# NON-INTERVENTIONAL FINAL STUDY REPORT

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| **Study Title:** | Non-interventional study to assess the safety profile of idelalisib in patients with refractory follicular lymphoma (FL) |
| **EU PAS register number** | EUPAS19618 |
| **Active substance:** | Idelalisib |
| **Medicinal product:** | Zydelig |
| **Study No.:** | GS-EU-313-4172 |
| **Product reference** | EU/1/14/938/001 and EU/1/14/938/002 |
| **Procedure number:** | NA |
| **Marketing authorization holder(s)** | Gilead Sciences Ireland UC, Carrigtohill County Cork, T45 DP77 Ireland |
| **Joint PASS:** | No |
| **Research question and objectives** | To assess the overall safety profile and effectiveness of idelalisib monotherapy in patients with refractory FL |
| **Country(-ies) of study** | Austria, Belgium, France, Germany, Greece, Ireland, Italy, Portugal, Spain, Sweden and the United Kingdom |
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## CONFIDENTIAL STATEMENT

# 1. ABSTRACT

**Study GS-EU-313-4172**
**Gilead Sciences Europe Ltd.**
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**United Kingdom**

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

**Keywords:** Refractory follicular lymphoma, idelalisib

**Rationale and background:** The Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion on the Pharmacovigilance Risk Assessment Committee (PRAC) recommendations following their review under Article 20 of the new safety findings for idelalisib. As a condition of the CHMP recommendations, additional safety information concerning the use of idelalisib to treat patients with refractory follicular lymphoma (FL) was requested. In addition, this study was expanded to include the collection of idelalisib effectiveness parameters.

**Research questions and objectives:**

The objectives of this study were as follows:

- **Primary:** To assess the overall safety profile of idelalisib monotherapy in patients with refractory FL.
  - Adverse Events (AEs) were collected, and rates of Serious AEs (SAEs) were estimated. Focus was given to special health outcomes of interest (HOIs) such as transaminase elevation, hepatocellular injury, severe diarrhea/colitis, pneumonitis, rash, Stevens-Johnson syndrome - Toxic epidermal necrolysis (SJS-TEN), and serious infections (including opportunistic infections such as Pneumocystis jirovecii pneumonia [PJP] and cytomegalovirus [CMV]) as listed in the Zydelig Risk Management Plan (RMP) for Europe (EU) (Version 2.4).
- **Secondary:** To assess the effectiveness of idelalisib monotherapy in patients with refractory FL.
  - Effectiveness of idelalisib was assessed by overall response rate (ORR), duration of response (DOR), progression-free survival (PFS), time to next treatment (TTNT), and overall survival (OS).

**Study Design:** Multi-center, observational, retrospective cohort study.

**Patients and study size:** A sample size of approximately 250 patient-years of idelalisib observation data was targeted. Patients were identified and enrolled in Europe: Austria, Belgium, France, Germany, Greece, Ireland, Italy, Portugal, Spain, Sweden and the United Kingdom.

**Data Sources:** The primary data source was the patient's medical records. Review of electronic or paper medical records and entry of data into the study electronic Case Report Form (eCRF) was performed by trained site personnel. All data was anonymized and collected for those patients meeting all eligibility criteria. Each patient was identified by a unique eCRF generated subject identifier. Medical record abstraction was performed by internal study team members of the site, who were trained on the abstraction method to ensure records were acceptable for review and inclusion in the study. Retrospective data was entered as close to the start of the study as possible. Prospective data was entered as close to the patient's last visit as possible.

**Variables collected**

Patient's data was collected retrospectively from the date of treatment initiation with idelalisib until 6 months after treatment discontinuation or until patient started a new treatment regimen for FL (including entering a clinical trial for an investigational medicinal product [IMP]) or until the latest recorded date or death, whichever was the latest.

The study period can be broken up into the following periods:

- Baseline period: Approximately 30 days prior to idelalisib treatment initiation
- Treatment period: From treatment initiation up to and including the last day of treatment
- Follow-up period: Up to 180 days (6 months) following the conclusion of idelalisib treatment
    - Treatment emergent adverse event (TEAE) Assessment: Time under treatment plus 30 days following idelalisib treatment discontinuation
    - PTAE Assessment: Up to 150 days (5 months) following the TEAE Assessment period

The last possible date for the study period was 28 October 2021.

