Focus will be given to special health outcomes of interest (HOIs) such as transaminase elevation, severe diarrhoea/colitis, pneumonitis, neutropenia, rash, Stevens-Johnson syndrome – Toxic epidermal necrolysis (SJS-TEN) and serious infections (including opportunistic infections such as Pneumocystis jirovecii pneumonia [PJP] and cytomegalovirus [CMV]) as listed in the Zydelig Risk Management Plan (RMP) for the EU (Version 2.0).
Study Design:	A retrospective cohort study enrolling patients who were or are being treated with idelalisib for refractory FL according to the product information and treatment guidelines in routine clinical practice after the country specific approval date. Patient's data will be collected from the date of treatment initiation with idelalisib until 6 months after treatment discontinuation. The study design allows for both retrospective and prospective data to be collected. The start of data collection is defined as the entry of the first patient into the eCRF. In the data analysis, any data prior to the start of the study will be considered retrospective. Any data after that date will be considered prospective.

Population:

Inclusion criteria:

- Adult patients (age ≥ 18) who were or are being treated for refractory FL according to the product information for idelalisib and treatment guidelines in routine clinical practice.

Exclusion criteria:

- Patients included in clinical trials on idelalisib within the timeframe of this study.

Variables:

This is a non-interventional study. Only data available from routine medical practise will be collected within the study. All variables collected will be identical in nature and independent of the method of data collection (retrospective/prospective).

At treatment initiation (baseline):

Demographics

- Gender, year of birth

Baseline Disease assessment

- Organ involvement
- Lymph nodes (bulky disease)
- Bone marrow involvement

Medical history

- Follicular Lymphoma History
  - Date of diagnosis
  - FL Stage 1, 2 or 3a
  - Ann Arbor disease stage
- ECOG Performance Status , if available

Treatment history:

- Prior treatment regimens for FL:
  - Drug names for each regimen
  - Number of cycles or duration that regimen administered
  - Reasons for discontinuation

Idelalisib treatment (start date, dose at baseline)

Co-medications:

- Current medications
- Name of medications
- Indication
- Start date or estimated duration on medication

Routine laboratory parameters and results:

- Hemoglobin, erythrocyte count; total leukocytes, absolute neutrophil count, lymphocytes, monocytes, platelet count
- Serum chemistry including sodium, potassium, urea, uric acid, creatinine, lactate dehydrogenase (LDH)
- Liver function test: ALT, AST, ALP, GGT, total bilirubin, albumin, total protein

During observation period (visits based on local clinical practice, collected retrospectively and prospectively):

Collection of SAEs, SSRs, ADRs and SADRs (see protocol section 11.1). Focus will be given to special HOIs:

- any grade bowel perforation
- ≥ grade 3 diarrhoea and/or colitis
- any grade Progressive Multifocal Leukoencephalopathy (PML)
- any grade pneumonitis
- ≥ grade 3 rash by MST
- infection (specifically ≥ grade 3 infection, ≥ grade 3 febrile neutropenia, ≥ grade 3 neutropenia, any grade Cytomegalovirus [CMV] infection, and any grade Pneumocystis jirovecii pneumonia [PJP])
- Transaminase elevation
- Stevens-Johnson syndrome – Toxic epidermal necrolysis (SJS-TEN)

Idelalisib treatment

- Change in idelalisib dose (date), including interruption of dosing and reason
- Co-medications (changes)

	Routine laboratory parameters and results (when available): • Hemoglobin, erythrocyte count; total leukocytes, absolute neutrophil count, lymphocytes, monocytes, platelet count • Serum chemistry including sodium, potassium, urea, uric acid, creatinine, LDH • Liver function test: ALT, AST, ALP, GGT, total bilirubin, albumin, total protein Discontinuation (as defined by stopping treatment for more than 30 days) information • Date and reason for discontinuation • In case of death: — Date and cause of death
Data Sources:	The primary data source will be the patient's medical records. Review of electronic or paper medical records and entry of data into the study electronic Case Report Form (eCRF) will be performed by trained site personnel. All data will be anonymised and collected for those patients meeting all eligibility criteria. Each patient will be identified by a unique eCRF generated subject identifier. For the retrospective data, medical record abstraction will be performed by internal study team members of the site, who will be trained on the abstraction method to ensure records are acceptable for review and inclusion in the study. Retrospective data will be entered as close to the start of the study as possible. Prospective data will be entered as close as to the patient's last visit as possible.
Study Size:	This study aims to include patients who have been or are currently being treated with idelalisib according to the product information and treatment guidelines in routine clinical practice for the treatment of refractory FL, after marketing authorisation in the EU (September 2014) and Australia (January 2015). Assuming a median treatment period of 8 months, a retrospective timeframe of around 3 years and a prospective observation period of 2.5 years, it is expected that data of approximately 300 patient-years will be collected. Patients will be identified and enrolled in Europe (pending outcome of study feasibility: Australia, Austria, Belgium, France, Germany, Greece, Ireland, Italy, Portugal, Spain, Sweden, Switzerland and the United Kingdom) and Australia.

