NON-INTERVENTIONAL POST-AUTHORIZATION SAFETY STUDY REPORT

Prospective non-interventional post authorization safety study (PASS) of idelalisib in Germany

Final Study Report

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1. ABSTRACT

Title

Prospective non-interventional post authorization safety study (PASS) of idelalisib in Germany

Keywords

CLL ▪ FL ▪ therapy ▪ Germany ▪ non-interventional

Rationale and background

The efficacy and safety of idelalisib was established by data from randomized and single arm clinical trials in patients with chronic lymphocytic leukemia (CLL) and indolent non-Hodgkin's lymphoma (iNHL), such as Gilead sponsored trials GS-US-312-0116 (NCT01539512) and extension study GS-US-312-0117 (NCT01539291) and 101-09 (NCT01282424). These clinical studies investigated the efficacy and safety of idelalisib in predefined populations, therefore providing high internal validity.

Data generated in real-life settings allows for investigating the external validity of the effects seen in clinical studies. Thus, the real-life treatment outcomes of the drug can be investigated in observational studies such as non-interventional studies (NIS). This prospective NIS of idelalisib in subjects with CLL and follicular lymphoma (FL) allowed the evaluation of up to 3 years treatment outcomes and confirmation of the safety profile for idelalisib.

Study design

Two-cohort (CLL and FL) prospective non-interventional study (NIS)

Setting

Hospitals and private practitioners, specialized on treating oncological patients in Germany.

Subject and study size, including dropouts

The NIS was planned to enroll 300 study subjects in total in about 100 participating sites in Germany.

Between September 2015 and May 2020, a total of 179 study subjects (screening failure: n=2) were enrolled into the study by 60 sites. 147 subjects were included in the final analysis (125 CLL cohort, 22 FL cohort) and 30 subjects were excluded from final analysis due to protocol violations, including off-label use.

Enrolled subjects were adults (aged ≥18 years) diagnosed with CLL or FL and with decision for treatment with idelalisib in routine clinical practice and in accordance with the Summary of Product Characteristics (SmPC).

Idelalisib was administered in routine clinical practice until progressive disease, death, unacceptable toxicity, or discontinuation due to other reasons, whichever occurred first. Subjects were observed for a maximum of 36 months or until discontinuation of idelalisib.

Treatment periods (TP 01 – TP 12) were defined as respective consecutive documentation periods of 3 months (+/- 4 weeks).

Variables and Data Sources

Primary Endpoints

Effectiveness:

- Progression Free Survival (PFS) (rate and time to progression)
- Overall Response Rate (ORR)
- Overall Survival (OS) (rate and survival duration)

Secondary Endpoints

Safety:

The safety data collected included Adverse Drug Reactions (ADRs), Serious Adverse Drug Reactions (SADRs) and fatal events (regardless of causality). Fatal events could be either fatal SADR (assessed as related to idelalisib treatment) or fatal Serious Adverse Events (SAE) (assessed as non-related). Adverse Events (AEs) and SAEs (except for fatal events) not related to idelalisib were not collected.

- Incidence of ADRs and SADRs as well as fatal SAEs (regardless of causality) and cause of death
- Incidence, risk factors, management, and outcome of ADRs of special interest:
  - diarrhea/colitis
  - pneumonitis
  - liver enzyme elevation
- Type, incidence, and outcome of Special Situation Reports (SSRs)
- Health resource utilization: frequency and type of hospitalization

Quality of Life:

Patient-Reported Outcome (PRO); physical and mental health-related quality of life and health status using standardized, general, and disease-specific questionnaires:

- European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ)-C30
- EORTC QLQ-CLL16
- SF-12 Health Survey

Results

Primary Endpoints

Progression Free Survival:

- CLL cohort: Median PFS was not reached with an estimated 6-month PFS rate of 82.25% (95% CI: 73.51 - 88.33) [censored: n=95 (76.00%)].
- FL cohort: Median PFS was 3.5 months (95% CI: 2.3 – 7.7) with an estimated 6-month PFS rate of 32.15% (95% CI: 13.23 - 52.92) [censored: n=8 (36.36%)].

Overall Survival:

- CLL cohort: Median OS was not reached with an estimated 6-month OS rate of 91.62% (95% CI: 84.43 - 95.58) [censored: n=107 (85.60%)].
- FL cohort: Median OS was not reached with an estimated 6-month OS rate of 77.16% (95% CI: 49.74 - 90.82) [censored: n=17 (77.27%)].

Overall Response Rate:

- CLL cohort: The ORR (n=88) was 70.40% (95% CI: 61.86 - 77.72) with a Complete Remission (CR) reported in 12 (9.60%) subjects and a Partial Remission (PR) in 76 (60.80%) subjects.
- FL cohort: The ORR (n=8) was 36.36% (95% CI: 19.64 - 57.14) with all 8 subjects reported with a PR. No FL subjects were reported with a CR.

Overall Response Rate II (only subjects with at least one response assessment):

- CLL cohort: 109 subjects were documented with at least one response assessment, resulting in an ORR II (n=88) of 80.73% (95% CI: 72.26 - 87.11).
- FL cohort: 17 subjects were documented with at least one response assessment, resulting in an ORR II of 47.06% (95% CI: 26.16 - 69.04).

