NON-INTERVENTIONAL POST-AUTHORIZATION SAFETY STUDY PROTOCOL

Study Title:	A Cross-Sectional Post-Authorization Safety Study to Assess Healthcare Provider Awareness of Risks Associated with Zydelig® in the European Union
Protocol ID:	GS-EU-313-4226
Protocol Version/Date:	Original: 06 December 2016 Version 1.1: 19 April 2017
EU PAS Register No:	EUPAS16606
Active substance:	Idelalisib
Medicinal Product:	Zydelig®
Marketing Authorization Number:	EU 1/14/938/001 EU/1/14/938/002
Procedure number:	N/A
Joint PASS:	No
Research Question and Objectives:	The objective of this study is to determine the HCPs' level of knowledge about the infection risks associated with Zydelig treatment and the corresponding recommendations to minimize these risks.
Countries of study:	France, Germany, Italy, Spain, United Kingdom
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1. TABLE OF CONTENTS

1.1. LIST OF IN-TEXT TABLES

2. GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

ANC	Absolute neutrophil count
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CLL	Chronic lymphocytic leukemia
CMV	Cytomegalovirus
CRO	Contract Research Organization
DHPC	Direct Healthcare Professional Communication
DSPH	Drug Safety & Public Health
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EC	European Commission
EU	European Union
GPP	Good Pharmacoepidemiology Practices (guidelines for)
GVP	Good Pharmacovigilance Practices (guidelines for)
HCP	Healthcare Professional (Provider)
HMA	Heads of Medicines Agencies
IEC	Independent Ethics Committee
iNHL	Indolent Non-Hodgkin Lymphoma
PAS	Post-Authorization Study
PASS	Post-Authorization Safety Study
PJP	*Pneumocystis jirovecii* pneumonia
PRAC	Pharmacovigilance Risk Assessment Committee
REMS	Risk Evaluation and Mitigation Strategy
SmPC	Summary of Product Characteristics
US, USA	United States, United States of America

3. RESPONSIBLE PARTIES

Table Responsible Parties

Responsibility	Name, Title, Qualifications, Affiliation, Address	Contact Information
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Vendor (TBD)	(TBD)	(TBD)

4. PROTOCOL SYNOPSIS/ABSTRACT

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Study Title:	A Cross-Sectional Post-Authorization Safety Study to Assess Healthcare Provider Awareness of Risks Associated with Zydelig® in the European Union
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 Zydelig (idelalisib). The Summary of Product Characteristics (SmPC) was updated in March 2016 to reflect provisional precautionary measures. Following completion of the review, the SmPC was revised to amend the first line indication for patients with chronic lymphocytic leukemia (CLL). Additional safety information about serious infections were included, including risk minimization measures to prevent infection in all indications related to *Pneumocystis jirovecii* pneumonia (PJP) and cytomegalovirus infection (CMV). A Direct Healthcare Professional Communication (DHPC) was sent to healthcare providers (HCPs) in European countries where Zydelig was commercially available in August 2016. This survey will be conducted to measure knowledge of the key risks and recommended precautionary measures as added to the SPC and communicated in the DHPC.
Research Question and Objectives:	The objective of this study is to determine the HCPs' level of knowledge about the infection risks associated with Zydelig treatment and the corresponding recommendations to minimize these risks.

Study Design:	This non-interventional, cross sectional study consists of a survey of medical oncologists and hematologists in the European Union (EU). The survey will be conducted approximately 12 months after the distribution of DHPC in the largest 5 EU representative-countries. Oncologists and hematologists will be invited to participate on a volunteer/"opt-in" basis. Survey reminders will be sent during the survey recruitment period. Data from all respondents will be included in the analysis and final report. Qualitative pilot testing of the survey will be done in all countries where the survey is being performed. The survey final questions may be revised based on the results of the qualitative testing. Translation of the questionnaire and validation of the translation will be done prior to launching the survey in non-English speaking countries.
Population:	The study population will be comprised of hematologists and oncologists who potentially manage patients with CLL or follicular lymphoma. Inclusion Criteria: • Registered oncologists and hematologists • Registered medical doctors who are currently enrolled in an advanced training program leading to specialization in oncology and/or hematology Exclusion Criteria: • Oncologists or hematologists who are employed by Gilead Sciences or affiliates • Oncologists or hematologists who participated in the pre-testing of the survey
Variables:	HCP knowledge will be evaluated and expressed as proportions or scores. Demographic variables will include medical specialty, practice setting, and country.
Data Sources:	The data source for the survey will be eligible HCPs who volunteer and agree to participate. The survey will be developed in both an electronic and paper format.
Study Size:	A minimum of 150 completed surveys will be the target for the final analysis.