Data Analysis:	Continuous variables will be summarized by mean, standard deviation, median, lower quartile, upper quartile, minimum and maximum. Categorical variables will be summarized by number and percentage of patients in each categorical definition including 95% confidence intervals. Multivariate Poisson regression analyses will be used to estimate adjusted rates of ADRs and SADRs. Multivariate Cox Proportional Hazard analyses will be used to model time-to-event data, and time to ADRs and SADRs. Kaplan Meier will be used to illustrate time-to-event analyses. Stratified analyses will be used to account for potential behavioral changes of the site staff after the initiation of the study that might introduce bias between retrospective and prospective data collection.	
Milestones:	Start of data collection:	Q1 2018
	End of Data collection:	Q3 2020
	Interim report:	Q1 2019
	Progress report:	Q1 2019
	Final Study report:	Q4 2020

This study will be conducted in accordance with the guidelines of Good Pharmacoepidemiology Practices (GPPs) and Heads of Medicines Agencies (HMA) Good Pharmacovigilance Practices (GVP) including archiving of essential documents.

5. AMENDMENTS AND UPDATES

This is the updated protocol version 1.1.

Amendment or Update Number	Date	Section of Study Protocol	Amendment or Update	Reason
1.1	13 June 2017	The entire protocol was updated.	1.1	Incorporating PRAC feedback.

- **Protocol Modifications**

Protocol modifications may only be made by Gilead Sciences. Approval must be obtained before changes can be implemented.

6. MILESTONES

Milestone	Planned Date
Start of data collection	Q1 2018
End of data collection	Q3 2020
Study interim report on retrospective data analysis	Q1 2019
Study progress report	Q1 2019
Final report of study results	Q4 2020

7. RATIONALE AND BACKGROUND

7.1. Rationale for the Current Study

An increased risk of death and a higher incidence of serious adverse events (SAEs, predominantly infectious events) among subjects receiving idelalisib in combination with standard regimens compared to the control groups were observed in three Phase 3 studies evaluating treatment in first-line CLL and early-line iNHL patient populations by an independent data monitoring committee. The European Commission (EC) was notified of these findings and a review of these data was conducted by the Pharmacovigilance Risk Assessment Committee (PRAC) under Article 20 of Regulation (EC) No 726/2004. This review assessed the impact of these findings on the risk-benefit balance of Zydelig (idelalisib) in the approved EU indications. The PRAC review concluded that the risk-benefit profile for idelalisib remained positive for approved indications, with some updates to the indication and introduction of warnings and precautions in the Summary of Product Characteristics (SmPC) for risk minimization measures to minimize the risk of serious infections.

The risk-benefit balance of idelalisib monotherapy for the treatment of patients with follicular lymphoma (FL) that are refractory to 2 prior lines of treatment was considered to remain positive provided that the agreed risk minimization measures are applied. However, as no controlled study was conducted in this indication, the PRAC required Gilead to collect additional safety data in patients with refractory FL in order to better describe the safety profile of idelalisib in this population.

8. RESEARCH QUESTIONS AND OBJECTIVES

The primary objective of this study is:

To assess the overall safety profile of idelalisib monotherapy in patients with refractory FL.

Serious Adverse Events (SAEs) will be collected and according rates will be estimated. Focus will be given to special health outcomes of interest (HOIs) such as transaminase elevation, severe diarrhoea/colitis, pneumonitis, neutropenia, rash, Stevens-Johnson syndrome – Toxic epidermal necrolysis (SJS-TEN) and serious infections (including opportunistic infections such as Pneumocystis jirovecii pneumonia [PJP]) and cytomegalovirus [CMV] as listed in the Zydelig Risk Management Plan (RMP) for the EU (Version 2.0).

9. RESEARCH METHODS

9.1. Study Design

A retrospective cohort study enrolling patients who were or are being treated with idelalisib for refractory FL according to the product information and treatment guidelines in routine clinical practice after the country specific approval date.

Patient's data will be collected from the date of treatment initiation with idelalisib until 6 months after treatment discontinuation.

