NON-INTERVENTIONAL (NI) STUDY REPORT

PASS information

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Country(-ies) of study	France, Germany, Italy, Spain, United Kingdom

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

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1. ABSTRACT

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

Keywords: Zydelig; idelalisib; infection; *Pneumocystis jirovecii* pneumonia (PJP) and cytomegalovirus infection (CMV); risk minimisation; survey

Rationale and background: On 15 September 2016, 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), related to an increased risk of serious infections and death in three clinical trials in unapproved indications. Following completion of the Article 20 review, the SmPC was revised to amend the first line indication for patients with chronic lymphocytic leukemia (CLL). Additional safety information about serious infections was incorporated, including risk minimisation measures to prevent infection related to PJP and CMV. In August 2016, a Direct Healthcare Professional Communication (DHPC) was sent to healthcare professionals (HCPs) in European countries where Zydelig was commercially available, outlining the measures described in the SmPC to minimize the risk of infection, the risk minimization measures for all CLL and FL patients which included PJP prophylaxis, and monitoring and screening recommendations for evidence of infections. In order to assess the effectiveness of the additional information provided in the DHPC and incorporated into the SmPC, this post authorization safety study was initiated, comprised of a survey questionnaire that measures HCPlevel of knowledge of the key risks and recommended precautionary measures for Zydelig.

Research question and objectives: The objective of this study was to determine HCPs level of knowledge about the infection risks associated with Zydelig treatment and the corresponding recommendations to minimise these risks.

Study design: Cross-sectional study.

Setting: A convenience sample of HCPs from France, Germany, Italy, Spain and the United Kingdom (UK) was recruited. The target population was not limited to HCPs who received the DHPC, but represented practice specialities which might prescribe Zydelig.

Subjects and study size, including dropouts: To be eligible, HCPs must have agreed to take part in the study, work at a clinic that includes patients with CLL or FL, and not participated in the cognitive pre-testing. A total of 5451 invitations were sent to HCPs in the 5 participating countries. Among the invited HCPs, 142 completed at least 1 question, giving a survey response rate of 2.6% (142/5451). Of these respondents, 10 (7.0%) were ineligible. Of the eligible HCPs, 131 completed all effectiveness endpoint questions and these HCPs comprise the analysis set for this report.

Variables and data sources: The survey questionnaire for HCPs was developed to assess the awareness of the information in the DHPC regarding the safety of Zydelig, the indication for treatment with Zydelig, and HCPs' knowledge on other (non-infection-related) risks associated with Zydelig therapy, and brief demographic information of the HCPs.

Statistical methods: All analyses were descriptive and were conducted using SAS® version 9.4 or above. Qualitative variables were described by the absolute and relative (%) frequency of each category and number of missing data. Two-sided 95% Confidence Interval (CI) for proportions was calculated for the effectiveness endpoints using exact methods. The threshold for acceptable awareness of each main effectiveness endpoint was defined as 80%. All analyses were performed overall and by country. The following subgroups were also evaluated for the main outcomes: speciality (oncology / haematology / oncology and haematology / other), mode of survey completion (on-line / paper), receipt of the DHPC (yes / no + don't know) and prescription of Zydelig within last 6 months (yes / no).

Results: The majority of respondents had prescribed Zydelig (80.2%). Approximately half of respondents practiced in a teaching / academic or university hospital (50.4%). Most respondents were specialised in haematology (61.1%) or haematology and oncology (30.5%).

Effectiveness endpoints were evaluated in 3 domains. For the *neutropenia domain*, nearly all HCPs knew that neutropenia is a risk of Zydelig therapy (91.6%, 95% CI 85.5-95.7%). Approximately two-thirds were aware of the recommended frequency for monitoring absolute neutrophil count (ANC) during the first 6 months of treatments (68.7%, 95% CI 60.0-76.5) and knew the recommended Zydelig dosing if laboratory results revealed ANC <500/mm^3 in patients (67.9%, 95% CI 59.2-75.8). For the *indication domain*, the majority of HCPs knew the minimum number of prior lines of therapies needed before starting combination therapy with Zydelig and rituximab in patients with CLL with 17p deletion or *TP53* mutations (73.3%, 95% CI 64.8-80.6), and the minimum number of prior lines of therapy needed before starting combination therapy with Zydelig and rituximab in patients with CLL with no 17p deletion or *TP53* mutations (80.2%, 95% CI 72.3-86.6). Two thirds of HCPs knew the minimum number of prior lines of therapy necessary before starting monotherapy with Zydelig in patients with FL (66.4%, 95% CI 57.6-74.4). For the *serious infection* domain, nearly all HCPs knew the risk of serious infection (97.7%, 95% CI 93.5-99.5) and measures required to be taken to minimise potential risk for PJP infections in patients receiving Zydelig (93.1%, 95% CI 87.4-96.8). Approximately half of HCPs knew which populations the risk of serious infection was most relevant for (54.2%, 95% CI 45.3-62.9), and the majority of HCPs were aware of the requirement of prophylaxis for PJP (89.3%, 95% CI 82.7-94.0), the recommended length of PJP prophylaxis during treatment with Zydelig (87.8%, 95% CI 80.9-92.9), when interruption or discontinuation of Zydelig treatment should be considered for patients who are CMV positive (71.0%, 95% CI 62.4-78.6), and that it is not appropriate to initiate Zydelig in patients experiencing ongoing systemic infections (82.4%, 95% CI 74.8-88.5). For the composite question regarding which patients should receive regular clinical and laboratory monitoring for CMV, although the proportion of HCPs who answered all 4 items correctly was low (22.9%, 95% CI 16.0-31.1), knowledge levels for each individual item within this composite outcome was above 80% for 2 items and 53.4% and 32.8% for 2 further items. Results for most of the effectiveness endpoints were similar between countries. Knowledge of the recommended frequency for monitoring ANC during the

first 6 months of treatment was higher for France and Germany than for other countries. In Germany and the UK, knowledge regarding the minimum number of prior lines of therapy was higher for the CLL indication, and lower for the FL indication, in comparison with other countries. With respect to serious infections, knowledge of when to interrupt treatment for CMV positive patients was lower for France than for the other countries. Knowledge levels of all effectiveness endpoints were largely comparable between HCPs irrespective of receiving the DHPC or having prescribed Zydelig.

In terms of non-infectin risks, nearly all of HCPs were aware that the following are additional risks associated with Zydelig therapy: transaminase elevations (92.4%, 95% CI 86.4-96.3), pneumonitis (92.4%, 95% CI 86.4-96.3), and diarrhoea / colitis (96.2%, 95%CI 91.3-98.7). Approximately half of the HCPs were also aware that risks of Zydelig therapy include Stevens-Johnson Syndrome (SJS) or Toxic Epidermal Necrolysis (TEN) (54.2%, 95% CI 45.3-62.9).

Approximately two-thirds of all HCPs recalled receiving the DHPC (70.2%) and nearly one-third of all HCPs reported that their primary source of information was the SmPC (29%).

Discussion and conclusions: After extending the survey recruitment period for 6 weeks in an endeavour to meet the target, 142 HCPs were recruited, almost reaching the recruitment target of 150. It was determined, given the relatively good response rates within each country (with the exception of France), that an adequate number was achieved to identify overall and country specific trends. The overall survey response rate was 2.6% (142/5451), which is lower than response rates seen from similar surveys distributed in European countries.

The primary effectiveness endpoints were analysed in 3 domains. The neutropenia domain consisted of 3 items. Only 1 of these items, knowledge that neutropenia is a risk of Zydelig (91.6%), met the pre-specified threshold of 80% or higher. The other 2 items approached the 80% threshold. The Zydelig indication domain consisted of 3 items. The pre-specified 80% or higher threshold was met for 1 item: knowledge of the minimum number of prior lines of therapy needed before starting combination therapy with Zydelig and rituximab in patients with CLL with no 17p deletion or *TP53* mutations (80.2%). The remaining 2 items were close to the threshold. The serious infection domain consisted of 8 items. Five of the 8 items reached the pre-specified 80% knowledge threshold: the risk of serious infection (97.7%), measures required to be taken to minimise risk for PJP infections in patients receiving Zydelig (93.1%), prophylaxis for PJP (89.3%), the recommended length for prophylaxis with PJP during treatment with Zydelig (87.8%), and that it is not appropriate to initiate Zydelig in patients experiencing ongoing systemic infections (82.4%). One item was close to the threshold (knowledge of when interruption or discontinuation of Zydelig treatment should be considered for patients who are CMV positive). Of the remaining 2 items in the serious infection domain, approximately half of HCPs were aware of one (knowledge of populations the risk of serious infection was most relevant for), while for the remaining item, few HCPs knew which patients should receive regular clinical and laboratory monitoring for CMV.

Performance across countries, in terms of knowledge levels on the effectiveness endpoints, was comparable. Knowledge levels of all effectiveness endpoints were largely comparable between HCPs irrespective of whether they had received the DHPC, or prescribed Zydelig.

In terms of non-infectin risks, knowledge rates regarding the risk were above the 80% threshold for: transaminase elevations, pneumonitis, and diarrhoea/ colitis. Approximately half of the HCPs were aware that SJS or TEN is a risk of Zydelig therapy.

Although two-thirds of all HCPs recalled receiving the DHPC, the the SmPC was the most commonly reported primary source of information regarding the risks of Zydelig therapy, highlighting the importance of label information.

The current survey study was conducted using rigorous methodologies and findings were consistent across countries, so the results are largely generalisable. However, the low response rate (2.6%) and potential for selection and reporting bias need to be taken into account when drawing conclusions across domains and for generalisability.

In conclusion, whilst the majority of the HCPs received the DHPC, the SmPC was the most commonly reported primary source of information regarding the risks of Zydelig therapy. Knowledge levels across the 3 domains analysed were moderate. For the neutropenia and Zydelig indication domains, HCPs had 80% or greater knowledge of the information included in the DHPC for only 1 out of the 3 items of each domain. For the serious infection domain, HCPs had 80% or greater knowledge of the information included in the DHPC for 5 out of the 8 items. Knowledge levels of the non-infectin risks of Zydelig were good, with 3 out of 6 items reaching the 80% knowledge threshold. Knowledge levels between those that did, and did not, receive the DHPC were largely comparable. Based on the results of this study, it appears that HCPs' knowledge of the infection risks associated with Zydelig treatment and the corresponding recommendations to minimise these risks was good.

Marketing Authorisation Holder(s): Gilead Sciences Ireland UC

Names and affiliations of Principal Investigator(s): David Magnuson, PharmD, Gilead Sciences, USA

2. LIST OF ABBREVIATIONS

Throughout this report, to enable consistency to the study protocol and final survey questionnaire, Zydelig (brand name) and idelalisib (trade name) are used interchangeably.

The following abbreviations and specialist terms are used in this report.

Abbreviation	Definition
AE	Adverse Event
ANC	Absolute Neutrophil Count
BR	Bendamustine and Rituximab
CI	Confidence Interval
CLL	Chronic Lymphocytic Leukemia
CMV	Cytomegalovirus
DHPC	Direct to Healthcare Professional Communication
EC	Ethics Committee
EU	European Union
FL	Follicular Lymphoma
HCP	Healthcare Professional/ Provider
iNHL	Indolent Non-Hodgkins Lymphoma
MD	Missing Data
PJP	*Pneumocystis jirovecci* pneumonia
PRAC	Pharmacovigilance Risk Assessment Committee
SAP	Statistical Analysis Plan
SmPC	Summary of Product Characteristics
SJS	Stevens-Johnson Syndrome
TEN	Toxic Epidermal Necrolysis
UK	United Kingdom

3. INVESTIGATORS

Principal Investigator(s) of the Protocol

Name, degree(s)	Title	Affiliation
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4. OTHER RESPONSIBLE PARTIES

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5. MILESTONES

Milestone	Planned date	Actual date	Comments
Start of data collection	September 2017	24 November 2017	
End of data collection	31 July 2018	17 September 2018	The survey close was extended to endeavour to obtain minimal response rates in all countries
Registration in the EU PAS register	Q3 2017	27 July 2017	
Final report of study results	12 December 2018	12 December 2018	

6. RATIONALE AND BACKGROUND

On 15 September 2016, 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 (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 chronic lymphocytic leukemia (CLL) and in combination with either BR or rituximab alone as early-line treatment for indolent non-Hodgkin Lymphoma (iNHL). 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 Zydelig remained positive for approved indications, with the adoption of risk minimisation measures to minimise the risk of serious infections.