Data Analysis:	Responses to questions for all completed surveys will be analyzed using descriptive statistics. Continuous variables will be described by the mean, standard deviation, median and range. Categorical variables will be described by the number and proportion in each category. The amount of missing data for each variable will be reported. Data will be presented by summary tables and/or graphs. No formal hypothesis testing will be conducted. An 80% threshold for prescriber awareness is generally considered acceptable. The numbers of invitees and respondents will be recorded, and the response rates will be reported overall and by country.
Milestones:	Start of data collection: The survey will be conducted approximately 12 months after the distribution of the DHPC in each country (approximately end of Q3 2017). End of data collection: Approximately 10 weeks after initiation of the survey in each country. Interim reports: No interim report is planned. Final report of study results: Approximately 6 months after final survey data collected (end of Q4 2018).

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

5. AMENDMENTS AND UPDATES

This is the original protocol.

6. MILESTONES

Milestone	Planned Date
DHPC materials distributed	22 Aug 2016 to 01 Sep 2106
Regulatory/ethics submissions/notifications in first country (UK)	Submission: 01 Aug 2017 Anticipated Approval: 2 Oct 2017
Cognitive Pre-Testing in First Country	16 Oct 2017
Translations into other languages	23 Oct 2017
Remaining regulatory and ethics submissions/notifications to begin	6 Oct 2017
Survey Launch in First Country	16 Nov 2017
Start of data collection	The survey will be conducted approximately12 months after DHPC in each country (approximately end of Q3 2017).
End of data collection	Approximately 10 weeks after initiation of the survey in each country
Registration in the EU PAS register	Approximately beginning Q3 2017
Interim reports	No interim report is planned
Final report of study results	Approximately 6 months after final survey data collected (end of Q4 2018)

7. RATIONALE AND BACKGROUND

7.1. Rationale for the Current Study

During a routine review of ongoing study data, the Data Monitoring Committee saw an increased risk of death and a higher incidence of serious adverse events (SAEs, predominantly infectious events) in subjects receiving idelalisib versus placebo in drug combinations or in patient populations being studied in 3 Phase 3 trials of non-approved indications (specifically in combination with bendamustine and rituximab (BR) in front-line treatment for CLL and in combination with either BR or rituximab (R) alone as early-line treatment for indolent non-Hodgkin Lymphoma). Gilead notified the European Medicines Agency (EMA) 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 was conducted to assess the impact of the findings on the risk-benefit balance of Zydelig (idelalisib) in the approved European Union (EU) indications. The PRAC review concluded that the risk-benefit profile for idelalisib remained positive for approved indications, with the adoption of risk minimization measures to minimize the risk of serious infections.

The SmPC has been revised to update the indication in first line treatment of patients with CLL to only allow treatment of adult patients with 17p deletion or *TP53* mutation who are ineligible for any other therapies. In addition, the SmPC now includes warnings and precautions of use related to: 1) informing patients about the risk of serious infections, 2) screening for infections prior to and during treatment, including PJP and CMV, 3) addition of neutropenia monitoring, and 4) prophylaxis for PJP following treatment termination.