**Baseline Variables:**

| Subject | Variables Collected |
|---|---|
| Patient characteristics | Year of birth<br>Gender |
| Baseline Disease assessment | Organ (Spleen and/or Liver) assessment<br>Lymph nodes (bulky disease)<br>Bone marrow involvement |
| Medical history | • Follicular Lymphoma History<br>o Date of diagnosis<br>o FL Grade 1, 2 or 3a<br>o Ann Arbor disease stage<br>• Prior treatment regimens for FL:<br>- Drug names for each regimen and number of cycles or duration regimen was administered<br>- Reasons for discontinuation<br>- Start date and end date of last treatment prior to idelalisib<br>• Comorbidities<br>• FL international prognostic index factors<br>• Eastern Cooperative Oncology Group (ECOG) performance status and/or Karnofsky performance status, if available |

**Laboratory Values** (collected at baseline and throughout observation period):

| Subject | Variables Collected |
|---|---|
| Chemistry and Liver function tests and hematology: | Alanine transaminase (ALT) (U/L), Aspartate transaminase (AST) (U/L), Sodium (mmol/L), Potassium (mmol/L), Blood urea nitrogen (mmol/L), Creatinine (umol/L), Alkaline phosphatase (U/L), Total bilirubin (umol/L), Total protein (g/L), Albumin (g/L), Lactate dehydrogenase (U/L), Uric acid (umol/L), Gamma glutamyl transferase (U/L), Hemoglobin (g/L), Lymphocytes (GI/L), Monocytes (GI/L), Neutrophils (GI/L), Platelets (GI/L), Red blood cells (TI/L), and White blood cells (GI/L). |

**Safety Variables:**

Safety variables are categorized as either a treatment emergent (TE), i.e. event that began on or after the date of the first dose of idelalisib and on or before the date of the last dose of idelalisib plus 30 days (i.e. within the treatment period plus month 1 (M1) of follow-up) or post treatment i.e. event that began on or after the beginning of month 2 (M2) of follow-up and before the end of month 6 (M6) of follow-up.

| Subject | Variables collected |
|---|---|
| Safety events | All AEs.<br>HOIs, including bowel perforation, severe diarrhea/colitis, Progressive multifocal leukoencephalopathy (PML), pneumonitis, rash, Stevens-Johnson Syndrome – Toxic Epidermal Necrolysis (SJS-TEN) and serious infections, transaminase elevation and hepatocellular injury.<br>Special situation reports.<br>Pregnancy reports.<br>Death reports. |
| Effectiveness variables | 1) Clinical Response category – Responder/Non-responder<br>2) Radiological confirmation corresponding to clinical response, where available.<br>3) Radiological response assessment, where available -complete response (CR), partial response (PR), and stable disease (SD) (Lugano Criteria 2007 or Lugano Criteria 2014).<br>4) In patients who experience progression – date of documented progression with or without radiological confirmation |

**Idelalisib treatment:**

| Subject | Variables collected |
|---|---|
| Idelalisib administration | Idelalisib dose, treatment duration (days), interruption(s) of dosing, change(s) of dosing. |
| Discontinuation | Date and reason of discontinuation. |

**Concomitant medication:**

| Subject | Variables collected |
|---|---|
| Concomitant medication | Concomitant medications. |

**Statistical methods:** Continuous variables were summarized by mean, standard deviation, median, lower quartile, upper quartile, minimum and maximum. Categorical variables were summarized by number and percentage of patients in each categorical definition including 95% confidence intervals (CIs).

- *Safety Analyses*

- The number and percentage of subjects who experienced at least 1 ≥ Grade 4 TEAEs were listed and summarized
- The incidence of AEs ≥ Grade 3, SAEs, AEs leading to interruption, reduction, or discontinuation of idelalisib, clinically significant laboratory abnormalities, and special HOIs were summarized
- The timing and relationship of idelalisib to ≥ Grade 3 TEAEs, SAEs, AEs leading to interruption, reduction, or discontinuation of idelalisib were also summarized
- Multivariable Poisson regression analyses were used to estimate rates of adverse drug reactions (ADRs), serious adverse drug reactions (SADRs) and HOIs, adjusted for potential confounders (demographics, baseline disease assessment, medical history, treatment history and treatment changes)

- *Effectiveness Analyses*
  - For effectiveness analysis, only subjects who were initiated on idelalisib at least 12 months prior to the start date of effectiveness data collection were included
  - ORR was evaluated in the Effectiveness Analysis Set (subjects who did not have sufficient baseline or on study tumor assessment to characterize response were removed from primary analysis)
  - Estimates and the corresponding 95% CIs based on the Clopper-Pearson exact method were provided
  - The time-to-event effectiveness endpoints including PFS, DOR, and OS were analyzed using the Kaplan Meier (KM) method in the Full Analysis Set, and the analyses of DOR included subjects who achieved a clinical response
  - Kaplan Meier curves were used to illustrate all time to event data
  - Multivariable Cox regression models were fitted for each of the effectiveness endpoints adjusting for potential confounders (demographics, baseline disease assessment, medical history, treatment history, treatment changes and duration of exposure)
  - The proportional hazards assumptions for Cox regression models were assessed graphically and using Schoenfeld residuals

**Results:**

The study included a total of 247 patients, of which 198 were evaluated for effectiveness. The study investigation focused on patients with refractory FL treated with idelalisib.