The Summary of Product Characteristics (SmPC) was 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 was updated to include 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 *Pneumocystis jirovecci* pneumonia (PJP) and cytomegalovirus (CMV), 3) addition of neutropenia monitoring, and 4) prophylaxis for PJP both throughout Zydelig treatment and following treatment termination.

Following the conclusion of the Article 20 procedure and concurrent with the SmPC update, in August 2016 a distribution of a Direct to Healthcare Professional Communication (DHPC) was performed in European countries where Zydelig was commercially available. The DHPC was sent to oncologists, haematologists, and pharmacists to inform them of the new precautionary measures and updates to the SmPC.

This current study was intended to determine the healthcare professionals (HCP) level of knowledge regarding appropriate patient selection for treatment, the infection risks associated with Zydelig treatment and the corresponding recommendations to minimise these risks. As this objective was broader than an assessment of the effectiveness of the DHPC, participation was not limited only to those providers who had received the DHPC or Zydelig prescribers; rather participation was more extensive, including HCPs in charge of prescribing Zydelig and following up with the patient, as well as monitoring of the risks. This survey was conducted in the 5 largest EU countries: France, Germany, Italy, Spain, and the United Kingdom (UK) as they represent approximately 80% of the sales of Zydelig in Europe.

This non-interventional survey study was classified as a Post-authorisation Safety Study. Surveys are widely known as an accepted methodology to evaluate knowledge levels. Specifically, Module XVI of European Good Pharmacovigilance Practice, *'selection of tools and effectiveness indicators'*, endorses the use of "scientifically rigorous survey methods" to assess the awareness of the target audience and the level of knowledge achieved by educational interventions and/or information provision {Agency 2017}.

7. RESEARCH QUESTION AND OBJECTIVES

The overall objective of the study was to determine the HCP level of knowledge regarding the infection risks associated with Zydelig treatment and the corresponding recommendations to minimise these risks.

The specific objectives were:

- Primary Objectives:
  - — *Neutropenia domain*: Assess HCP knowledge of the risk of neutropenia with Zydelig therapy, the appropriate monitoring of absolute neutrophil count (ANC) in all patients on Zydelig, and the management of patients with low neutrophil counts by determining the percentage of respondents who provided correct responses to the neutropenia-related questions,
  - — *Zydelig indication domain*: Assess HCP knowledge of 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. Assess HCP knowledge of the risk of off-label use in first line CLL in patients without 17p deletion or *TP53* mutation and early line indolent non-Hodgkins lymphoma therapy, and assess HCP knowledge of the minimum number of prior lines of therapy necessary before starting monotherapy with Zydelig in patients with follicular lymphoma (FL). This was done by estimating the percentage of respondents who provided correct responses to the indication-related and off--label use questions, and
  - — *Serious infection domain*: Assess HCP knowledge on the requirement for PJP prophylaxis, regular screening for CMV infection, and monitoring for respiratory symptoms and appropriate actions for dose modification/interruptions, by estimating the percentage of respondents who provided correct responses to the serious infection-related questions.
- Other Objectives:
  - — Other risks (not related to infections) – assess HCP knowledge on other risks (non-infection-related) associated with Zydelig therapy by estimating the percentage of respondents who provided correct responses to the other risk-related questions,
  - — Assess HCP receipt of the DHPC by estimating the percentage of respondents who acknowledge receiving the DHPC, and
  - — Describe the primary source from which HCPs learned about the risks associated with Zydelig by estimating the percentage of respondents who indicate the relevant information source listed on the survey questionnaire.

8. AMENDMENTS AND UPDATES

Number	Date	Section of study protocol	Amendment or update	Reason
1.1	19 April 2017	All sections	Updated throughout based on comments from PRAC's assessment of protocol	Updated in response to PRAC's assessment of protocol

9. RESEARCH METHODS

9.1. Study Design

This was a cross-sectional non-interventional survey among medical oncologists and haematologists in selected countries in the EU. The survey was conducted 14 months after the distribution of the DHPC in France, Germany, Italy, Spain, and the UK. The survey was launched for data collection on 24 November 2017. Data collection was planned to close 31 July 2018, but in an effort to increase response rates this was extended to 17 September 2018.

9.2. Setting

The survey measured HCPs understanding of the correct indication for treatment, the infection related risks associated with Zydelig and the subsequent risk minimisation recommendations communicated through the DHPC. The survey also asked how HCPs learned about the risks associated with Zydelig.

The survey questionnaire collected data from currently practicing oncologists and haematologists in France, Germany, Italy, Spain, and the UK who treat patients with CLL or FL representing specialities considered likely to prescribe Zydelig. A convenience sample[a] of HCPs was recruited; these HCPs represented practice specialities which are considered likely to prescribe Zydelig. As the intention of the survey was to understand the HCP level of knowledge regarding the infection risks associated with Zydelig treatment and the corresponding recommendations to minimise these risks, the survey was distributed to HCPs without reference to any distribution list of the DHPC. Invitation letters were sent to HCPs included on the sampling lists by either email or postal mail, using the available contact information. If both were available, email was used as a default. The invitation letter included information about the survey, a unique access code to the online platform, and instructions for accessing the survey via the internet. In all countries HCPs were invited to participate on a volunteer/"opt-in" basis.

9.3. Subjects

9.3.1. Eligibility Criteria

9.3.1.1. Inclusion Criteria

In order to be eligible to participate in this study physicians were either:

- Registered oncologists and/or haematologists.
- Registered medical doctors who are currently enrolled in an advanced training program leading to specialisation in oncology and/or haematology.

[a] A convenience sample is one of the main types of non-probability sampling methods. A convenience sample is made up of people who are easy to reach.

9.3.1.2. Exclusion Criteria

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

9.3.2. Potential Participant Selection

A convenience sample of HCPs was targeted using contact information from lists provided by Gilead. Initial invitations were sent by country, as soon as each country-specific start-up activity was completed (e.g., regulatory notifications/approvals completed, survey database set-up, etc.).

To endeavour to meet the target sample size of 150 completed surveys overall, as well as minimum targets per country, the strategies below were employed.

- Up to 2 reminders were sent to HCPs who had not yet completed the survey, using the available contact information.
- In countries not meeting the targets, additional HCPs were contacted from either initial lists or new HCP lists.
- In Spain and France, the local Gilead affiliates used their network to remind local HCPs of relevance to complete the survey.

Invitations were sent via email or post, when a HCP had both methods of contact information available, the default used was email. Invites were sent in total to 5451 HCPs, specifically:

- In France, a list of 907 HCP email addresses were compiled, all of these were invited to participate in the survey. Subsequently, to supplement the initial list a further 47 HCP contact details were sourced, and these were also invited to participate.
- In Germany, a list of 1280 HCP postal addresses and 40 email addresses were compiled, of these 1256 HCPs received a postal invite and 40 an email invite.
- In Italy, a list of 1226 HCP postal addresses and 95 email addresses were compiled, of these all HCPs received an invite.
- In Spain, a list of 1911 HCP postal addresses and 54 email addresses were compiled, of these 1068 HCPs received a postal invite and 54 an email invite. Subsequently, to supplement the initial list, a further 10 HCP contact details were sourced (email), and these were also invited to participate. In addition local Gilead affiliates were active in requesting local contacts to complete the survey.
- In the UK, a list of 600 HCP postal addresses and 148 email addresses were compiled, of these all HCPs received an invite.

HCPs who completed the survey were compensated for their time according to local laws and regulations, with the exception of Spain where for logistical reasons no payments were offered.

9.4. Variables

The survey sought 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*

9.5. Data Sources and Measurement

9.5.1. Cognitive Pre-testing of the Survey Questionnaire

The survey questionnaire underwent cognitive pre-testing with 10 HCPs in 5 countries who matched the profile of potential prescribers of Zydelig; specifically, 3 HCPs from the UK for the survey base language, 2 HCPs each from France, Italy, and Spain. In Germany, only 1 HCP agreed to perform the pre-testing, however as this HCP provided a thorough pre-testing and in order to launch the survey on time, it was decided to proceed based on 1 set of comments. Pre-testing was completed after the survey base language questionnaire was finalised and had been translated. Reviewers who participated in the pre-testing received a fair market value honorarium and were not eligible to participate in the survey.

The objective of the pre-testing was to identify any survey questions that required clarification or revision based on areas of confusion or miscomprehension revealed by participants in the cognitive pre-test interviews. Pre-testing was completed through 1-on-1 interviews conducted by

personnel experienced in the conduct of cognitive pre-testing and linguistic validation of survey questionnaires. During the conduct of the pre-test, the survey questionnaire was presented item by item, and feedback was obtained for each question using a pre-developed interviewer guide. The interviewer also recorded any unsolicited feedback received from participating HCPs on the survey questions or wording.

The cognitive pre-test resulted in minor revisions to the UK base version and all of the country-specific versions of the physician questionnaire. In the UK pre-test it was noted that Zydelig should be referred to as idelalisib, so this was adapted for all countries. For individual countries, minor changes to clarify wording (e.g., more correct technical terminology, simpler language, aligning with DHPC wording, adjustments of abbreviations), and minor changes to adjust the initial translations to accommodate local standards or ways of saying things (e.g., in some countries, “true/false” was more commonly expressed as “yes/no”, practice setting and specialisation response choices were adapted to be consistent with local standard of care, etc.) were identified.

9.5.2. Survey Administration

All data for this study were collected through self-administered internet surveys provided in each participating country’s local language. Confirmit software was used for all countries.

The survey questions consisted of multiple-choice, yes/no, and true/false questions with no free text allowed. It was expected that completion of the survey would take approximately 20 minutes. The survey began with a secure survey administration module where HCPs entered their pre-assigned unique identifier, selected their country and language, and then indicated their acceptance of the terms of the survey research agreement. If agreed, HCPs then completed the eligibility screening question, and if eligible, HCPs were able to continue to the main survey questions.

The survey was open for data collection from November 2017 to September 2018. Metrics on survey completion were tracked to monitor progress (e.g., number of completed surveys) and to identify non-responders to facilitate sending reminders.

9.6. Bias

A primary limitation of surveys is selection bias due to the use of a convenience sample and/or low response rates. Given that it was not feasible to have a random sample of HCPs who prescribed Zydelig in Europe to participate in the study, to minimise selection bias, a representative sample of HCPs who prescribed Zydelig in Europe was sought by inviting HCPs from from France, Germany, Italy, Spain, and the UK to participate in the survey. These countries were selected for the following reasons:

- A representative sample of EU countries was chosen based on market share and geographic variation to promote a representative sample that could be generalised to the broader group of EU countries where the DHPC had been disseminated.

- In some countries, this survey may be required to be submitted to each HCP's local ethics committee (EC) for approval prior to conducting the survey. If this occurred, HCPs would see the survey questionnaire and protocol in advance, which could bias their responses. Additionally, the delay to wait for EC approvals could lengthen the time from when HCPs received the educational materials to when the survey was completed, thus predisposing survey results to lag-time bias. Therefore, countries with these known feasibility constraints that could potentially bias the survey results were not considered for participation in the survey.

Another limitation is that the study relied on self-reporting. It is possible that HCPs may have inaccurately reported the information due to either recall bias or social desirability bias.

To minimise information bias, response sets for all multiple-choice questions were randomised for the on-line survey. HCPs were also instructed to complete the survey in 1 sitting to minimise the likelihood of looking up the correct answers and were not able to revise their answers after advancing to each subsequent question. Additionally, HCPs were intentionally not contacted to clarify or revise their survey responses related to awareness of, and knowledge on, the Zydelig DHPCs.

9.7. Study Size

A sample of 150 completed HCP surveys was targeted for this survey. The target minimum number of responders was 30 for France, Germany, and the UK, 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 HCP awareness 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%

9.8. Data Transformation

Surveys were entered in Confirmit, a software platform specifically designed for the creation, delivery, analysis, and reporting of surveys. Data collected in this study were stored at secure servers, were maintained by trained data managers, and were maintained in compliance with applicable local or national regulations.

Detailed methodology for data transformations, particularly complex transformations (e.g., many raw variables used to derive an analytic variable), are documented in the Statistical Analysis Plan (SAP), which is maintained by the sponsor and vendor as a stand-alone document.