Following the conclusion of the Article 20 procedure and concurrent with the SmPC update, distribution of a Direct Healthcare Professional Communication (DHPC) was performed in European countries where Zydelig was commercially available in August 2016. This survey will be conducted in the 5 largest EU countries: France, Germany, Italy, Spain and the United Kingdom as they represent approximately 80% of the sales of Zydelig in Europe. The DHPC was sent to oncologists, hematologists and pharmacists to make them aware of the new precautionary measures and updates to the SmPC to minimize the risks. This survey will be sent to oncologists and hematologists as they are the HCPs in charge of prescribing Zydelig and following up the patient, including monitoring of the risks.

8. RESEARCH OBJECTIVES

8.1. Objective

The objective of this study is to determine the HCPs' level of knowledge about the infection risks associated with Zydelig treatment and the corresponding recommendations to minimize these risks.

The objectives of the DHPC were:

- To advise on the risk of neutropenia with Zydelig therapy, the appropriate monitoring of absolute neutrophil counts (ANC) in all patients on Zydelig, and the management of patients with low neutrophil counts

- To advise on the updated indication of Zydelig, particularly to reflect that it should not be used as first line treatment with chronic lymphocytic leukemia (CLL) with the exception of patients with 17p deletion or *TP53* mutation who are not eligible for any other therapies

- To advise on the need for *Pneumocystis jirovecii* pneumonia (PJP) prophylaxis, regular screening for CMV infection, and monitoring for respiratory symptoms and appropriate actions for dose modification/interruptions

- To advise on the indication and the risk of off-label use with Zydelig therapy in first line CLL in patients without 17p deletion/*TP53* mutation, and early line iNHL therapy

9. RESEARCH METHODS

9.1. Study Design

This non-interventional, cross sectional study consists of a survey of medical oncologists and hematologists in selected countries in the EU.

The survey will be conducted approximately 12 months after the distribution of the DHPC. In each country, medical oncologists and hematologists will be identified and the survey will be sent by email to participate in the survey on a volunteer/"opt-in" basis. Survey reminders will be sent during the survey recruitment period. Depending on uptake, another wave of invitations will be sent via email and post. Data from all respondents will be included in the analysis and final report.

The survey is planned for France, Germany, Italy, Spain and the United Kingdom.

9.2. Setting

The survey questionnaire will collect data from currently practicing oncologists and hematologists in the United Kingdom, Italy, Spain, France and Germany who treat patients with CLL or FL representing specialties considered likely to prescribe Zydelig, The survey will measure a HCP's understanding of both the infection related risks associated with Zydelig and the subsequent risk minimization recommendations communicated through the DHPC.

The survey will also ask how HCPs heard about the risks associated with Zydelig.

In order to be eligible to participate in this study subjects must be either:

- Registered oncologists and hematologists
- Registered medical doctors who are currently enrolled in an advanced training program leading to specialization in oncology and/or hematology

The following subjects will be ineligible to participate in this study:

- Oncologists or hematologists who are employed by Gilead Sciences or affiliates
- Oncologists or hematologists who participated in the pre-testing of the survey

Potential participants for this study have been identified using distribution lists acquired from the contract research organization (CRO), professional societies and internal databases.
The following numbers of eligible participants were estimated for each country:

- France 301
- Germany 318
- Italy 641
- Spain 811
- United Kingdom 514

Every eligible HCP identified from the aforementioned sources will be contacted and sent an email with a link to the electronic survey or by post, a paper version of the same survey as well as a link to the electronic survey. Each identified participant will be provided a unique identification code in order to complete the survey thus ensuring a participant may only provide one response. No sampling methodology will be used.

9.3. Variables

The survey will seek to measure the responses to the following key messages communicated in the DHPC: The variables measured are the responses provided to specific questions associated with the key messages.