The study design allows for both retrospective and prospective data to be collected. The start of data collection is defined as the entry of the first patient into the eCRF. In the data analysis, any data prior to the start of the study will be considered retrospective. Any data after that date will be considered prospective.

9.2. Setting

The study will be conducted in the following countries (pending outcome of study feasibility): Australia, Austria, Belgium, France, Germany, Greece, Ireland, Italy, Portugal, Spain, Sweden, Switzerland and the United Kingdom.

Countries selected for this study include those in which an Early Access Program (EAP) for idelalisib in refractory FL patients has been running since the time of marketing authorisation (MA) for idelalisib. Additional countries without an active EAP were included based on the volume of idelalisib prescribing since the time of the MA. Sites within these countries will be selected based on whether they have been prescribing idelalisib for refractory FL patients in accordance with the approved product information for idelalisib. Final number of sites per country will depend on the available number of patients per site.

The study is expected to last 36 months from the start of data collection (Q1 2018) until submission of the CSR (Q4 2020).

Inclusion criteria:

- Adult patients (age ≥ 18) who were or are being treated for refractory FL according to the product information for idelalisib and treatment guidelines in routine clinical practice.

Exclusion criteria:

- Patients included in clinical trials on idelalisib within the timeframe of this study.

9.3. Variables

This is a non-interventional study. Only data available from routine medical care will be collected within the study. All variables collected will be identical in nature and independent of the method of data collection (retrospective/prospective).

At treatment initiation (baseline):

Demographics

- Gender, year of birth

Baseline Disease assessment

- Organ involvement
- Lymph nodes (bulky disease)
- Bone marrow involvement

Medical history

- Follicular Lymphoma History
  - Date of diagnosis
  - FL Stage 1, 2 or 3a
  - Ann Arbor disease stage
- ECOG Performance Status , if available

Treatment history:

- Prior treatment regimens for FL:
  - Drug names for each regimen
  - Number of cycles or duration that regimen administered
  - Reasons for discontinuation

Idelalisib treatment (start date, dose at baseline)

Co-medications:

- Current medications
- Name of medication
- Indication
- Start date or estimated duration on medication

Routine laboratory parameters and results (when available):

- Hemoglobin, erythrocyte count; total leukocytes, absolute neutrophil count, lymphocytes, monocytes, platelet count
- Serum chemistry including sodium, potassium, urea, uric acid, creatinine, lactate deydrogenase (LDH)
- Liver function test: ALT, AST, ALP, GGT, total bilirubin, albumin, total protein

During observation period (visits based on local clinical practice, collected retrospectively and prospectively):

Collection of SAEs, SSRs, ADRs and SADRs (see protocol section 11.1). Focus will be given to HOIs:

- any grade bowel perforation
- ≥ grade 3 diarrhoea and/or colitis
- any grade PML
- any grade pneumonitis
- ≥ grade 3 rash by MST
- infection (specifically ≥ grade 3 infection, ≥ grade 3 febrile neutropenia, ≥ grade 3 neutropenia, any grade CMV infection, and any grade PJP)
- Transaminase elevation
- SJS-TEN

Idelalisib treatment

- Change in idelalisib dose (date), including interruption of dosing and reason
- Co-medications (changes)

Routine laboratory parameters and results (when available):

- Hemoglobin, erythrocyte count; total leukocytes, absolute neutrophil count, lymphocytes, monocytes, platelet count
- Serum chemistry including sodium, potassium, urea, uric acid, creatinine, LDH
- Liver function test: ALT, AST, ALP, GGT, total bilirubin, albumin, total protein

Discontinuation (as defined by stopping treatment for more than 30 days) information

- Date and reason for discontinuation
- In case of death:
  - Date and cause of death

9.4. Data Sources

The primary data source will be the patient's medical records. Review of electronic or paper medical records, data identification, abstraction and data transcription will be performed by trained site personnel. This will include all safety information that is entered into the patient's medical records (i.e., events and special situations). Data capture is electronic and therefore data collection will occur at time of data entry by the site. The investigator will seek to ensure data entry for retrospective data is conducted as close as possible to the identification of an eligible subject at the start of the study and prospective data as close as possible at the time of each patient's visit.

All data will be anonymised and collected for those patients meeting all eligibility criteria. Each patient will be identified by a unique eCRF generated subject identifier. For the retrospective data, medical record abstraction will be performed by internal study team members of the site, who will be trained on the abstraction method to ensure records are acceptable for review and inclusion in the study.

9.5. Study Size

This study aims to include patients who have been or are currently being treated with idelalisib according to the product information and treatment guidelines for the treatment of refractory FL after marketing authorization in the EU (September 2014) and Australia (January 2015).