9.9. Statistical Methods

The primary analysis population includes all HCPs who met the inclusion/exclusion criteria and provided a response to all survey questions (questions 1-13). Denominators used to calculate knowledge levels for individual survey questions reflect the number of respondents who completed each individual survey question including responses of 'I don't know/not sure'. The primary analysis set was used to summarise all endpoints.

9.9.1. Main Summary Measures

The main endpoints are summarised in this section. Details regarding the derivation of all items that comprised the main endpoints are provided in the SAP.

9.9.1.1. Main Effectiveness Endpoints

The primary effectiveness endpoints are defined in Table 2.

Table 2. Primary Effectiveness Endpoints

Study objective assessed	Corresponding variable	Operational definition
Neutropenia domain: Assess HCP knowledge 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	Knowledge that neutropenia is a risk of idelalisib	Calculated as the percentage of respondents who answer “Yes” to question 1a
	Knowledge of recommended frequency for monitoring ANC during first 6 months of treatment	Calculated as the percentage of respondents who answer “At least every 2 weeks” to question 12
	Knowledge of recommended idelalisib dosing if laboratory results reveal ANC < 500/mm^3 in patients receiving idelalisib	Calculated as the percentage of respondents who answer “Discontinue treatment with idelalisib” to question 13
Zydelig indication domain: Assess HCP knowledge on: a) 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, b) the risk of off-label use in first line CLL in patients without 17p deletion/*TP53* mutation and early line iNHL therapy, and c) the minimum number of prior lines of therapy necessary before starting monotherapy with idelalisib in patients with FL	Knowledge of the minimum number of prior lines of therapies needed before starting combination therapy with idelalisib and R in patients with CLL with 17p deletion or *TP53* mutations	Calculated as the percentage of respondents who answer “None” to question 2
	Knowledge of the minimum number of prior lines of therapies needed before starting combination therapy with idelalisib and R in patients with CLL with no 17p deletion or *TP53* mutations	Calculated as the percentage of respondents who answer “1” to question 3
	Knowledge of the minimum number of prior lines of therapy necessary before starting monotherapy with idelalisib in patients with FL	Calculated as the percentage of respondents who answer “2” to question 4

Study objective assessed	Corresponding variable	Operational definition
Serious infection domain: Assess HCP knowledge on: a) the risk of serious infection and populations this risk is most relevant for, b) PJP prophylaxis including recommended length for prophylaxis, c) which patients to monitor for CMV infection, d) when to interrupt or discontinue idelalisib treatment for CMV positive patients, e) when it is appropriate to initiate idelalisib in patients with certain types of ongoing systemic infections, and f) measures to be taken to minimize the risk for PJP	Knowledge of the risk of serious infection	Calculated as the percentage of respondents who answer "Yes" to question 1c
	Knowledge of which populations are the risk of serious infections most relevant for	Calculated as the percentage of respondents who answer "Both of the above patient categories" to question 5
	Knowledge regarding prophylaxis for PJP	Calculated as the percentage of respondents who answer "All patients should receive prophylaxis for PJP" to question 6
	Knowledge of recommended length for prophylaxis with PJP during treatment with idelalisib	Calculated as the percentage of respondents who answer "For the entire length of idelalisib treatment and then for 2-6 months after idelalisib discontinuation, depending on clinical judgement" to question 7
	Knowledge of which patients should regular clinical and laboratory monitoring for CMV be conducted.	Calculated as the percentage of respondents who correctly answer question 8 ("False" to 8a and "True" to 8b/8c/8d)
	Knowledge of when interruption or discontinuation of idelalisib treatment should be considered for patients who are CMV positive	Calculated as the percentage of respondents who answer "At the time clinical symptoms of CMV infection become evident" to question 9
	Knowledge of when it is appropriate to initiate idelalisib in patients suffering from ongoing systemic infections	Calculated as the percentage of respondents who correctly answer question 10 ("No" to 10a/10b/10c)
	Knowledge of measures required to be taken to minimize potential risk for PJP infections in patients receiving idelalisib	Calculated as the percentage of respondents who correctly answer question 11 ("Yes" to 11a/11b)

Knowledge levels were derived as the proportion of HCPs who provided correct responses to the corresponding questions regarding the items above. The threshold for acceptable awareness of each main effectiveness endpoint was defined in the protocol as 80%. For each of the individual main effectiveness endpoints, the percentage of correct answers was estimated and assessed against the 80% target.

9.9.1.2. Other Endpoints

- HCP knowledge on other (non-infection-related risks) associated with Zydelig therapy, calculated as the percentages of respondents who answer each of the following items to question 1 correctly:
  - 1b (transaminase elevations) as “Yes”
  - 1d (migraine headaches) as “No”
  - 1e (pneumonitis) as “Yes”
  - 1f (diarrhea/colitis) as “Yes”
  - 1g (arthritis) as “No”, and
  - 1h (Stevens-Johnson syndrome [SJS] or toxic epidermal necrolysis [TEN] as “Yes”.
- HCP receipt of the DHPC, calculated as the percentage of respondents who answer “Yes” to receiving the DHPC letter.
- Distribution of all response choices to questions 1-13 (regarding risks associated with idelalisib, question 14 (the primary source from which HCPs learnt about the risks of idelalisib), and question 15 (regarding recall of receipt of the DHPC letter for idelalisib).

9.9.2. Main Statistical Methods

Detailed statistical methods are described in the SAP. All analyses were descriptive and were conducted using SAS® version 9.4 or above.

Descriptive statistics for continuous analyses included n, mean, standard deviation, median, interquartile range, and range. Descriptive statistics for categorical analyses included count and percentage, including counts for missing categories as applicable.

Frequency point-estimates with two-sided 95% CIs using the binomial distribution (e.g., Wald or Clopper-Pearson method, as appropriate) were constructed to describe the proportion of prescribers aware of specified risks.

No hypothesis testing was performed.

All analyses were performed overall and by country. In addition, the effectiveness endpoints (primary analysis) were performed overall, and also stratified by the following subgroups:

- specialisation (oncology/ haematology/ oncology and haematology/ other),
- receipt of the DHPC (yes / no + don’t know), and
- prescribed idelalisib within last 6 months (yes / no).

In the SAP it was planned to analyse the subgroup of mode of survey completion (on-line / paper), however this was not needed as no paper surveys were completed.

9.9.3. Missing Values

Missing data (MD) were reviewed solely for the purposes of deriving the effectiveness endpoints. No replacement or imputation was performed. Descriptive statistics for continuous variables include the available n, and descriptive statistics for categorical variables include a category of "missing" when applicable.

9.9.4. Sensitivity Analyses

None.

9.9.5. Amendments to the Statistical Analysis Plan

None.

9.10. Quality Control

ICON Plc was responsible for following of their standard operating procedures to ensure data quality and integrity, including archiving of statistical programs, appropriate documentation of data cleaning and validation of derived variables, and description of available data. Based on social science research principles for knowledge assessment surveys, to reduce bias from asking respondents to change their original survey responses *post hoc* {Banerjee 2014}, limited data validation and cleaning was performed.

10. RESULTS

10.1. Participants

A summary of response rates is provided in Table 3 (note: specialism was not collected for non-respondents). A total of 5451 invitations were sent to HCPs in the 5 participating countries. Among the invited HCPs, 142 HCPs completed at least 1 question, giving a survey response rate of 2.6% (142/5451). The response rate ranged from 1.8% in Spain (20/1132) to 6.3% in the UK (47/748). A summary of survey administration details and HCP eligibility is provided in Table 4. In the overall survey, of these HCPs, 10 (7.0%) were ineligible. One HCP did not agree to take part in the survey once entering and 4 worked at a clinical practice that does not include patients with CLL or FL. Five respondents did not participate as they indicated that they had participated in the cognitive pre-testing, however a cross-check of their ID number revealed that this was not the case. No participants who had completed the pre-testing were invited to participate in the survey.

Of the eligible HCPs, 131 completed all effectiveness endpoint questions (questions 1-13), this sample formed the analysis set, which is the focus of the results section of this report.

All surveys were completed online, the protocol stipulated that paper surveys were to be included as a mode of completion for surveys sent by postal mail if required, however the paper survey mode was not needed so was not implemented.

Table 3. Responders and non-Responders, Overall and by Country

	Overall	France	Germany	Italy	Spain	United Kingdom
Responded (n.%)						
N	5451	954	1296	1321	1132	748
Yes	142 (2.6)	22 (2.3)	25 (1.9)	28 (2.1)	20 (1.8)	47 (6.3)
No[a]	5309 (97.4)	932 (97.7)	1271 (98.1)	1293 (97.9)	1112 (98.2)	701 (93.7)

a Information of specialities of non-responders was not available.

Table 4. Survey Administration, Eligibility, and Analysis Sets Overall and by Country

	Overall N=142	France N=22	Germany N=25	Italy N=28	Spain N=20	United Kingdom N=47
Survey Modality (n, %)						
Paper[a]	0	0	0	0	0	0
On-line	142 (100)	22 (100)	25 (100)	28 (100)	20 (100)	47 (100)
Survey Status (n, %)						
Completed at least 1 eligibility question	142 (100)	22 (100)	25 (100)	28 (100)	20 (100)	47 (100)
Completed at least 1 effectiveness endpoint question [b]	132 (93.0)	16 (72.7)	25 (100)	26 (92.9)	18 (90.0)	47 (100)
Completed all effectiveness endpoint questions [b]	131 (92.3)	16 (72.7)	25 (100)	26 (92.9)	18 (90.0)	46 (97.9)
Eligibility (n, %)						
Yes	132 (93.0)	16 (72.7)	25 (100)	26 (92.9)	18 (90.0)	47 (100)
No	10 (7.0)	6 (27.3)	0	2 (7.1)	2 (10.0)	0
If no: reasons for exclusion (n, %)						
Not agree to take part in this survey	1 (10.0)	0	0	0	1 (50.0)	0
Clinical practice does not include patients with CLL or FL	4 (40.0)	4 (66.7)	0	0	0	0
Participation in the pre-testing[c]	5 (50.0)	2 (33.3)	0	2 (100)	1 (50.0)	0
Analysis Set (n, %)						
Primary analysis set (Eligible HCPs who have completed all effectiveness endpoint questions)	131 (92.3)	16 (72.7)	25 (100)	26 (92.9)	18 (90.0)	46 (97.9)

CLL = chronic lymphocytic leukaemia, FL = follicular lymphoma
a The protocol stipulated that paper surveys were to be included as a mode of completion for surveys sent by postal mail, but the paper survey mode was not needed so was not implemented.
b Effectiveness endpoint questions= questions 1-13.
c A cross-check of ID numbers, after study completion, revealed that none of these respondents had in fact participated in pre-testing.

10.2. Descriptive Data

Table 5 provides a summary of characteristics of HCPs overall and by country. Approximately half of respondents practiced in a teaching/academic or university hospital (50.4%). The majority of the remaining respondents practiced in a general or district hospital (37.4%). Most respondents were specialised in haematology (61.1%) or haematology and oncology (30.5%). A small portion were specialised in oncology only (2.3%). The majority of respondents had prescribed Zydelig (80.2%); 35.1% was for patients with CLL, 6.1% was for patients with FL and 38.9% was for patients with CLL or FL. Nearly half of all respondents had prescribed Zydelig within a time frame of 3 months or less (41.9%).

All countries had a sufficient number of respondents to identify country-specific trends. Practice setting varied across countries. In Italy and Spain, the majority of respondents practiced in teaching/academic or university hospitals (53.8% and 72.2% respectively), whereas in France the majority practiced in general or district hospitals and in Germany almost half was reported as ‘other’ (52.0%). In the UK, the allocation was comparable across the types of hospital settings (50%). Medical specialisation varied slightly across countries. In France, Italy, Spain, and the UK, the majority of respondents were haematology specialists (81.3%, 57.7%, 94.4%, and 73.9% respectively). However, in Germany, the majority of respondents were haematology and oncology specialists (92.0%). In terms of prescribing Zydelig, half of the respondents in Spain (50.0%) and 30.8% of respondents in Italy had not prescribed Zydelig. In Germany, only 1 respondent had never prescribed Zydelig (4.0%).