- To advise on the risk of neutropenia with Zydelig therapy, the appropriate monitoring of ANC in all patients on Zydelig, and the management of patients with low neutrophil counts
  - Responses to Questions 1A, 12, and 13
- To advise on the updated indication of Zydelig, particularly to reflect that it should not be used as first line treatment with CLL with the exception of patients with 17p deletion or *TP53* mutation who are not eligible for any other therapies
  - Responses to Questions 2 and 3
- To advise on the need for PJP prophylaxis, regular screening for CMV infection, and monitoring for respiratory symptoms and appropriate actions for dose modification/interruptions
  - Responses to Questions 6, 7, 8, 9, 10 and 11
- To advise on the indication and the risk of off-label use with Zydelig therapy in first line CLL in patients without 17p deletion/*TP53* mutation, and early line iNHL therapy
  - Responses to Questions 2 and 3

9.4. Data Sources

A survey consisting of multiple choice questions that effectively measure a HCP's understanding of the infection associated risks of prescribing Zydelig and the subsequent risk minimization recommendations will be developed in conjunction with commercial partners.

The survey will be developed in both an electronic and paper format in order to maximize the number of responses from eligible HCPs. Both formats of the survey will be identical in terms of questions and content.

The survey will be designed to be completed in one sitting, taking a maximum of 20 minutes to finish. The electronic version will have built in checks ensuring a question must be completed before the participant is allowed to proceed to the next. The paper version of the survey will have clear and simple to follow instructions to complete each section of the survey before proceeding to the next.

9.4.1. Pre-testing of the survey

In order to ensure the questions for the survey can be understood by HCPs, qualitative pilot testing will be conducted by approximately 3 eligible HCPs in the United Kingdom. The survey will be translated and qualitative testing will be done by 2 eligible HCPs in each of the other countries (i.e., France, Germany, Italy and Spain). Surveys will be translated for each country prior to testing. Reviewers will provide recommendations for revisions to the questionnaires. Based on the feedback, the final questions for the survey may be revised. Reviewers who participate in the pre-testing will receive an honorarium and will not be eligible to participate in the survey.

9.4.2. Translation of the survey

Translation of the survey will be done in any non-English speaking countries. All translations to the respective languages will be done using forward and backward translations.

9.4.3. Distribution of the survey

In order to reach hematologists and oncologists the following approaches will be used:

- A CRO will be engaged to provide a commercial distribution list of eligible HCPs
- Internal company databases of HCPs will be searched
- Professional societies such as the Royal College of Physicians in the UK will be contacted and asked to forward the survey to their eligible members
- Internet searches for eligible practices may also be conducted

The initial invitation to participate will be sent by email. Subsequent reminders will be sent by email and a paper copy will also be sent. Clear instructions of how to complete the survey will be included and only one survey response per participant will be included for analysis.

9.5. Study Size

A target of 150 completed surveys will be obtained for the final analysis. The target minimum number of responders is per country is 30 for France, Germany, and the United Kingdom, 10 for Italy, and 20 for Spain. Table 1 shows the margins of error for different numbers of responders. With a target of 150 responders and the observed value of prescriber understanding of 80%, the true value is estimated to lie within the margin of 72.7% – 86.1%.

Table 1. Precision of Margin of Error with Different Numbers of Responders

Number of Responders	Margin of Error	
100	70.8%	87.3%
150	72.7%	86.1%
200	73.8%	85.3%

9.6. Data Management

At first, the survey will be sent via email to the list of available HCP email addresses in the 5 EU countries. If the survey is answered by fewer than 150 HCPs, another wave of emails will be sent as a reminder to those unresponsive HCPs and an invitation will be sent by post to HCPs. In this letter sent by post, HCPs may be invited to answer the survey online or to send the completed survey by post. For invitations mailed by post, a paper survey and pre-addressed and postage pre-paid envelope to return the paper survey will be included in the invitation pack.

The electronic survey questionnaires will be self-administered online via a secure commercial electronic data entry system. Participants will receive specific access codes to enable them to enter the survey. Paper survey responses will be entered manually into the electronic data entry system by the responsible CRO in accordance with a Data Entry Guidelines document and comprehensive quality control checks will be performed.

In order to ensure the quality and integrity of the study results, the electronic data entry system will be designed to flag or prevent incomplete or inconsistent data being collected. In addition, as the possibility of independent verification of data is limited for a study of this nature, the CRO will perform automated and/or manual data review to identify and remove any respondent with data that appears unreliable (e.g., electronic survey completed too fast to consist of real data). Any such data handling decisions will be transparently documented in the study documents.