Prevalence data for iNHL in the EU are limited. HAEMACARE, a European cancer registry-based project on hematologic malignancies funded by the European Commission, provides European incidence rates but not prevalence data {Sant 2010}. Australian prevalence data could not be identified. The Decision Resources Group (http://www.decisionresourcesgateway.com/index.aspx) estimated a 10-year limited-duration prevalence for FL in 5 major EU countries (France, Germany, Italy, Spain, and United Kingdom) over the 2011-2021 forecast period based on cancer registry databases in the EU-5. The EU prevalence estimates for FL ranged from 1.4 (Spain) in 2011 to 3.1 (France) per 10,000 in 2015 (RMP, section 1.1.1.4.2).

Based on the pivotal studies 101-09, GS-US-313-0124 and GS-US-313-0125 the median treatment period is estimated to be 8 months, taking into account that studies GS-US-313-0124 and GS-US-313-0125 were terminated early. Thus, a retrospective timeframe of around 3 years and a prospective observation period of another 2.5 years allow data of approximately 300 patient-years to be collected.

A sample size of 300 patient-years is based on the chance to find a proportion of adverse events of 3.2% with a precision of 2%. The table below shows the relationship between various detectable single proportions of AEs and precision of the estimate.

Proportions found in studies 101-09, GS-US-313-0124 and GS-US-313-0125 were 1.4% (≥ Grade 3 diarrhea and/or colitis), 2.0% ((≥ Grade 3 febrile neutropenia), 6.1% ((≥ Grade 3 infection) and 8.1% ((≥ Grade 3 rash).

Proportion of AEs	3.2%	5.2%	7.6%
Precision	0.02	0.025	0.03

9.6. Data Management

An eCRF will be created in a commercial electronic data capture system to collect the data listed in the Variables (Section 9.3) section of the protocol. Personal identifying data such as names and social security numbers will not be collected. The study CRF will be archived in the study Trial Master File (TMF).

After training in the use of the electronic data capture tool and assignment of a unique log-in and password, site staff will enter relevant data into the eCRF. The data will be stored in secure network drives with access for authorized personnel only. Investigators will electronically sign the eCRFs to confirm responsibility for the data.

9.7. Data Analysis

Categorical variables will be summarized descriptively by number and percentage of patients in each categorical definition including 95% confidence intervals. Continuous variables will be summarized descriptively by mean, standard deviation, median, lower quartile, upper quartile, minimum and maximum.

Multivariate Poisson regression analyses will be used to estimate rates of ADRs and SADRs, adjusted for potential confounders (demographics, baseline disease assessment, medical history, treatment history, treatment changes; see section 9.3).

Multivariate Cox Proportional Hazard analyses will be used to model time-to-event data, and time to ADRs, SADRs and AESIs.

Kaplan Meier curves will be used to illustrate time-to-event analyses.

Special focus will be given to the differences in retrospective and prospective data collection. Although not by intention, data might be collected differently in retrospect compared to patient's data that will be collected prospectively. Retrospective patients will be recruited through systematic search of the sites' patient data management system, whereas prospective data will be collected from those patients prescribed idelalisib after the start of the study. Behavioral changes of the site staff after the initiation of the study might play a role in differential data collection. Thus, missing data for the retrospective data might be an issue. Stratified analyses will be conducted to account for this potential bias.

The extent of missing data in the study will be described and tabulated. Imputation methods will be used to account for missing values in the dataset for those variables used in multivariate modeling (demographics, baseline disease assessment, medical history, treatment history) and changes in idelalisib treatment following the current ENCePP guidelines (Methodological Standards in Pharmacoepidemiology: Section 5.3. Handling of missing data;

http://www.encepp.eu/standards_and_guidances/methodologicalGuide5_3.shtml {Rubin 1987}, {Moons 2006}, {Welch 2014}. Multiple imputation by chained equations (MICE) as sequential regression multiple imputation will be used handling of missing data {Azur 2011}. Using MICE, missing values are imputed based on the observed values for a given individual and the relationships within the data for other participants.

9.8. Quality Control

In order to ensure the quality and integrity of the study results, the electronic data capture system will contain automatic checks for data completeness and to identify inconsistent data and respective queries will be generated when necessary. Data and queries will be remotely monitored for consistency and completeness. The study monitor will only review on site the data for which patients have consented.

9.9. Limitations of the Research Methods

This study has the characteristic disadvantages of retrospective studies, for example selection bias, information bias and missing values.