Table 5. Respondent Characteristics Overall and by Country

	Overall N=131	France N=16	Germany N=25	Italy N=26	Spain N=18	United Kingdom N=46
Practice setting (n, %)						
Teaching/Academic/University hospital	66 (50.4)	6 (37.5)	10 (40.0)	14 (53.8)	13 (72.2)	23 (50.0)
General/district hospital	49 (37.4)	9 (56.3)	1 (4.0)	11 (42.3)	5 (27.8)	23 (50.0)
Primary care clinic	1 (0.8)	0	1 (4.0)	0	0	0
Other	15 (11.5)	1 (6.3)	13 (52.0)	1 (3.8)	0	0
MD	0	0	0	0	0	0
Medical specialisation (n, %)						
Oncology	3 (2.3)	0	1 (4.0)	0	0	2 (4.3)
Haematology	80 (61.1)	13 (81.3)	1 (4.0)	15 (57.7)	17 (94.4)	34 (73.9)
Haematology and Oncology	40 (30.5)	1 (6.3)	23 (92.0)	5 (19.2)	1 (5.6)	10 (21.7)
Other	8 (6.1)	2 (12.5)	0	6 (23.1)	0	0
MD	0	0	0	0	0	0
Previous prescription of idelalisib (n, %)						
Yes, for patients with CLL	46 (35.1)	4 (25.0)	14 (56.0)	2 (7.7)	3 (16.7)	23 (50.0)
Yes, for patients with FL	8 (6.1)	0	0	3 (11.5)	4 (22.2)	1 (2.2)
Yes, for both CLL and FL	51 (38.9)	11 (68.8)	10 (40.0)	13 (50.0)	2 (11.1)	15 (32.6)
No, I have not prescribed idelalisib	26 (19.8)	1 (6.3)	1 (4.0)	8 (30.8)	9 (50.0)	7 (15.2)
MD	0	0	0	0	0	0

	Overall N=131	France N=16	Germany N=25	Italy N=26	Spain N=18	United Kingdom N=46
If yes, last time prescribed idelalisib (n, %)[a]						
0-<3 months ago	44 (41.9)	7 (46.7)	10 (41.7)	10 (55.6)	2 (22.2)	15 (38.5)
3-<6 months ago	26 (24.8)	4 (26.7)	6 (25.0)	4 (22.2)	3 (33.3)	9 (23.1)
6-<12 months ago	22 (21.0)	2 (13.3)	5 (20.8)	4 (22.2)	2 (22.2)	9 (23.1)
> 12 months ago	12 (11.4)	2 (13.3)	3 (12.5)	0	2 (22.2)	5 (12.8)
I don’t know/am not sure	1 (1.0)	0	0	0	0	1 (2.6)

CLL = chronic lymphocytic leukaemia, FL = follicular lymphoma, MD = missing data, NA = not applicable
a denominator represents respondents that have previously prescribed idelalisib.

10.3. Outcome Data

Endpoints were summarised for the analysis population (all HCPs who met the inclusion/exclusion criteria and responded to all survey questions regarding the safety of Zydelig).

10.4. Main Results

The primary effectiveness endpoint results are provided for the analysis set overall, and by country, in Table 6. HCPs knowledge were analysed in 3 key domains: neutropenia, indication, and serious infection.

For the neutropenia domain, nearly all HCPs knew that neutropenia is a risk of Zydelig (91.6%, 95% Confidence Interval (CI) 85.5-95.7%). Approximately two-thirds were aware of the recommended frequency for monitoring ANC during the first 6 months of treatments (68.7%, 95% CI 60.0-76.5) and knew the recommended Zydelig dosing if laboratory results revealed ANC <500/mm^3 in patients receiving Zydelig (67.9%, 95% CI 59.2-75.8).

For the indication domain, the majority of HCPs knew the minimum number of prior lines of therapies needed before starting combination therapy with Zydelig and rituximab in patients with CLL with 17p deletion or *TP53* mutations (73.3%, 95% CI 64.8-80.6), and the minimum number of prior lines of therapy needed before starting combination therapy with Zydelig and rituximab in patients with CLL with no 17p deletion or *TP53* mutations (80.2%, 95% CI 72.3-86.6). Two thirds of HCPs knew the minimum number of prior lines of therapy necessary before starting monotherapy with Zydelig in patients with FL (66.4%, 95% CI 57.6-74.4).

For the serious infection domain, nearly all HCPs knew the risk of serious infection (97.7%, 95% CI 93.5-99.5) and measures required to be taken to minimise potential risk for PJP infections in patients receiving Zydelig (93.1%, 95% CI 87.4-96.8). Approximately half of HCPs knew which populations the risk of serious infection were most relevant for (54.2%, 95% CI 45.3-62.9). The majority of HCPs were aware of the requirement of prophylaxis for PJP (89.3%, 95% CI 82.7-94.0), the recommended length of PJP prophylaxisduring treatment with Zydelig (87.8%, 95% CI 80.9-92.9), when interruption or discontinuation of Zydelig treatment should be considered for patients who are CMV positive (71.0%, 95% CI 62.4-78.6), and that it is not appropriate to initiate Zydelig in patients experiencing ongoing systemic infections (82.4%, 95% CI 74.8-88.5). For the composite question regarding which patients should receive regular clinical and laboratory monitoring for CMV, although the proportion of HCPs who answered all 4 items correctly was low (22.9%, 95% CI 16.0-31.1), knowledge levels for each individual item within this composite outcome was above 80% for 2 items and 53.4% and 32.8% for 2 further items.

Results for most of the effectiveness endpoints were similar between countries. For the neutropenia domain, knowledge of the recommended frequency for monitoring ANC during the first 6 months of treatment was higher for France and Germany than for other countries. For the indication domain, in Germany and the UK, knowledge regarding the minimum number of prior lines of therapy was higher for the CLL indication, and lower for the FL indication, in

comparison with other countries. With respect to serious infections, knowledge of when to interrupt treatment for CMV positive patients was lower for France than for the other countries.

The primary effectiveness endpoints for the analysis set by specialisation, receipt of the DHPC, and by whether HCPs prescribed Zydelig are presented in Table 7, Table 8, and Table 9, respectively. No analysis was conducted for the subgroup 'mode of survey completion' as no paper surveys were completed.

Oncology and other specialities had too few responses to analyse trends. For the neutropenia domain, HCPs with a haematology and oncology specialism had higher levels of knowledge than those with a straight haematology specialisation. For the indication domain, this trend was reversed, with HCPs with a haematology specialisation having higher levels of knowledge. For the serious infection domain, this was mixed, but responses were largely comparable.

Knowledge levels of all effectiveness endpoints were largely comparable between HCPs that received the DHPC (N=92), and those that did not receive it, or could not recall receiving it, (N=39). Minor exceptions were, in comparison with those that did not receive the DHPC, those that did had higher levels of knowledge regarding: recommended length for prophylaxis with PJP during treatment with idelalisib (91.3% vs. 79.5%), when it is appropriate to initiate Zydelig in patients suffering from ongoing systemic infections (85.9% vs. 74.4%), and measures required to be taken to minimise potential risk for PJP infections in patients receiving idelalisib (98.9% vs. 79.5%). Conversely, HCPs that did receive the DHPC were less aware than those that did not receive the DHPC regarding which patients should undergo regular clinical and laboratory monitoring for CMV (19.6% vs. 30.8%).

There was little difference in knowledge levels for all effectiveness endpoints between HCPs that had prescribed Zydelig (N = 70), and those that had not (N=35). Minor exceptions were, in comparison with those that did not prescribe Zydelig, those that did, had higher levels of knowledge regarding: recommended frequency for monitoring ANC during first 6 months of treatment (72.9% vs. 60.0%), and which populations are the risk of serious infection most relevant for (61.4% vs. 48.6%). Conversely, HCPs that did not prescribe Zydelig were less aware than those that did prescribe Zydelig regarding the minimum number of prior lines of therapies needed before starting combination therapy with idelalisib and rituximab in patients with CLL with 17p deletion or *TP53* mutations (75.7% vs. 88.6%), and which patients should undergo regular clinical and laboratory monitoring for CMV (12.9% vs. 28.6%).

Table 6. Effectiveness Endpoints – Primary Knowledge Levels Overall and by Country

	Overall N=131	France N=16	Germany N=25	Italy N=26	Spain N=18	United Kingdom N=46
Neutropenia domain						
Knowledge that neutropenia is a risk of idelalisib						
N	131	16	25	26	18	46
n (%)	120 (91.6)	13 (81.3)	25 (100)	23 (88.5)	14 (77.8)	45 (97.8)
95% CI	[85.5 ; 95.7]	[54.4 ; 96.0]	[86.3 ; 100]	[69.8 ; 97.6]	[52.4 ; 93.6]	[88.5 ; 99.9]
Knowledge of recommended frequency for monitoring ANC during first 6 months of treatment						
N	131	16	25	26	18	46
n (%)	90 (68.7)	14 (87.5)	20 (80.0)	16 (61.5)	11 (61.1)	29 (63.0)
95% CI	[60.0 ; 76.5]	[61.7 ; 98.4]	[59.3 ; 93.2]	[40.6 ; 79.8]	[35.7 ; 82.7]	[47.5 ; 76.8]
Knowledge of recommended idelalisib dosing if laboratory results reveal ANC < 500/mm^3 in patients receiving idelalisib						
N	131	16	25	26	18	46
n (%)	89 (67.9)	11 (68.8)	17 (68.0)	19 (73.1)	13 (72.2)	29 (63.0)
95% CI	[59.2 ; 75.8]	[41.3 ; 89.0]	[46.5 ; 85.1]	[52.2 ; 88.4]	[46.5 ; 90.3]	[47.5 ; 76.8]
Indication domain						
Knowledge of the minimum number of prior lines of therapies needed before starting combination therapy with idelalisib and rituximab in patients with CLL with 17p deletion or *TP53* mutations						
N	131	16	25	26	18	46
n (%)	96 (73.3)	8 (50.0)	21 (84.0)	16 (61.5)	11 (61.1)	40 (87.0)
95% CI	[64.8 ; 80.6]	[24.7 ; 75.3]	[63.9 ; 95.5]	[40.6 ; 79.8]	[35.7 ; 82.7]	[73.7 ; 95.1]

	Overall N=131	France N=16	Germany N=25	Italy N=26	Spain N=18	United Kingdom N=46
Knowledge of the minimum number of prior lines of therapies needed before starting combination therapy with idelalisib and rituximab in patients with CLL with no 17p deletion or *TP53* mutations						
N	131	16	25	26	18	46
n (%)	105 (80.2)	11 (68.8)	22 (88.0)	19 (73.1)	13 (72.2)	40 (87.0)
95% CI	[72.3 ; 86.6]	[41.3 ; 89.0]	[68.8 ; 97.5]	[52.2 ; 88.4]	[46.5 ; 90.3]	[73.7 ; 95.1]
Knowledge of the minimum number of prior lines of therapy necessary before starting monotherapy with idelalisib in patients with FL						
N	131	16	25	26	18	46
n (%)	87 (66.4)	13 (81.3)	14 (56.0)	20 (76.9)	15 (83.3)	25 (54.4)
95% CI	[57.6 ; 74.4]	[54.4 ; 96.0]	[34.9 ; 75.6]	[56.4 ; 91.0]	[58.6 ; 96.4]	[39.0 ; 69.1]
Serious Infection domain						
Knowledge of the risk of serious infection						
N	131	16	25	26	18	46
n (%)	128 (97.7)	15 (93.8)	24 (96.0)	26 (100)	17 (94.4)	46 (100)
95% CI	[93.5 ; 99.5]	[69.8 ; 99.8]	[79.6 ; 99.9]	[86.8 ; 100]	[72.7 ; 99.9]	[92.3 ; 100]
Knowledge of which populations are the risk of serious infection most relevant for						
N	131	16	25	26	18	46
n (%)	71 (54.2)	9 (56.3)	13 (52.0)	12 (46.2)	9 (50.0)	28 (60.9)
95% CI	[45.3 ; 62.9]	[29.9 ; 80.2]	[31.3 ; 72.2]	[26.6 ; 66.6]	[26.0 ; 74.0]	[45.4 ; 74.9]
Knowledge regarding prophylaxis for PJP						
N	131	16	25	26	18	46
n (%)	117 (89.3)	15 (93.8)	21 (84.0)	22 (84.6)	17 (94.4)	42 (91.3)
95% CI	[82.7 ; 94.0]	[69.8 ; 99.8]	[63.9 ; 95.5]	[65.1 ; 95.6]	[72.7 ; 99.9]	[79.2 ; 97.6]