The data entry system will be made available for a fixed time period (approximately 10 weeks overall) until the required 150 responses have been received. After that time, the system will be closed for data entry and the data extracted and analyzed.

A data management plan in the form of a survey manual will be created to define how the data will be collected, validated and transferred to the sponsor. The data will be stored in secure network drives with access for authorized personnel only.

9.7. Data Analysis

Responses to questions for all completed surveys will be analyzed using descriptive statistics (count, ranges, proportions, and /or scores). The results of each survey will be described separately, and the results will be presented overall, as well as by country, provider specialty where sample size allows, and by method of survey (electronic or paper). Continuous variables will be described by the mean, standard deviation, median and range. Categorical variables will be described by the number and proportion in each category. Frequency point-estimates with two-sided 95% confidence intervals (CIs) using the binomial distribution (e.g., Wald or Clopper-Pearson method, as appropriate) will be constructed to describe the proportion of prescribers aware of specified risks. An 80% threshold for prescriber awareness is generally considered acceptable awareness. This is the threshold used in other risk minimization programs, such as the Risk Evaluation and Mitigation Strategy (REMS) program in the United States (US).

The amount of missing data for each variable will be reported. Data will be presented by means of summary tables, graphs and listings. The numbers of invitees and respondents will be recorded, and the response rates will be reported overall, by country and by specialty.

Analyses will be performed according to a pre-specified statistical analysis plan.

9.8. Quality Control

The electronic data entry system will require that respondents answer certain questions before proceeding in order to ensure that surveys are completed as fully as possible. The data will be stored on a secure network drive or a secure and validated cloud-based data storage system, with access to only authorized personnel from the study team and their delegates.

Posted versions of the survey will have clear instructions directing participants to complete each question before proceeding. It is however still likely that there may be discrepancies in the responses between the electronic and paper version of the survey; therefore a stratified analysis will be conducted.

9.9. Limitations of the Research Methods

This study may be limited by social desirability bias if prescribers are hesitant to admit their lack of awareness of the specified risks. The survey instruments will be designed with the intention of minimizing this possible bias. In addition, random sampling will not be feasible for these surveys and non-response is a common problem in observational studies. However, the study will attempt to obtain as representative a sample as possible. The surveys will be administered online for respondents in most countries, which may exclude participants who are less comfortable with internet surveys. However, the number of respondents who are uncomfortable with internet surveys is expected to be low, and paper surveys would produce a larger respondent burden

which would be expected to deter participation. For this reason, a first wave of electronic invitation will be sent and, if the uptake is less than 150, a second wave of electronic and paper invitations will be sent. The survey is unable to assess awareness both before and after the distribution of the DHPC or changes in awareness as a result of the DHPC. Although this survey can only assess knowledge following the distribution of DHPC, it will still provide an important assessment of the awareness of the prescribing population of the risks of interest.

9.10. Other Aspects

Every effort will be made to ensure that this study is completed. Gilead will only terminate the study if there is sufficient cause following consultation with the PRAC. Should this be necessary, Gilead will arrange discontinuation procedures and notify the appropriate regulatory authorities 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, and European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP), including archiving of essential documents.

10.2. Independent Ethics Committee (IEC) Review

This study will not collect patient-level data. All national and EU regulations will be followed regarding the requirement for Independent Ethics Committee (IEC) review and approval for this study.

10.3. Informed Consent

Each survey participant will be asked to provide consent to use their responses to the questions for the purposes of the study. Each survey participant's confidentiality will be protected and only reported to Gilead if the participant reports safety information and provides permission to be contacted for follow-up by Gilead.

10.4. Confidentiality

The collected data will contain no participant identifiable fields.