In order to reduce selection bias, subject's eligibility criteria have been well defined. However, this is not a type of bias easy to prevent or measure. A selection bias introduced by the choice of sites that contribute patient data cannot totally be avoided. However, a selection of sites in multiple countries will help to reduce this kind of bias. Countries selected for this study include

those in which an EAP for idelalisib in refractory FL patients has been running since the time of MA for idelalisib. Additional countries without an active EAP were included based on the volume of idelalisib prescribing since the time of the MA. Sites within these countries will be selected based on whether they have been prescribing idelalisib for refractory FL patients in accordance with the approved product information for idelalisib. Thus, the final number of sites per country will depend on the available number of patients per site.

This study is a non-comparative non-interventional study, as a result confounding by indication (ie confounding indicated by study drug) should be a minimal issue in the absence of a comparator. Multivariate analyses will aim to minimize potential confounding by indication by including disease assessment and according treatment in the analyses.

In reference to protocol Section 10.3 (Informed Consent) Gilead will collect informed consents for patients being identified prospectively. Informed consent will not be collected for deceased patients or patients identified retrospectively, unless specifically required by an appropriate ethics committee or required by country National Data Protection Laws for a participating centre. Not using an informed consent form (ICF) for deceased patients or patients identified in retrospect allows incorporating data which otherwise would lead to a patient population that is strongly biased towards survivors and a potential risk of death could be underestimated.

Information bias can be prevented by using standard measurement instruments, like eCRF and appropriate training of personnel entering the data. Appropriate training of personnel entering data is also important to avoid missing values when checking the patients' medical records.

Stratified analyses will be taken into consideration to account for potential behavioral changes of the site staff after the initiation of the study that might introduce bias between retrospective and prospective data collection. These stratified analyses also account for the fact that less documentation might be available in data collected retrospectively.

Patterns of missing data will be determined using the methodology outlined by Chen {Chen 1999}. Here, it has to be determined if the "Missing At Random" (MAR) criterion is fulfilled. If the assumptions of MAR or missing completely at random (MCAR) are met then a multiple imputation approach will be used. If this assumption doesn't hold, a full case or regression approach may be used.

Multiple imputation by chained equations (MICE) also referred to as sequential regression multiple imputation, is a validated statistical method for the handling of missing data {Azur 2011}. Using MICE, missing values are imputed based on the observed values for a given individual and the relationships within the data for other participants.

9.10. Other Aspects

9.10.1. Joint Investigator/Gilead Responsibilities

9.10.1.1. Access to Information for Monitoring

The study monitor is responsible for routine review of the eCRFs at regular intervals throughout the study to verify adherence to the protocol and the completeness and consistency of the data being entered on the forms. The study monitor will only review on site the data for which patients have consented. Other data will be remotely monitored and source data will not be verified. The investigator agrees to cooperate with the study monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

9.10.1.2. Study Discontinuation

Gilead reserves the right to terminate the study at any time. Gilead will only terminate the study if there is sufficient cause following consultation with the PRAC. Investigator reserves the right to terminate the study at their site at any time. Should this be necessary, both parties will arrange discontinuation procedures and notify the appropriate regulatory agencies, HRECs, and IECs, in accordance with local legislation.

10. PROTECTION OF HUMAN SUBJECTS

10.1. Good Pharmacoepidemiology and Pharmacovigilance Practices

The study will be conducted in accordance with the guidelines of Good Pharmacoepidemiology Practices (GPPs), Heads of Medicines Agencies (HMA) Good Pharmacovigilance Practices (GVP) including archiving of essential documents.

10.2. Independent Ethics Committee (IEC) or Human Research Ethics Committee (HREC) Review

Gilead (or the investigator) will submit this protocol and any accompanying material to be provided to the subject (such as advertisements, subject information sheets, or descriptions of the study used to obtain informed consent) to an IEC or HREC. The investigator will not begin patient screening/data collection until approval from the IEC or HREC has been documented and provided as a letter to the investigator.

Any subsequent modifications made to the protocol or any accompanying material to be provided to the subject after initial IEC or HREC approval will also be submitted for IEC or HREC approval prior to use, with the exception of those necessary to reduce immediate risk to study subjects.

10.3. Informed Consent

Gilead will collect informed consents for patients being identified prospectively. Informed consent will not be collected for deceased patients or patients identified retrospectively, unless specifically required by an appropriate ethics committee or required by country National Data Protection Laws, for a participating centre.