	Overall N=131	France N=16	Germany N=25	Italy N=26	Spain N=18	United Kingdom N=46
Knowledge of recommended length for prophylaxis with PJP during treatment with idelalisib						
N	131	16	25	26	18	46
n (%)	115 (87.8)	15 (93.8)	23 (92.0)	21 (80.8)	16 (88.9)	40 (87.0)
95% CI	[80.9 ; 92.9]	[69.8 ; 99.8]	[74.0 ; 99.0]	[60.6 ; 93.4]	[65.3 ; 98.6]	[73.7 ; 95.1]
Knowledge of which patients should regular clinical and laboratory monitoring for CMV be conducted						
N	131	16	25	26	18	46
n (%)	30 (22.9)	2 (12.5)	6 (24.0)	6 (23.1)	4 (22.2)	12 (26.1)
95% CI	[16.0 ; 31.1]	[1.6 ; 38.3]	[9.4 ; 45.1]	[9.0 ; 43.6]	[6.4 ; 47.6]	[14.3 ; 41.1]
Knowledge of when interruption or discontinuation of idelalisib treatment should be considered for patients who are CMV positive						
N	131	16	25	26	18	46
n (%)	93 (71.0)	7 (43.8)	22 (88.0)	20 (76.9)	13 (72.2)	31 (67.4)
95% CI	[62.4 ; 78.6]	[19.8 ; 70.1]	[68.8 ; 97.5]	[56.4 ; 91.0]	[46.5 ; 90.3]	[52.0 ; 80.5]
Knowledge of when it is appropriate to initiate idelalisib in patients suffering from ongoing systemic infections						
N	131	16	25	26	18	46
n (%)	108 (82.4)	9 (56.3)	21 (84.0)	21 (80.8)	17 (94.4)	40 (87.0)
95% CI	[74.8 ; 88.5]	[29.9 ; 80.2]	[63.9 ; 95.5]	[60.6 ; 93.4]	[72.7 ; 99.9]	[73.7 ; 95.1]
Knowledge of measures required to be taken to minimise potential risk for PJP infections in patients receiving idelalisib						
N	131	16	25	26	18	46
n (%)	122 (93.1)	15 (93.8)	24 (96.0)	22 (84.6)	16 (88.9)	45 (97.8)
95% CI	[87.4 ; 96.8]	[69.8 ; 99.8]	[79.6 ; 99.9]	[65.1 ; 95.6]	[65.3 ; 98.6]	[88.5 ; 99.9]

ANC = absolute neutrophil count, CI = confidence interval, CLL = chronic lymphocytic leukaemia, CMV = cytomegalovirus, FL = follicular lymphoma, PJP = pneumocystis jirovecii pneumonia

Table 7. Effectiveness Endpoints – Primary Knowledge Questions: by Specialisation

	Overall N=131	Haematology N=80	Oncology N=3	Haematology and Oncology N=40	Other N=8
Neutropenia domain					
Knowledge that neutropenia is a risk of idelalisib					
N	131	80	3	40	8
n (%)	120 (91.6)	71 (88.8)	3 (100)	39 (97.5)	7 (87.5)
95% CI	[85.5 ; 95.7]	[79.7 ; 94.7]	[29.2 ; 100]	[86.8 ; 99.9]	[47.3 ; 99.7]
Knowledge of recommended frequency for monitoring ANC during first 6 months of treatment					
N	131	80	3	40	8
n (%)	90 (68.7)	49 (61.3)	1 (33.3)	33 (82.5)	7 (87.5)
95% CI	[60.0 ; 76.5]	[49.7 ; 71.9]	[0.8 ; 90.6]	[67.2 ; 92.7]	[47.3 ; 99.7]
Knowledge of recommended idelalisib dosing if laboratory results reveal ANC < 500/mm^3 in patients receiving idelalisib					
N	131	80	3	40	8
n (%)	89 (67.9)	55 (68.8)	1 (33.3)	29 (72.5)	4 (50.0)
95% CI	[59.2 ; 75.8]	[57.4 ; 78.7]	[0.8 ; 90.6]	[56.1 ; 85.4]	[15.7 ; 84.3]
Indication domain					
Knowledge of the minimum number of prior lines of therapies needed before starting combination therapy with idelalisib and rituximab in patients with CLL with 17p deletion or *TP53* mutations					
N	131	80	3	40	8
n (%)	96 (73.3)	64 (80.0)	2 (66.7)	29 (72.5)	1 (12.5)
95% CI	[64.8 ; 80.6]	[69.6 ; 88.1]	[9.4 ; 99.2]	[56.1 ; 85.4]	[0.3 ; 52.7]

	Overall N=131	Haematology N=80	Oncology N=3	Haematology and Oncology N=40	Other N=8
Knowledge of the minimum number of prior lines of therapies needed before starting combination therapy with idelalisib and rituximab in patients with CLL with no 17p deletion or *TP53* mutations					
N	131	80	3	40	8
n (%)	105 (80.2)	67 (83.8)	3 (100)	31 (77.5)	4 (50.0)
95% CI	[72.3 ; 86.6]	[73.8 ; 91.1]	[29.2 ; 100]	[61.5 ; 89.2]	[15.7 ; 84.3]
Knowledge of the minimum number of prior lines of therapy necessary before starting monotherapy with idelalisib in patients with FL					
N	131	80	3	40	8
n (%)	87 (66.4)	57 (71.3)	1 (33.3)	25 (62.5)	4 (50.0)
95% CI	[57.6 ; 74.4]	[60.0 ; 80.8]	[0.8 ; 90.6]	[45.8 ; 77.3]	[15.7 ; 84.3]
Serious Infection domain					
Knowledge of the risk of serious infection					
N	131	80	3	40	8
n (%)	128 (97.7)	79 (98.8)	3 (100)	39 (97.5)	7 (87.5)
95% CI	[93.5 ; 99.5]	[93.2 ; 100]	[29.2 ; 100]	[86.8 ; 99.9]	[47.3 ; 99.7]
Knowledge of which populations are the risk of serious infection most relevant for					
N	131	80	3	40	8
n (%)	71 (54.2)	41 (51.3)	2 (66.7)	23 (57.5)	5 (62.5)
95% CI	[45.3 ; 62.9]	[39.8 ; 62.6]	[9.4 ; 99.2]	[40.9 ; 73.0]	[24.5 ; 91.5]
Knowledge regarding prophylaxis for PJP					
N	131	80	3	40	8
n (%)	117 (89.3)	76 (95.0)	2 (66.7)	34 (85.0)	5 (62.5)
95% CI	[82.7 ; 94.0]	[87.7 ; 98.6]	[9.4 ; 99.2]	[70.2 ; 94.3]	[24.5 ; 91.5]

	Overall N=131	Haematology N=80	Oncology N=3	Haematology and Oncology N=40	Other N=8
Knowledge of recommended length for prophylaxis with PJP during treatment with idelalisib					
N	131	80	3	40	8
n (%)	115 (87.8)	71 (88.8)	2 (66.7)	35 (87.5)	7 (87.5)
95% CI	[80.9 ; 92.9]	[79.7 ; 94.7]	[9.4 ; 99.2]	[73.2 ; 95.8]	[47.3 ; 99.7]
Knowledge of which patients should regular clinical and laboratory monitoring for CMV be conducted					
N	131	80	3	40	8
n (%)	30 (22.9)	17 (21.3)	0	10 (25.0)	3 (37.5)
95% CI	[16.0 ; 31.1]	[12.9 ; 31.8]	[0.0 ; 70.8]	[12.7 ; 41.2]	[8.5 ; 75.5]
Knowledge of when interruption or discontinuation of idelalisib treatment should be considered for patients who are CMV positive					
N	131	80	3	40	8
n (%)	93 (71.0)	50 (62.5)	1 (33.3)	35 (87.5)	7 (87.5)
95% CI	[62.4 ; 78.6]	[51.0 ; 73.1]	[0.8 ; 90.6]	[73.2 ; 95.8]	[47.3 ; 99.7]
Knowledge of when it is appropriate to initiate idelalisib in patients suffering from ongoing systemic infections					
N	131	80	3	40	8
n (%)	108 (82.4)	68 (85.0)	1 (33.3)	32 (80.0)	7 (87.5)
95% CI	[74.8 ; 88.5]	[75.3 ; 92.0]	[0.8 ; 90.6]	[64.4 ; 90.9]	[47.3 ; 99.7]
Knowledge of measures required to be taken to minimise potential risk for PJP infections in patients receiving idelalisib					
N	131	80	3	40	8
n (%)	122 (93.1)	76 (95.0)	2 (66.7)	37 (92.5)	7 (87.5)
95% CI	[87.4 ; 96.8]	[87.7 ; 98.6]	[9.4 ; 99.2]	[79.6 ; 98.4]	[47.3 ; 99.7]

ANC = absolute neutrophil count, CI = confidence interval, CLL = chronic lymphocytic leukaemia, CMV = cytomegalovirus,
FL = follicular lymphoma, PJP = pneumocystis jirovecii pneumonia

Table 8. Effectiveness Endpoints – Primary Knowledge Questions: by Receipt of the DHPC

	Overall N=131	Yes, I received the DHPC N=92	No, I did not receive the DHPC/I don't know (combined) N=39
Neutropenia domain			
Knowledge that neutropenia is a risk of idelalisib			
N	131	92	39
n (%)	120 (91.6)	86 (93.5)	34 (87.2)
95% CI	[85.5 ; 95.7]	[86.3 ; 97.6]	[72.6 ; 95.7]
Knowledge of recommended frequency for monitoring ANC during first 6 months of treatment			
N	131	92	39
n (%)	90 (68.7)	62 (67.4)	28 (71.8)
95% CI	[60.0 ; 76.5]	[56.8 ; 76.8]	[55.1 ; 85.0]
Knowledge of recommended idelalisib dosing if laboratory results reveal ANC < 500/mm^3 in patients receiving idelalisib			
N	131	92	39
n (%)	89 (67.9)	63 (68.5)	26 (66.7)
95% CI	[59.2 ; 75.8]	[58.0 ; 77.8]	[49.8 ; 80.9]
Indication domain			
Knowledge of the minimum number of prior lines of therapies needed before starting combination therapy with idelalisib and rituximab in patients with CLL with 17p deletion or *TP53* mutations			
N	131	92	39
n (%)	96 (73.3)	74 (80.4)	22 (56.4)
95% CI	[64.8 ; 80.6]	[70.9 ; 88.0]	[39.6 ; 72.2]

	Overall N=131	Yes, I received the DHPC N=92	No, I did not receive the DHPC/I don't know (combined) N=39
Knowledge of the minimum number of prior lines of therapies needed before starting combination therapy with idelalisib and rituximab in patients with CLL with no 17p deletion or *TP53* mutations			
N	131	92	39
n (%)	105 (80.2)	76 (82.6)	29 (74.4)
95% CI	[72.3 ; 86.6]	[73.3 ; 89.7]	[57.9 ; 87.0]
Knowledge of the minimum number of prior lines of therapy necessary before starting monotherapy with idelalisib in patients with FL			
N	131	92	39
n (%)	87 (66.4)	60 (65.2)	27 (69.2)
95% CI	[57.6 ; 74.4]	[54.6 ; 74.9]	[52.4 ; 83.0]
Serious Infection domain			
Knowledge of the risk of serious infection			
N	131	92	39
n (%)	128 (97.7)	90 (97.8)	38 (97.4)
95% CI	[93.5 ; 99.5]	[92.4 ; 99.7]	[86.5 ; 99.9]
Knowledge of which populations are the risk of serious infection most relevant for			
N	131	92	39
n (%)	71 (54.2)	49 (53.3)	22 (56.4)
95% CI	[45.3 ; 62.9]	[42.6 ; 63.7]	[39.6 ; 72.2]
Knowledge regarding prophylaxis for PJP			
N	131	92	39
n (%)	117 (89.3)	84 (91.3)	33 (84.6)
95% CI	[82.7 ; 94.0]	[83.6 ; 96.2]	[69.5 ; 94.1]