Patient characteristics were similar between the effectiveness analysis set (EAS) and full analysis set (FAS). Within the FAS, the median age of patients was 67 years (range: 57-75 years). The majority of patients were male (54.7%). The median time from diagnosis was 5.7 years (IQR: 3.1 – 9.5). The majority of patients had an FL grade ≥ 2 (50.6%) and Ann Arbor stage IV at treatment initiation (50.2%). Approximately 26.3% and 23.1% of patients had an ECOG performance status of 0 and 1, respectively. The mean duration of time from diagnosis to initiation of idelalisib was 7 (StD: 5.4) years.

Overall, 237 (96%) patients experienced any TEAE, equating to an adjusted rate of 3.21 per person-years (95% CIs: 2.60, 3.96). Those that were classified as Grade 3 or 4 or categorized as serious were experienced by 154 (62.3%) and 133 (53.8%) patients respectively. The number of patients who experienced a TEAE related to idelalisib was 174 (70.4%), equating to an adjusted rate of 1.55 per person-years (95% CIs: 1.25, 1.93).

A total of 55 (22.3%) patients experienced a PTAE. Those that were classified as Grade 3 or 4 or categorized as serious were experienced by 22 (8.9%) and 26 (10.5%) patients, respectively. The adjusted rate of experiencing any PTAE was 0.19 per person-year (95% CIs: 0.14, 0.25).

Among the patients in the EAS, the ORR was 57.6% (95% CIs: 50.4, 64.6), while the median DOR was 21.9 months (95% CIs: 11.8, 27.6). Additionally, median PFS was 12.2 months (95% CIs: 8.4, 16.1), while median OS was not reached.

**Discussion:**

This study was conducted to ascertain the risk-benefit balance of idelalisib monotherapy for the treatment of patients with refractory follicular lymphoma. The study population corresponds to the usual profile of later line FL patients (i.e., elderly, heavily pre-treated with advanced disease). Within the treatment period and the first month of follow-up, 96% of patients had experienced an AE and 10.9% had died.

The majority of patients (70.4%) received 150 mg dose of idelalisib with a median duration of exposure to idelalisib of 6.7 months. The duration of exposure, patient demographics and disease characteristics of this refractory FL population were comparable to the registrational Study 101-09. As is the case with Study 101-09, subjects in this study were drawn from a patient population that was highly refractory and heavily pretreated with a median of 3 therapies.

The occurrence for HOI ≥ grade 3 infections was 11.7% and for HOI ≥ grade 3 diarrhea and/or colitis was 7.3%, which was slightly lower than observed in the registration Study 101-09, 26.4% and 19.2% respectively. SAEs were reported in about half of the patients and TEAEs were consistent with Study 101-09. Permanent discontinuation of idelalisib due to TEAEs was 71.7% (which includes disease progression and lack of efficacy, in addition to AEs). This value is inflated, though, as some sites entered progressive disease or lack of efficacy as an AE term. In other words, patients who were determined to have discontinued idelalisib due to an AE could have experienced an AE, progressive disease, or lack of efficacy. From Table 3, approximately 39.3% of patients discontinued idelalisib due to an AE, which is higher than the 28% reported in Study 101-09. However, it is important to note that the current study was conducted using real-world data, while Study 101-09 was a Phase 2 clinical trial of a relatively new molecule. Clinical trials often have strict selection criteria, making it difficult to generalize the findings to the real-world population of patients who might receive the intervention of interest.

The overall response rate (ORR) in the efficacy evaluable (n=198) study population was 57.6% which was remarkably similar to that was observed in the registrational Study 101-09 (57.6%) (Wagnor-Johnston 2019). In this highly refractory population, idelalisib demonstrated a clinically meaningful PFS of 12.2 months, consistent with the 11.0 months PFS reported at the 6-year follow-up of Study 101-09. In the current study, median OS was not reached which is unsurprising given the limited follow-up for survival in this study; the observed median OS for the registrational study 101-09 was greater than 5 years (61.2months).

**Conclusion:**

The conclusions for the study are as follows:

- Safety:
    - A large proportion of patients experienced AEs due to idelalisib.
        - The majority were grade ≥3 and related to idelalisib therapy.
    - No new safety signals were observed
    - In general, the safety findings are similar to those in the registrational study 101-09 and representative of the established safety profile of idelalisib in an older, previously treated, highly refractory FL population.
- Effectiveness:
    - Idelalisib was effective in the FL population (ORR= 57.6%).
        - 18.7% of the patients achieved a CR, while 38.9% of the patients achieved a PR.
    - In this highly refractory and heavily pre-treated population, patients receiving idelalisib achieved a clinically meaningful PFS (KM estimate of 12.2 months) and median survival was not reached. The DOR was approximately 21.9 months.
- These findings corroborate those from the registrational study (Study 101-09) of idelalisib in patients with relapsed/ refractory follicular lymphoma and demonstrate that the overall risk-benefit balance remains favorable in this patient group who have limited treatment options.

**Marketing Authorization Holder:** Gilead Sciences Ireland UC, Carrigtohill County Cork, T45 DP77 Ireland