All data used in this study will be anonymized and collected in an eCRF with a unique subject identifier for each patient by each participating centre. In case the IEC or HREC requires a written informed consent to be obtained the investigator will be responsible for obtaining written informed consent from each prospective patient participating in this study after adequate explanation of the aims, methods, and objectives, and alternatives of the study prior to study participation and before collection of data. The investigator must utilize the most current IEC or HREC approved consent form for documenting written informed consent. Each informed consent will be appropriately signed and dated by the subject or the subject's legally authorized representative and the person conducting the consent discussion, and also by an impartial witness if required by IEC or HREC or local requirements.

10.4. Confidentiality

The investigator and Gilead must assure that subjects' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. Only a unique identifier (as allowed by local law) and a unique study identification code should be recorded on any study-related document.

The investigator agrees that all information received from Gilead, including but not limited to this protocol, CRFs, 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.

11. MANAGEMENT AND REPORTING OF SAFETY INFORMATION

11.1. Investigator Reporting Requirements to Gilead

The following safety information is required to be collected and reported for this study from the time the subject is prescribed idelalisib until 6 months after completion of therapy or early discontinuation of idelalisib.

- Adverse Events (AEs) leading to dose modification, interruption or discontinuation
- All Serious Adverse Events (SAEs)
- Special Situation Reports (SSRs)
- Adverse Drug Reactions (ADRs)
- Serious Adverse Drug Reactions (SADRs)
- Pregnancy or partner-pregnancy

Timelines for reporting to Gilead are as follows:

- Within 3 calendar days of knowledge of all SAEs
- Within 30 calendar days of knowledge of any non-serious AEs, SSRs, Pregnancy or partner-pregnancy

Details of the methods for reporting AEs, ADRs, SAEs, SADRs or SSRs to Gilead DSPH will be described in the CRF completion guidelines. If reporting of events is by electronic submission via eCRF, this method must always be used unless the eCRF system is not functioning. If for any reason it is not possible to record death, AE, ADRs, SAE, SADRs and SSR information electronically, the details should be recorded on the appropriate paper reporting forms (e.g., the Non-Interventional Study AE/SAE Report Form or the Non-Interventional Study Special Situations Report Form) and submitted by fax or e-mail, within the timelines given above to Gilead DSPH:

E-mail: Safety_FC@gilead.com

Fax: +1 (650) 522-5477

As soon as it is possible to do so, any death, AE, ADR, SAE, SADR and SSR reported via paper must be transcribed into the eCRF database according to the instructions in the eCRF completion guidelines.

11.1.1. Instructions for Reporting Pregnancies

The following information is required to be collected and reported for this study if a patient or patient-partner becomes pregnant while taking idelalisib:

All pregnancies (including partner pregnancies) that occur from the time the subject is prescribed idelalisib until 6 months after completion of therapy or early discontinuation of idelalisib are to be reported to Gilead DSPH using the pregnancy report form. The pregnancy itself is not considered an AE nor is an induced elective abortion to terminate a pregnancy without medical reasons.

A non-elective premature termination of pregnancy (e.g. a spontaneous abortion, an induced therapeutic abortion due to complications or other medical reasons) must be reported within 3 calendar days as an SAE via fax or email. The underlying medical reason for this procedure should be recorded as the SAE term. A spontaneous abortion is always considered to be an SAE. Furthermore, any SAE occurring as an adverse pregnancy outcome post study must be reported to Gilead DSPH.

Timelines for reporting to Gilead are as follows:

- Within 30 calendar days of knowledge of the pregnancy
- Within 3 calendar days of knowledge of all pregnancy related serious adverse events (regardless of causality, e.g., a spontaneous abortion, hospitalization, etc.)

Pregnancy information should be reported on the pregnancy report form, and the outcome should be reported on pregnancy outcome report form. However, if the event qualifies as an SAE then an SAE form should be completed. If reporting of events is by electronic submission via eCRF, this method must always be used unless the eCRF system is not functioning. If for any reason it is not possible to record pregnancy or pregnancy outcome information electronically, the details should be recorded on the appropriate paper reporting form and submitted by fax or e-mail, within the timelines given above to Gilead DSPH:

E-mail: Safety_FC@gilead.com

Fax: +1 (650) 522-5477

As soon as it is possible to do so, any pregnancy or pregnancy outcome reported via paper must be transcribed into the eCRF database according to the instructions in the eCRF completion guidelines.

11.2. Gilead Reporting Requirements to Regulatory Authorities

Gilead is responsible for analysing reports of all safety information and reporting to regulatory agencies as determined by country-specific legislation or regulations.

Assessment of expectedness for all safety reports will be determined by Gilead using reference safety information specified in the product label.

11.3. Definitions

11.3.1. 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 unfavourable 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 lack of efficacy, overdose, drug abuse/misuse reports, or occupational exposure. Pre-existing 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.