	Overall N=131	Yes, I received the DHPC N=92	No, I did not receive the DHPC/I don't know (combined) N=39
Knowledge of recommended length for prophylaxis with PJP during treatment with idelalisib			
N	131	92	39
n (%)	115 (87.8)	84 (91.3)	31 (79.5)
95% CI	[80.9 ; 92.9]	[83.6 ; 96.2]	[63.5 ; 90.7]
Knowledge of which patients should regular clinical and laboratory monitoring for CMV be conducted			
N	131	92	39
n (%)	30 (22.9)	18 (19.6)	12 (30.8)
95% CI	[16.0 ; 31.1]	[12.0 ; 29.1]	[17.0 ; 47.6]
Knowledge of when interruption or discontinuation of idelalisib treatment should be considered for patients who are CMV positive			
N	131	92	39
n (%)	93 (71.0)	65 (70.7)	28 (71.8)
95% CI	[62.4 ; 78.6]	[60.2 ; 79.7]	[55.1 ; 85.0]
Knowledge of when it is appropriate to initiate idelalisib in patients suffering from ongoing systemic infections			
N	131	92	39
n (%)	108 (82.4)	79 (85.9)	29 (74.4)
95% CI	[74.8 ; 88.5]	[77.0 ; 92.3]	[57.9 ; 87.0]
Knowledge of measures required to be taken to minimise potential risk for PJP infections in patients receiving idelalisib			
N	131	92	39
n (%)	122 (93.1)	91 (98.9)	31 (79.5)
95% CI	[87.4 ; 96.8]	[94.1 ; 100]	[63.5 ; 90.7]

ANC = absolute neutrophil count, CI = confidence interval, CLL = chronic lymphocytic leukaemia, CMV = cytomegalovirus, FL = follicular lymphoma, PJP = pneumocystis jirovecii pneumonia

Table 9. Effectiveness Endpoints – Primary Knowledge Levels: by Prescribed Idelalisib in Past 6 months

	Overall N=105	Yes, I have prescribed idelalisib N=70	No, I have not prescribed idelalisib N=35
Neutropenia domain			
Knowledge that neutropenia is a risk of idelalisib			
N	105	70	35
n (%)	96 (91.4)	65 (92.9)	31 (88.6)
95% CI	[84.4 ; 96.0]	[84.1 ; 97.6]	[73.3 ; 96.8]
Knowledge of recommended frequency for monitoring ANC during first 6 months of treatment			
N	105	70	35
n (%)	72 (68.6)	51 (72.9)	21 (60.0)
95% CI	[58.8 ; 77.3]	[60.9 ; 82.8]	[42.1 ; 76.1]
Knowledge of recommended idelalisib dosing if laboratory results reveal ANC < 500/mm^3 in patients receiving idelalisib			
N	105	70	35
n (%)	71 (67.6)	46 (65.7)	25 (71.4)
95% CI	[57.8 ; 76.4]	[53.4 ; 76.7]	[53.7 ; 85.4]
Indication domain			
Knowledge of the minimum number of prior lines of therapies needed before starting combination therapy with idelalisib and rituximab in patients with CLL with 17p deletion or *TP53* mutations			
N	105	70	35
n (%)	84 (80.0)	53 (75.7)	31 (88.6)
95% CI	[71.1 ; 87.2]	[64.0 ; 85.2]	[73.3 ; 96.8]

	Overall N=105	Yes, I have prescribed idelalisib N=70	No, I have not prescribed idelalisib N=35
Knowledge of the minimum number of prior lines of therapies needed before starting combination therapy with idelalisib and rituximab in patients with CLL with no 17p deletion or *TP53* mutations			
N	105	70	35
n (%)	88 (83.8)	58 (82.9)	30 (85.7)
95% CI	[75.3 ; 90.3]	[72.0 ; 90.8]	[69.7 ; 95.2]
Knowledge of the minimum number of prior lines of therapy necessary before starting monotherapy with idelalisib in patients with FL			
N	105	70	35
n (%)	72 (68.6)	50 (71.4)	22 (62.9)
95% CI	[58.8 ; 77.3]	[59.4 ; 81.6]	[44.9 ; 78.5]
Serious Infection domain			
Knowledge of the risk of serious infection			
N	105	70	35
n (%)	104 (99.1)	69 (98.6)	35 (100)
95% CI	[94.8 ; 100]	[92.3 ; 100]	[90.0 ; 100]
Knowledge of which populations are the risk of serious infection most relevant for			
N	105	70	35
n (%)	60 (57.1)	43 (61.4)	17 (48.6)
95% CI	[47.1 ; 66.8]	[49.0 ; 72.8]	[31.4 ; 66.0]

	Overall N=105	Yes, I have prescribed idelalisib N=70	No, I have not prescribed idelalisib N=35
Knowledge regarding prophylaxis for PJP			
N	105	70	35
n (%)	96 (91.4)	63 (90.0)	33 (94.3)
95% CI	[84.4 ; 96.0]	[80.5 ; 95.9]	[80.8 ; 99.3]
Knowledge of recommended length for prophylaxis with PJP during treatment with idelalisib			
N	105	70	35
n (%)	93 (88.6)	62 (88.6)	31 (88.6)
95% CI	[80.9 ; 94.0]	[78.7 ; 94.9]	[73.3 ; 96.8]
Knowledge of which patients should regular clinical and laboratory monitoring for CMV be conducted			
N	105	70	35
n (%)	19 (18.1)	9 (12.9)	10 (28.6)
95% CI	[11.3 ; 26.8]	[6.1 ; 23.0]	[14.6 ; 46.3]
Knowledge of when interruption or discontinuation of idelalisib treatment should be considered for patients who are CMV positive			
N	105	70	35
n (%)	71 (67.6)	46 (65.7)	25 (71.4)
95% CI	[57.8 ; 76.4]	[53.4 ; 76.7]	[53.7 ; 85.4]
Knowledge of when it is appropriate to initiate idelalisib in patients suffering from ongoing systemic infections			
N	105	70	35
n (%)	83 (79.1)	54 (77.1)	29 (82.9)
95% CI	[70.0 ; 86.4]	[65.6 ; 86.3]	[66.4 ; 93.4]

	Overall N=105	Yes, I have prescribed idelalisib N=70	No, I have not prescribed idelalisib N=35
Knowledge of measures required to be taken to minimise potential risk for PJP infections in patients receiving idelalisib			
N	105	70	35
n (%)	99 (94.3)	66 (94.3)	33 (94.3)
95% CI	[88.0 ; 97.9]	[86.0 ; 98.4]	[80.8 ; 99.3]

ANC = absolute neutrophil count, CI = confidence interval, CLL = chronic lymphocytic leukaemia, CMV = cytomegalovirus,
FL = follicular lymphoma, PJP = pneumocystis jirovecii pneumonia

10.5. Other Analyses

Knowledge of non-infection related risks

HCP knowledge on other (non-infection-related risks) associated with Zydelig therapy, are provided for the analysis set overall, and by country in Table 10.

Overall, nearly all HCPs were aware that the following are risks associated with Zydelig therapy: transaminase elevations (92.4%, 95% CI 86.4-96.3), pneumonitis (92.4%, 95% CI 86.4-96.3), and diarrhoea / colitis (96.2%, 95%CI 91.3-98.7). Approximately half of the HCPs were also aware risks of Zydelig therapy include SJS or TEN (54.2%, 95% CI 45.3-62.9). Less than half of the HCPs were aware that migraine and arthritis are not risks associated with Zydelig (48.9%, 95% CI 40.0-57.7 and 42.8% 95% CI 34.1-51.7 respectively).

Some variations across countries were noted in terms of these knowledge levels. Spain had slightly lower levels of awareness that transaminase elevations, pneumonitis, and SJS or TEN, are risks associated with Zydelig therapy (72.2%, 95% CI 46.5-90.3; 83.3, 95% CI 58.6-96.4; 38.9%, 95% CI 17.3-64.3; respectively). Italian HCPs were slightly more aware that migraine was not a risk of Zydelig therapy (65.4%, 95% CI 44.3-82.8). HCPs in both Germany and the UK were less aware that arthritis was not a risk of Zydelig therapy (36.0%, 95% CI 18.0-57.5; 30.4%, 95% CI 17.7-45.8). Finally, HCPs in France were less aware that SJS or TEN, were risks of Zydelig therapy (31.3%, 95% CI 11.0-58.7).

Distribution of Survey Responses

Distribution of the responses to all survey questions are provided for the analysis set overall, and by country, in Table 11. Risks Associated with Zydelig, Primary Source of Information Regarding Risks of Zydelig, and Receipt of the DHPC are presented. The questions pertaining to the risks associated with Zydelig are discussed in detail in the previous sections in terms of knowledge levels, so are not reviewed here in depth.

In terms of primary sources of information regarding the risks of Zydelig, nearly one-third of all HCPs reported that they had received information from the SmPC (29%). Other popular sources of information were: conference / congress (19.1%), journal (15.3%), pharmaceutical company representative - in person (15.3%), and the DHPC from a pharmaceutical company (11.5%). In Spain the most commonly reported primary source of information was a pharmaceutical representative - in person (44.4%) and in Italy this was at a conference/ congress (30.8%). In France and Italy, the DHPC from a pharmaceutical company was not commonly reported as the primary source of information (6.3% and 3.8% respectively).

The majority of all HCPs recalled receiving the DHPC (70.2%). This was slightly higher in Germany (88.0%) and lower in Italy (46.2%).

Table 10. Other Analyses: HCPs' Knowledge of Other Risks Associated with Idelalisib Overall and by Country

	Overall N=131	France N=16	Germany N=25	Italy N=26	Spain N=18	United Kingdom N=46
Transaminase elevations						
N	131	16	25	26	18	46
n (%)	121 (92.4)	16 (100)	25 (100)	25 (96.2)	13 (72.2)	42 (91.3)
95% CI	[86.4 ; 96.3]	[79.4 ; 100]	[86.3 ; 100]	[80.4 ; 99.9]	[46.5 ; 90.3]	[79.2 ; 97.6]
Migraine headaches						
N	131	16	25	26	18	46
n (%)	64 (48.9)	8 (50.0)	14 (56.0)	17 (65.4)	10 (55.6)	15 (32.6)
95% CI	[40.0 ; 57.7]	[24.7 ; 75.3]	[34.9 ; 75.6]	[44.3 ; 82.8]	[30.8 ; 78.5]	[19.5 ; 48.0]
Pneumonitis						
N	131	16	25	26	18	46
n (%)	121 (92.4)	16 (100)	24 (96.0)	24 (92.3)	15 (83.3)	42 (91.3)
95% CI	[86.4 ; 96.3]	[79.4 ; 100]	[79.6 ; 99.9]	[74.9 ; 99.1]	[58.6 ; 96.4]	[79.2 ; 97.6]
Diarrhoea/colitis						
N	131	16	25	26	18	46
n (%)	126 (96.2)	16 (100)	24 (96.0)	24 (92.3)	17 (94.4)	45 (97.8)
95% CI	[91.3 ; 98.7]	[79.4 ; 100]	[79.6 ; 99.9]	[74.9 ; 99.1]	[72.7 ; 99.9]	[88.5 ; 99.9]
Arthritis						
N	131	16	25	26	18	46
n (%)	56 (42.8)	6 (37.5)	9 (36.0)	17 (65.4)	10 (55.6)	14 (30.4)
95% CI	[34.1 ; 51.7]	[15.2 ; 64.6]	[18.0 ; 57.5]	[44.3 ; 82.8]	[30.8 ; 78.5]	[17.7 ; 45.8]
SJS or TEN						
N	131	16	25	26	18	46
n (%)	71 (54.2)	5 (31.3)	15 (60.0)	14 (53.9)	7 (38.9)	30 (65.2)
95% CI	[45.3 ; 62.9]	[11.0 ; 58.7]	[38.7 ; 78.9]	[33.4 ; 73.4]	[17.3 ; 64.3]	[49.8 ; 78.6]

CI = confidence interval

Table 11. Other Analyses: Distribution of All Responses to Survey Questions – Risks Associated With Idelalisib, Primary Source of Information Regarding Risks of Idelalisib, and Receipt of the DHPC, Overall and by Country