11. MANAGEMENT AND REPORTING OF SAFETY INFORMATION

The objective of this study is to determine the HCPs' level of knowledge about the infection risks associated with Zydelig treatment and the corresponding recommendations to minimize these risks. This HCP survey is observational in nature and does not evaluate safety in individual patients. Adverse events will not be solicited in this observational study. In the event that adverse events are incidentally reported through the survey, reporting of these adverse events will be done by the clinical research organization (CRO) and sent to Gilead Drug Safety and Public Health (DSPH) within 24 hours of awareness by Gilead and/or CRO to Gilead DSPH, Safety_FC@gilead.com or fax + 1-650-522-5477. These events will be collected and reported to the regulatory agencies in accordance with standard safety reporting procedures. All study data will be in aggregate form only.

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 Module VIII. An interim report is not planned for this study. The final study report will be submitted within 6 months of study completion.

Future publications in the form of abstracts and manuscripts have not been planned. Gilead shall communicate to the EMA and the competent authorities of the Member States in which the product is authorized the final manuscript, if any, within two weeks after first acceptance for publication.

13. APPENDICES

Appendix 1. ENCePP Checklist for Study Protocols

Study title: A Cross-Sectional Post-Authorization Safety Study to Assess Healthcare Provider Awareness of Risks Associated with Zydelig® in the European Union

Study reference number: GS-EU-313-4226

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)	☐	☐	☒	
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:

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:

The objectives of these surveys are to determine healthcare provider level of knowledge of risks associated with prescribing Zydelig and to characterize prescribing practices in routine

[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.

clinical practice.

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?	☒	☐	☐	9.1
3.3 Does the protocol specify measures of occurrence? (e.g. incidence rate, absolute risk)	☐	☐	☒	
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)	☒	☐	☐	11

Comments:

Data from the surveys will be summarized descriptively (counts, proportions, etc.); no measure of association will be estimated.

Section 4: Source and study populations	Yes	No	N/A	Section Number
4.1 Is the source population described?	☒	☐	☐	9
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	9
4.2.2 Age and sex?	☐	☒	☐	
4.2.3 Country of origin?	☒	☐	☐	9
4.2.4 Disease/indication?	☒	☐	☐	9
4.2.5 Duration of follow-up?	☐	☒	☐	9
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

Comments:

The study population will be oncologists or hematologists who volunteer to participate.

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)	☐	☐	☒	

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)	☐	☐	☒	
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☐	☐	☒	
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	

Comments:

Study is cross-sectional survey of healthcare professionals.

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)	☐	☐	☒	
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:

Study is cross-sectional survey of healthcare professionals.

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

Comments:

Study is cross-sectional survey of healthcare professionals.

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)	☐	☐	☒	

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?	☐	☐	☒	
9.2 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)	☐	☐	☒	
9.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☐	☐	☒	
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☐	☐	☒	
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD)-10, Medical Dictionary for Regulatory Activities (MedDRA))	☐	☐	☒	
9.3.3 Covariates?	☐	☐	☒	
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments:

The data source is questionnaire responses from healthcare professionals.

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?	☐	☒	☐	
10.4 Does the plan describe methods for adjusting for confounding?	☐	☐	☒	
10.5 Does the plan describe methods for handling missing data?	☒	☐	☐	9.7
10.6 Is sample size and/or statistical power estimated?	☒	☐	☐	9.5

Comments:

Data from the surveys will be summarized descriptively (counts, proportions, etc.); no measure of association will be estimated.

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)	☒	☐	☐	9.8
11.2 Are methods of quality assurance described?	☐	☐	☒	
11.3 Is there a system in place for independent review of study results?	☐	☐	☒	

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?	☐	☐	☒	
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)	☐	☐	☒	
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☐	☐	☒	

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?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	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: David Magnuson, Pharm.D.

Date: 19 April 2017

Signature: 

Appendix 2. Investigator Signature Page

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A Cross-Sectional Post-Authorization Safety Study to Assess Healthcare Provider Awareness of Risks Associated with Zydelig® in the European Union

Original: 06 November 2016
Version 1.1: 19 April 2017

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

David Magnuson, PharmD

Gilead Study Director
Author

Signature

19 April 2017

Date

Anne-Ruth van Troostenburg de Bruyn
tGP MD(Lond) FFPM

EU QPPV & Sen Director, Drug Safety & Public Health

Signature

20 Apr 2017

Date