This study will only collect AEs that lead to dose modification, interruption or discontinuation.

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 AE and should be reported.
- Situations where an untoward medical occurrence has not occurred (e.g., hospitalization for elective surgery, social and/or convenience admissions)
- Any medical condition or clinically significant laboratory abnormality with an onset date before the consent form is signed. These are considered to be pre-existing conditions and should be documented on the medical history CRF (if applicable).

11.3.2. 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 had been 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.

11.3.3. Special Situations Reports

Special situation reports include reports of pregnancy, medication error, abuse, misuse, overdose, lack of effect; off-label use, product complaints and occupational exposure.

For instructions on reporting pregnancy, see 11.1.1.

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).

Lack of effect is defined as the failure of the expected or intended pharmacologic action or therapeutic effect as described in the pharmacology and/or indications section of the current product label.

Off-label use is defined as the intentional use of licensed medicinal product by a Health Care Professional for a medical purpose not in accordance with the authorized product information with respect to indication, dose, route of administration, or patient population (e.g., the elderly).

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

Occupational exposure is defined as exposure to a medicinal product as a result of one’s professional or non-professional occupation.

11.3.4. Adverse Drug Reaction

An adverse drug reaction (ADR) is defined as an untoward medical occurrence (unintended or noxious responses) considered causally related to an investigational or approved medicinal product at any dose administered. Adverse reactions may arise from medication errors, uses outside what is foreseen in the protocol or prescribing information (off-label use), misuse and abuse of the product, overdose, or occupational exposure.

11.3.5. Serious Adverse Drug Reaction

A serious adverse drug reaction (SADR) is defined as any SAE that is considered causally related to the medicinal product at any dose administered.

11.4. Clinical Laboratory Abnormalities

Laboratory abnormalities without clinical significance are not recorded as safety events. However, laboratory abnormalities (e.g., clinical chemistry, hematology, and urinalysis) that require medical or surgical intervention or lead to drug interruption, modification, or discontinuation and considered to be causally associated with the medicinal product must be recorded as an AE, or an SAE, if applicable. In addition, laboratory or other abnormal assessments (e.g., electrocardiogram, x-rays, vital signs) that are associated with signs and/or symptoms must be recorded as an AE or SAE if they meet the definition of an AE or SAE as described in Section 11.3. If the laboratory abnormality is part of a syndrome, record the syndrome or diagnosis (e.g., anemia), not the laboratory result (i.e., decreased hemoglobin).

11.5. Assessment of Causality for Study Drugs

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

- **No**: Evidence exists that the AE has an etiology other than the drug. For SAEs, an alternative causality must be provided (e.g., pre-existing condition, underlying disease, intercurrent illness, concomitant medication).

- **Yes**: There is a reasonable possibility that the event may have been caused by the medicinal product.

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

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

12.1. Study Report and Publications

A study report will be prepared and provided to the applicable regulatory agencies. Gilead will ensure that the report meets the standards set out in the Guideline on Good Pharmacovigilance Practices (GVP) Module VIII. Note that an abbreviated report may be prepared in certain cases. The final study report will be submitted within 12 months of study completion.

Any study publication will be prepared and provided to the European Medicines Agency (EMA). In this case, Gilead Sciences will follow the standards set out in the STROBE Guidelines for Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) {von Elm 2008}.

13. REFERENCES

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Chen HY, Little R. A test of missing completely at random for generalised estimating equations with missing data. Biometrika 1999;86:13.

Moons KG, Donders RA, Stijnen T, Harrell FE, Jr. Using the outcome for imputation of missing predictor values was preferred. J Clin Epidemiol 2006;59 (10):1092-101.

Rubin DB. Multiple Imputation for Nonresponse in Surveys. New York, NY: John Wiley & Sons, Inc, 1987:

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14. ANNEXES

Number	Document Reference Number	Date	Title
1	Annex 1	13 June 2017	ENCePP Checklist for Study Protocols
2	Annex 2	13 June 2017	Investigator Signature Page

Annex 1. ENCePP Checklist for Study Protocols

Study title: Non-interventional study to assess the safety profile of idelalisib in patients with refractory follicular lymphoma (FL)

Study reference number: GS-EU-313-4172

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	6
1.1.2 End of data collection[2]	☒	☐	☐	6
1.1.3 Study progress report(s)	☒	☐	☐	6
1.1.4 Interim progress report(s)	☒	☐	☐	6
1.1.5 Registration in the EU PAS register	☒	☐	☐	6
1.1.6 Final report of study results.	☒	☐	☐	6

Comments:

Study will be registered in the EU PAS register. No timelines given in the protocol.