	Overall N=131	France N=16	Germany N=25	Italy N=26	Spain N=18	United Kingdom N=46
Question 1: Which of the following are known risks associated with the use of idelalisib?						
Neutropenia (n, %)						
Yes	120 (91.6)	13 (81.3)	25 (100)	23 (88.5)	14 (77.8)	45 (97.8)
No	7 (5.3)	1 (6.3)	0	2 (7.7)	3 (16.7)	1 (2.2)
I don't know/am not sure	4 (3.1)	2 (12.5)	0	1 (3.8)	1 (5.6)	0
MD	0	0	0	0	0	0
Transaminase elevations (n, %)						
Yes	121 (92.4)	16 (100)	25 (100)	25 (96.2)	13 (72.2)	42 (91.3)
No	4 (3.1)	0	0	1 (3.8)	2 (11.1)	1 (2.2)
I don't know/am not sure	6 (4.6)	0	0	0	3 (16.7)	3 (6.5)
MD	0	0	0	0	0	0
Serious infections (n, %)						
Yes	128 (97.7)	15 (93.8)	24 (96.0)	26 (100)	17 (94.4)	46 (100)
No	3 (2.3)	1 (6.3)	1 (4.0)	0	1 (5.6)	0
I don't know/am not sure	0	0	0	0	0	0
MD	0	0	0	0	0	0

	Overall N=131	France N=16	Germany N=25	Italy N=26	Spain N=18	United Kingdom N=46
Migraine headaches (n, %)						
Yes	21 (16.0)	2 (12.5)	3 (12.0)	5 (19.2)	2 (11.1)	9 (19.6)
No	64 (48.9)	8 (50.0)	14 (56.0)	17 (65.4)	10 (55.6)	15 (32.6)
I don't know/am not sure	46 (35.1)	6 (37.5)	8 (32.0)	4 (15.4)	6 (33.3)	22 (47.8)
MD	0	0	0	0	0	0
Pneumonitis (n, %)						
Yes	121 (92.4)	16 (100)	24 (96.0)	24 (92.3)	15 (83.3)	42 (91.3)
No	2 (1.5)	0	1 (4.0)	0	1 (5.6)	0
I don't know/am not sure	8 (6.1)	0	0	2 (7.7)	2 (11.1)	4 (8.7)
MD	0	0	0	0	0	0
Diarrhoea/colitis (n, %)						
Yes	126 (96.2)	16 (100)	24 (96.0)	24 (92.3)	17 (94.4)	45 (97.8)
No	3 (2.3)	0	1 (4.0)	1 (3.8)	1 (5.6)	0
I don't know/am not sure	2 (1.5)	0	0	1 (3.8)	0	1 (2.2)
MD	0	0	0	0	0	0
Arthritis (n, %)						
Yes	24 (18.3)	6 (37.5)	9 (36.0)	3 (11.5)	1 (5.6)	5 (10.9)
No	56 (42.7)	6 (37.5)	9 (36.0)	17 (65.4)	10 (55.6)	14 (30.4)
I don't know/am not sure	51 (38.9)	4 (25.0)	7 (28.0)	6 (23.1)	7 (38.9)	27 (58.7)
MD	0	0	0	0	0	0

	Overall N=131	France N=16	Germany N=25	Italy N=26	Spain N=18	United Kingdom N=46
SJS or TEN (n, %)						
Yes	71 (54.2)	5 (31.3)	15 (60.0)	14 (53.8)	7 (38.9)	30 (65.2)
No	14 (10.7)	3 (18.8)	1 (4.0)	5 (19.2)	3 (16.7)	2 (4.3)
I don't know/am not sure	46 (35.1)	8 (50.0)	9 (36.0)	7 (26.9)	8 (44.4)	14 (30.4)
MD	0	0	0	0	0	0
Question 2: In patients with CLL with 17p deletion or *TP53* mutations, what is the minimum number of prior lines of therapy necessary before starting combination therapy with idelalisib and rituximab? (n, %)						
None	96 (73.3)	8 (50.0)	21 (84.0)	16 (61.5)	11 (61.1)	40 (87.0)
One	28 (21.4)	6 (37.5)	4 (16.0)	8 (30.8)	7 (38.9)	3 (6.5)
Two	4 (3.1)	2 (12.5)	0	1 (3.8)	0	1 (2.2)
I don't know/am not sure	3 (2.3)	0	0	1 (3.8)	0	2 (4.3)
MD	0	0	0	0	0	0
Question 3: In patients with CLL who do not have 17p deletion or *TP53* mutations, what is the minimum number of prior lines of therapy necessary before starting combination therapy with idelalisib and rituximab? (n, %)						
None	5 (3.8)	1 (6.3)	1 (4.0)	1 (3.8)	2 (11.1)	0
One	105 (80.2)	11 (68.8)	22 (88.0)	19 (73.1)	13 (72.2)	40 (87.0)
Two	13 (9.9)	3 (18.8)	2 (8.0)	4 (15.4)	2 (11.1)	2 (4.3)
I don't know/am not sure	8 (6.1)	1 (6.3)	0	2 (7.7)	1 (5.6)	4 (8.7)
MD	0	0	0	0	0	0

	Overall N=131	France N=16	Germany N=25	Italy N=26	Spain N=18	United Kingdom N=46
Question 4: In patients with FL, what is the minimum number of prior lines of therapy necessary before starting monotherapy with idelalisib? (n, %)						
None	0	0	0	0	0	0
One	31 (23.7)	3 (18.8)	10 (40.0)	5 (19.2)	2 (11.1)	11 (23.9)
Two	87 (66.4)	13 (81.3)	14 (56.0)	20 (76.9)	15 (83.3)	25 (54.3)
I don't know/am not sure	13 (9.9)	0	1 (4.0)	1 (3.8)	1 (5.6)	10 (21.7)
MD	0	0	0	0	0	0
Question 5: Regarding the risk of serious infection associated with idelalisib, for which populations is this risk most relevant? (n, %)						
First- or early-line patients	17 (13.0)	2 (12.5)	3 (12.0)	2 (7.7)	2 (11.1)	8 (17.4)
Relapsed/refractory patients	40 (30.5)	4 (25.0)	9 (36.0)	12 (46.2)	7 (38.9)	8 (17.4)
Both of the above patient categories	71 (54.2)	9 (56.3)	13 (52.0)	12 (46.2)	9 (50.0)	28 (60.9)
I don't know/am not sure	3 (2.3)	1 (6.3)	0	0	0	2 (4.3)
MD	0	0	0	0	0	0
Question 6: Which of the following is correct regarding idelalisib treatment and prophylaxis for PJP? (n, %)						
Recommended only for those patients with ANC <500/mm^3	7 (5.3)	1 (6.3)	2 (8.0)	2 (7.7)	1 (5.6)	1 (2.2)
All patients should receive prophylaxis for PJP	117 (89.3)	15 (93.8)	21 (84.0)	22 (84.6)	17 (94.4)	42 (91.3)
Prophylaxis is not recommended	2 (1.5)	0	2 (8.0)	0	0	0
I don't know/am not sure	5 (3.8)	0	0	2 (7.7)	0	3 (6.5)
MD	0	0	0	0	0	0

	Overall N=131	France N=16	Germany N=25	Italy N=26	Spain N=18	United Kingdom N=46
Question 7: What is the recommended length of prophylaxis for PJP during treatment with idelalisib? (n, %)						
For the first 6 months of idelalisib treatment and then discontinue prophylaxis	3 (2.3)	0	1 (4.0)	1 (3.8)	1 (5.6)	0
For the entire length of idelalisib treatment and then discontinue prophylaxis	6 (4.6)	1 (6.3)	0	3 (11.5)	1 (5.6)	1 (2.2)
For the entire length of idelalisib treatment and then for 2-6 months after idelalisib discontinuation, depending on clinical judgement	115 (87.8)	15 (93.8)	23 (92.0)	21 (80.8)	16 (88.9)	40 (87.0)
I don’t know/am not sure	7 (5.3)	0	1 (4.0)	1 (3.8)	0	5 (10.9)
MD	0	0	0	0	0	0
Question 8: For which patients initiating treatment with idelalisib should regular clinical and laboratory monitoring for CMV be conducted?						
All patients (n, %)						
True	70 (53.4)	10 (62.5)	16 (64.0)	14 (53.8)	8 (44.4)	22 (47.8)
False	43 (32.8)	3 (18.8)	7 (28.0)	10 (38.5)	7 (38.9)	16 (34.8)
I don’t know/am not sure	18 (13.7)	3 (18.8)	2 (8.0)	2 (7.7)	3 (16.7)	8 (17.4)
MD	0	0	0	0	0	0
Patients who are CMV-seropositive at the start of idelalisib therapy (n, %)						
True	107 (81.7)	12 (75.0)	23 (92.0)	21 (80.8)	15 (83.3)	36 (78.3)
False	14 (10.7)	3 (18.8)	1 (4.0)	3 (11.5)	1 (5.6)	6 (13.0)
I don’t know/am not sure	10 (7.6)	1 (6.3)	1 (4.0)	2 (7.7)	2 (11.1)	4 (8.7)
MD	0	0	0	0	0	0

	Overall N=131	France N=16	Germany N=25	Italy N=26	Spain N=18	United Kingdom N=46
Patients who have evidence of a history of CMV infection (n, %)						
True	108 (82.4)	12 (75.0)	24 (96.0)	18 (69.2)	16 (88.9)	38 (82.6)
False	16 (12.2)	3 (18.8)	1 (4.0)	5 (19.2)	1 (5.6)	6 (13.0)
I don't know/am not sure	7 (5.3)	1 (6.3)	0	3 (11.5)	1 (5.6)	2 (4.3)
MD	0	0	0	0	0	0
Patients with CMV viraemia but without signs of CMV infection (n, %)						
True	106 (80.9)	11 (68.8)	23 (92.0)	19 (73.1)	15 (83.3)	38 (82.6)
False	16 (12.2)	4 (25.0)	1 (4.0)	3 (11.5)	2 (11.1)	6 (13.0)
I don't know/am not sure	9 (6.9)	1 (6.3)	1 (4.0)	4 (15.4)	1 (5.6)	2 (4.3)
MD	0	0	0	0	0	0
Question 9: For patients who are CMV-seropositive during idelalisib therapy, when should interruption or discontinuation of treatment with idelalisib be considered? (n, %)						
When the patient tests seropositive but is asymptomatic	24 (18.3)	6 (37.5)	3 (12.0)	4 (15.4)	3 (16.7)	8 (17.4)
At the time clinical symptoms of CMV infection become evident	93 (71.0)	7 (43.8)	22 (88.0)	20 (76.9)	13 (72.2)	31 (67.4)
Idelalisib does not need to be interrupted or stopped in such circumstances	8 (6.1)	1 (6.3)	0	2 (7.7)	0	5 (10.9)
I don't know/am not sure	6 (4.6)	2 (12.5)	0	0	2 (11.1)	2 (4.3)
MD	0	0	0	0	0	0

	Overall N=131	France N=16	Germany N=25	Italy N=26	Spain N=18	United Kingdom N=46
Question 10: If the patient is suffering from one or more of the following ongoing systemic infections, is it appropriate to initiate idelalisib?						
Ongoing systemic viral infection (n, %)						
Yes	12 (9.2)	3 (18.8)	4 (16.0)	3 (11.5)	1 (5.6)	1 (2.2)
No	114 (87.0)	11 (68.8)	21 (84.0)	21 (80.8)	17 (94.4)	44 (95.7)
I don't know/am not sure	5 (3.8)	2 (12.5)	0	2 (7.7)	0	1 (2.2)
MD	0	0	0	0	0	0
Ongoing systemic bacterial infection (n, %)						
Yes	10 (7.6)	2 (12.5)	3 (12.0)	2 (7.7)	1 (5.6)	2 (4.3)
No	117 (89.3)	12 (75.0)	22 (88.0)	23 (88.5)	17 (94.4)	43 (93.5)
I don't know/am not sure	4 (3.1)	2 (12.5)	0	1 (3.8)	0	1 (2.2)
MD	0	0	0	0	0	0
Ongoing systemic fungal infection (n, %)						
Yes	13 (9.9)	5 (31.3)	3 (12.0)	3 (11.5)	1 (5.6)	1 (2.2)
No	113 (86.3)	9 (56.3)	22 (88.0)	22 (84.6)	17 (94.4)	43 (93.5)
I don't know/am not sure	5 (3.8)	2 (12.5)	0	1 (3.8)	0	2 (4.3)
MD	0	0	0	0	0	0
Question 11: Which of the following measures should be taken to minimise the potential risk for PJP infections in patients receiving idelalisib?						
Advise all patients to promptly report any new respiratory symptoms (n, %)						
Yes	128 (97.7)	16 (100)	24 (96.0)	26 (100)	16 (88.9)	46 (100)
No	2 (1.5)	0	1 (4.0)	0	1 (5.6)	0
I don't know/am not sure	1 (0.8)	0	0	0	1 (5.6)	0
MD	0	0	0	0	0	0