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:				
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	7
2.1.2 The objective(s) of the study?	☒	☐	☐	8
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	9
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	-
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	-

Comments:

Safety study without hypothesis testing.

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
[2] Date from which the analytical dataset is completely available.

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, new or alternative design)	☒	☐	☐	9.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.3
3.3 Does the protocol specify measures of occurrence? (e.g. incidence rate, absolute risk)	☒	☐	☐	9.7
3.4 Does the protocol specify measure(s) of association? (e.g. relative risk, odds ratio, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☐	☐	☒	-
3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☒	☐	☐	9, 11

Comments:

Only incidence rates (crude and adjusted) will be calculated. No comparisons will be made

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.1 Is the source population described?	☒	☐	☐	9.2
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	6
4.2.2 Age and sex?	☐	☒	☐	-
4.2.3 Country of origin?	☒	☐	☐	9.2
4.2.4 Disease/indication?	☒	☐	☐	9.2
4.2.5 Duration of follow-up?	☒	☐	☐	9.1
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	9.2

Comments:

Results will distinguish for age and sex. But the population will not be specifically defined for both characteristics.

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.1 Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	9.2

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☒	☐	☐	9.3
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☒	☐	☐	9.1
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☒	☐	

Comments:

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	8
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.3
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☒	☐	☐	9.9
6.4 Does the protocol describe specific endpoints relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease, disease management)	☐	☒	☐	-

Comments:

The safety analyses will have per definition an impact on disease management. However, this is not specifically discussed in the protocol.

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol describe how confounding will be addressed in the study?	☒	☐	☐	9.9
7.1.1. Does the protocol address confounding by indication if applicable?	☒	☐	☐	9.9
7.2 Does the protocol address:				
7.2.1. Selection biases (e.g. healthy user bias)	☒	☐	☐	9.9, 10
7.2.2. Information biases (e.g. misclassification of exposure and endpoints, time-related bias)	☒	☐	☐	9.9
7.3 Does the protocol address the validity of the study covariates?	☐	☒	☐	-

Comments:

Section 8: Effect modification	**Yes**	**No**	**N/A**	**Section Number**
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☒	☐	☐	9.9

Comments:

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	9
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9
9.1.3 Covariates?	☒	☐	☐	9
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	9
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9
9.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	9
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	9
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD)-10, Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	9
9.3.3 Covariates?	☒	☐	☐	9
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	-

Comments:

Only the patient's medical records will be used. No linkage between data sources.

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Is the choice of statistical techniques described?	☒	☐	☐	9.7
10.2 Are descriptive analyses included?	☒	☐	☐	9.7
10.3 Are stratified analyses included?	☒	☐	☐	9.9
10.4 Does the plan describe methods for adjusting for confounding?	☒	☐	☐	9
10.5 Does the plan describe methods for handling missing data?	☒	☐	☐	9.7
10.6 Is sample size and/or statistical power estimated?	☐	☒	☐	

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	9.6
11.2 Are methods of quality assurance described?	☒	☐	☐	9
11.3 Is there a system in place for independent review of study results?	☒	☐	☐	11, 12

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	9.9
12.1.2 Information bias?	☒	☐	☐	9.9
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☒	☐	☐	10.3
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	9.2, 9.5

Comments:

Section 13: Ethical issues	Yes	No	N/A	Section Number
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	10
13.2 Has any outcome of an ethical review procedure been addressed?	☒	☐	☐	10
13.3 Have data protection requirements been described?	☒	☐	☐	9, 10

Comments:

Section 14: Amendments and deviations	Yes	No	N/A	Section Number
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	5

Comments:

Section 15: Plans for communication of study results	Yes	No	N/A	Section Number
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	12
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12

Comments:

Name of the main author of the protocol: Heribert Ramroth

Date: 16 June 2017

Signature: _____

Annex 3. **Investigator Signature Page**

Gilead Sciences International Ltd.
Flowers Building, Granta Park
Cambridge, CB21 6GT
United Kingdom

NON-INTERVENTIONAL STUDY TO ASSESS THE SAFETY PROFILE OF IDELALISIB IN PATIENTS WITH REFRACTORY FOLLICULAR LYMPHOMA (FL)

V1.1 – 13 June 2017

This protocol has been approved by Gilead Sciences, Inc. The following signatures document this approval.

HERIBERT RAMROTH

Gilead Study Director (Printed)
Author

Signature

16 June 2017

Date

A R van Troostenburg de Bruyn

Gilead EU QPPV (Printed)

Signature

16 June 2017

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 study.

Principal Investigator Name (Printed)	Signature
Date	Site Number