	Overall N=131	France N=16	Germany N=25	Italy N=26	Spain N=18	United Kingdom N=46
All patients should be monitored for respiratory signs and symptoms throughout treatment with idelalisib (n, %)						
Yes	125 (95.4)	15 (93.8)	25 (100)	22 (84.6)	18 (100)	45 (97.8)
No	3 (2.3)	1 (6.3)	0	2 (7.7)	0	0
I don't know/am not sure	3 (2.3)	0	0	2 (7.7)	0	1 (2.2)
MD	0	0	0	0	0	0
Question 12: What is the recommended frequency for monitoring ANC during the first 6 months of treatment with idelalisib? (n, %)						
Only if clinically indicated	1 (0.8)	0	0	1 (3.8)	0	0
At least every 2 weeks	90 (68.7)	14 (87.5)	20 (80.0)	16 (61.5)	11 (61.1)	29 (63.0)
At least monthly	40 (30.5)	2 (12.5)	5 (20.0)	9 (34.6)	7 (38.9)	17 (37.0)
I don't know/am not sure	0	0	0	0	0	0
MD	0	0	0	0	0	0
Question 13: If laboratory results reveal an ANC <500 per mm3 for a patient being treated with idelalisib, what is recommended regarding idelalisib dosing? (n, %)						
Reduce the dose of idelalisib to 100 mg BID	31 (23.7)	3 (18.8)	7 (28.0)	5 (19.2)	4 (22.2)	12 (26.1)
Continue idelalisib at 150 mg BID	1 (0.8)	1 (6.3)	0	0	0	0
Discontinue treatment with idelalisib	89 (67.9)	11 (68.8)	17 (68.0)	19 (73.1)	13 (72.2)	29 (63.0)
I don't know/am not sure	10 (7.6)	1 (6.3)	1 (4.0)	2 (7.7)	1 (5.6)	5 (10.9)
MD	0	0	0	0	0	0

	Overall N=131	France N=16	Germany N=25	Italy N=26	Spain N=18	United Kingdom N=46
Question 14: Primary Source of information regarding risks of idelalisib (n, %)						
Conference/congress	25 (19.1)	3 (18.8)	5 (20.0)	8 (30.8)	2 (11.1)	7 (15.2)
DHPC/letter from a pharmaceutical company	15 (11.5)	1 (6.3)	4 (16.0)	1 (3.8)	2 (11.1)	7 (15.2)
Colleague	5 (3.8)	0	0	0	1 (5.6)	4 (8.7)
Journal	20 (15.3)	1 (6.3)	4 (16.0)	6 (23.1)	1 (5.6)	8 (17.4)
Scientific association	1 (0.8)	1 (6.3)	0	0	0	0
The internet (e.g., idelalisib product website)	5 (3.8)	2 (12.5)	0	1 (3.8)	1 (5.6)	1 (2.2)
Pharmaceutical company representative (in person)	20 (15.3)	0	5 (20.0)	5 (19.2)	8 (44.4)	2 (4.3)
Summary of Product Characteristics	38 (29.0)	8 (50.0)	7 (28.0)	4 (15.4)	2 (11.1)	17 (37.0)
Not applicable (I did not hear about risks of idelalisib)	0	0	0	0	0	0
Other	2 (1.5)	0	0	1 (3.8)	1 (5.6)	0
MD	0	0	0	0	0	0
Question 15: Do you remember receiving a DHPC letter for idelalisib that included important new information explaining the risks associated with idelalisib? (n, %)						
Yes	92 (70.2)	10 (62.5)	22 (88.0)	12 (46.2)	13 (72.2)	35 (76.1)
No	24 (18.3)	5 (31.3)	0	8 (30.8)	4 (22.2)	7 (15.2)
I don’t know/am not sure	15 (11.5)	1 (6.3)	3 (12.0)	6 (23.1)	1 (5.6)	4 (8.7)
MD	0	0	0	0	0	0

ANC = absolute neutrophil count, BID = twice a day, CLL = chronic lymphocytic leukaemia, CMV = cytomegalovirus, DHPC = Dear Healthcare Professional Communication, FL = follicular lymphoma, MD = missing data, PJP = pneumocystis jirovecii pneumonia

10.6. Adverse Events / Adverse Reactions

This on-line survey did not involve collection of patient-specific clinical outcomes, did not include questions intended to identify an adverse event (AE), and did not include a free text field where HCPs could report an AE. However, it was possible that an AE might have been reported via the study email address. In the event that an AE report was received, AEs were to be reported by sending to Gilead Pharmacovigilance and Epidemiology within 24 hours of awareness at Safety_FC@gilead.com or fax + 1-650-522-5477. Any reported AEs were to be processed and reported to the regulatory agencies in accordance with standard safety reporting procedures.

No AEs were reported in the course of this study.

11. DISCUSSION

11.1. Key Results and Interpretation

The objective of the current study was to determine HCPs' level of knowledge regarding the infection risks associated with Zydelig treatment and the corresponding recommendations to minimise these risks.

Although the recruitment target of 150 respondents was almost achieved, the study closed just below that target (n=142). However, it was determined, given the relatively good response rates within each country, that an adequate number was achieved to identify overall and country specific trends. The current survey response rate was 2.6% (142/5451), which is lower than response rates seen from similar surveys conducted in European countries, where a composite response rate across 7 European risk management measures effectiveness surveys was reported to be 3.7% (2615/70,631: {Qizilbash 2016}. The targeted minimum country responses were met for the Italy, Spain, and the UK.

The primary effectiveness endpoints were analysed in 3 domains. The neutropenia domain consisted of 3 items. Only one of these items, knowledge that neutropenia is a risk of Zydelig (91.6%, 95% CI 85.5-95.7), met the pre-specified threshold of 80% or higher. The other two items approached the 80% threshold; specifically, approximately two-thirds were aware of the recommended frequency for monitoring ANC during the first 6 months of treatments (68.7%, 95% CI 60.0-76.5) and knew the recommended Zydelig dosing if laboratory results revealed ANC <500/mm^3 in patients receiving Zydelig (67.9%, 95% CI 59.2-75.8).

The Zydelig indication domain consisted of 3 items. The pre-specified 80% or higher threshold was met for knowledge of the minimum number of prior lines of therapy needed before starting combination therapy with Zydelig and rituximab in patients with CLL with no 17p deletion or *TP53* mutations (80.2%, 95% CI 72.3-86.6). The remaining 2 items did not meet specifically the minimum number of prior lines of therapies needed before starting combination therapy with Zydelig and rituximab in patients with CLL with 17p deletion or *TP53* mutations (73.3%, 95% CI 64.8-80.6) and the minimum number of prior lines of therapy necessary before starting monotherapy with Zydelig in patients with FL (66.4%, 95% CI 57.6-74.4).

The serious infection domain consisted of 8 items. Five of the 8 items reached the pre-specified 80% knowledge threshold: the risk of serious infection (97.7%, 95% CI 93.5-99.5), measures required to be taken to minimise risk for PJP infections in patients receiving Zydelig (93.1%, 95% CI 87.4-96.8), prophylaxis for PJP (89.3%, 95% CI 82.7-94.0), the recommended length for prophylaxis with PJP during treatment with Zydelig (87.8%, 95% CI 80.9-92.9), and when it is appropriate to initiate Zydelig in patients experiencingexperiencingexperiencing ongoing systemic infections (82.4%, 95% CI 74.8-88.5). The following 2 items did not meet the 80% knowledge level: which populations the risk of serious infection was most relevant for (54.2%, 95% CI 45.3-62.9) and when interruption or discontinuation of Zydelig treatment should be considered for patients who are CMV positive (71.0%, 95% CI 62.4-78.6). Few HCPs knew which patients should receive regular clinical and laboratory monitoring for CMV (22.9%, 95% CI 16.0-31.1). For the composite question regarding which patients should receive regular

clinical and laboratory monitoring for CMV, although the proportion of HCPs who answered all 4 items correctly was low (22.9%, 95% CI 16.0-31.1), knowledge levels for each individual item within this composite outcome was above 80% for 2 items and 53.4% and 32.8% for 2 further items, indicating a higher level of knowledge than the composite score shows.

Performance across countries, in terms of knowledge levels on the effectiveness endpoints, was comparable for most questions.

Knowledge levels of all effectiveness endpoints were largely comparable between HCPs that received the DHPC, and those that did not receive it, or could not recall receiving it. There was little difference in knowledge levels for all effectiveness endpoints between HCPs that had prescribed Zydelig and those that had not.

In terms of other non-infectious risks, knowledge rates regarding the risk were above 80% for: transaminase elevations, pneumonitis, and diarrhoea/ colitis. Approximately half of the HCPs were aware that SJS or TEN is a risk of Zydelig therapy. Less than half of the HCPs were aware that migraine and arthritis are not risks associated with Zydelig, although this could represent a response bias due to the reporting of an item that is not a risk.

Although the majority of all HCPs recalled receiving the DHPC, it was not commonly reported as the primary source of information regarding the risks of Zydelig by HCPs (11.5%), and the SmPC remained the most commonly reported primary source of information regarding the risks of Zydelig therapy, highlighting the importance of this information.

11.2. Limitations

The primary limitation of this cross-sectional study was selection bias due to use of a convenience sample. The impact of selection bias can be minimised through robust outreach to recruit a representative sample. For this study, country selection was carefully considered to obtain a feasible, yet diverse, European sample by including countries from various regions of Europe where Zydelig is commercialised (the countries examined represented 80% of the market for Zydelig in Europe).

Another limitation is that the study relied on self-reporting. It is possible that HCPs may have inaccurately reported the information due to either recall bias or social desirability bias. Additionally, the impact of social desirability reporting bias in this study may be lower than expected. In a web-based survey of 3625 HCPs across 9 EU countries conducted under the Strengthening Collaborations for Operating Pharmacovigilance in Europe joint action initiative, a range of 28% to 97% of HCPs reported receiving and sometimes reading risk communication materials, suggesting HCPs are comfortable giving a truthful response (even if possibly “socially undesirable”) to this type of question {Alqvist-Radstad 2016}.

The low response rate of 2.6% also needs to be taken into account when interpreting results. This is lower than the target, and also lower than comparable European surveys. This can affect the main domain outcome findings, as well as the validity of subgroup comparisons. However, target numbers were reached for Italy, Spain and the UK and results in these countries did not vary greatly from others.

11.3. Generalisability

The 5 European countries that participated in this study were specifically selected to obtain a representative sample of HCPs prescribing Zydelig in the EU. Therefore, the results from this multi-country study are reasonably generalizable to HCPs in Europe who received the Zydelig additional risk minisation measure. The countries selected represented 80% of the Zydelig market. The low variability across countries in terms of responses also suggests that the results are generalizable to other markets. However, due to the low small number of respondents in some countries, and overall low response rate of 2.6%, some caution should be taken when generalising the results to specific countries.

12. OTHER INFORMATION

Not applicable.

13. CONCLUSIONS

In conlusion, whilst the majority of the HCPs received the DHPC, the SmPC was the most commonly reported primary source of information regarding the risks of Zydelig therapy.

Knowledge levels across the 3 domains analysed were overall good. For the neutropenia and Zydelig indication domains, HCPs had 80% or greater knowledge of the information included in the DHPC for only 1 out of the 3 items of each domain. For the serious infection domain, HCPs had 80% or greater knowledge of the information included in the DHPC for 5 out of the 8 items. Knowledge levels of the non-infectious risks of Zydelig were also moderate, with 3 out of 6 items reaching the 80% knowledge threshold. Knowledge levels between those that did, and did not, receive the DHPC were largely comparable.

Based on the results of this study, it appears that the HCPs had generally good knowledge of the infection risks associated with Zydelig treatment and the corresponding recommendations to minimise these risks are adequate.

14. REFERENCES

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Annex 1. List of Stand-Alone Documents

Number	Document reference number	Date	Title
1	Version 1.1	19 April 2017	Protocol
2	Version 1.0	11 October 2017	Survey Questionnaire
3	Version 1.0	27 November 2018	Statistical Analysis Plan
4	Version 1.0	30 October 2018	Statistical Table Shells

Annex 2. Additional Information

None.