Secondary Endpoints

Idelalisib Therapy:

- Number of study subjects with documented idelalisib treatment:

	TP 01	TP 02	TP 03	TP 04	TP 05	TP 06	TP 07	TP 08	TP 09	TP 10	TP 11	TP 12
CLL	n=125	n=92	n=73	n=49	n=36	n=27	n=22	n=17	n=14	n=12	n=11	n=11
FL	n=22	n=14	n=9	n=3	n=2	n=2	n=2	n=2	n=1	n=0	n=0	n=0

- Duration of therapy, i.e., observation period:
  - CLL cohort: The median observation time was 10.0 months (95% CI: 7.5 – 12.2) with 39 (31.20%) censored subjects. The 6-month observation rate was 67.58% (95% CI: 58.10 - 75.36).
  - FL cohort: The median observation time was 6.8 months (95% CI: 3.6 – 8.7) with 7 (31.82%) censored subjects. The 6-month observation rate was 53.69% (95% CI: 29.23 - 73.02).

- Number of subjects with ADRs and SADRs / fatal SADRs:
  - 93 (63.27%) subjects in the total subject population (CLL: n=82 CLL; FL: n=11) were documented with ≥1 ADR (184 events in total).
    - Of these, 52 (35.37%) subjects (CLL: n=48; FL: n=4) were reported with ≥1 SADR (73 events in total).
    - In 7 (4.76%) subjects (CLL: n=6; FL: n=1), the SADR was fatal (9 events in total, for two subjects two events were reported each). The reported fatal events (PT) were disease progression, lymphoma transformation (both for the same subject), urinary tract infection, multiple organ dysfunction syndrome (both for the same subject), bronchopulmonary aspergillosis, febrile neutropenia, pneumonia, pneumonitis, and diarrhoea.

- Most frequent ADRs (PT):
  - CLL cohort: The most frequently (≥3 subjects) reported ADRs were diarrhoea (n=35; 28.00%), pyrexia (n=6; 4.80%), pneumonia (n=5; 4.00%), alanine aminotransferase increased, fatigue, leukopenia, neutropenia, neutrophil count decreased (each n=4; 3.20%), aspartate aminotransferase increased, and pruritus (each n=3; 2.40%).
  - FL cohort: The most frequently (≥2 subjects) reported ADRs were diarrhoea (n=8; 36.36%), rash (n=3; 13.64%), and nausea (n=2; 9.09%).

- Incidence rate of ADRs (PT):
  - CLL cohort: The highest number of ADR events was reported for diarrhoea (35 subjects with ≥1 event) with an incidence rate at 0.334 events/person-year. The second highest number of ADR events was reported for pyrexia (6 subjects with ≥1 event) with an incidence rate of 0.053 events/person-year.
  - FL cohort: The highest number of ADR events was reported for diarrhoea (8 subjects with 1 event each) with an incidence rate of 0.833 events/person-year. The second highest number of ADR events was reported for rash (3 subjects with 1 event each) with an incidence rate of 0.269 events/person-year.

- Incidence rate of SADRs (PT):
  The highest number of SADR events was reported for diarrhoea (14 subjects with 1 event each) with an incidence rate of 0.111 events/person-year. Pneumonia (6 subjects with 1 event each) was the SADR with the second highest number of events with an incidence rate of 0.048 events/person-year.

- Fatal SAEs (PT):
  In total, 18 (12.24%) subjects (CLL: n=14; FL: n=4) were reported with non-related fatal SAEs (18 events). The reported fatal SAEs included chronic lymphocytic leukemia transformation, death (3 subjects), disease progression (2 subjects), embolism, lymphoma, multiple organ dysfunction syndrome, neoplasm malignant, Non-Hodgkin's lymphoma, pneumococcal sepsis, pneumonia (2 subjects), sepsis, sudden death, tumor lysis syndrome, and urinary tract infection.

- Overall number of death cases:
  24 subjects died in total (CLL: n=19 (1 subject was recorded with both related and non-related fatal SAEs); FL: n=5)
  - 7 subjects (9 events) were reported with fatal SADRs (see PTs above)
  - 18 subjects (18 events) were reported with non-related fatal SAEs (see PTs above)

Resource Utilization, i.e., Hospitalization:

- CLL cohort: 33 (26.40%) subjects were reported with hospitalization during TP 01 (32 unplanned), 19 (20.65%) subjects during TP 02 (18 unplanned), and 21 (28.77%) subjects during TP 03 (20 unplanned). Across all TPs, the majority of documented hospitalizations were unplanned.
- FL cohort: 7 (31.82%) subjects were reported with hospitalization during TP 01 (6 unplanned) and 2 (14.29%) subjects during TP 02 (both unplanned). No subjects were hospitalized in TP 03. All documented hospitalizations but 2 were unplanned.

Quality of Life:

The mean score of Global Health Status at baseline was 50.4 (StD = 22.53) out of a maximum score of 100. There was no major change in the mean score of Global Health Status between baseline and TP 01 (mean: 55.7; StD = 20.10) and subsequent TPs.

The number of analyzable questionnaires decreased throughout the TPs (from baseline (n=133) to TP 12 (n=8). The variation in scores across TPs was high.

Discussion

In total, 125 CLL subjects with a median observation time of 10.0 months were included in the final analysis and effectiveness data give an indication how clinical efficacy translates into effectiveness in routine clinical practice.

The enrolment rate was lower than expected, probably due to a change in the therapeutic landscape. Both median PFS and median OS were not reached, neither for the entire CLL cohort nor for subjects with *TP53* aberrations or unmutated *IGHV* status. The ORR and ORR II in the CLL cohort were similar to response rates seen in the pivotal clinical trial (GS-US-312-0016). Although these results are subject to limitations, they confirm the efficacy of idelalisib reported previously in clinical studies, including the efficacy in high-risk CLL patients with *TP53* aberrations.

Median PFS in the FL cohort was short compared to previously published clinical study data on idelalisib use in FL patients. However, these results have to be interpreted with caution due to the small number of FL subjects (N=22).

During the study, care was taken to ensure that idelalisib was used according to the current applicable version of the SmPC. Despite this, subjects were documented with off-label use and data from the date that the off-label use began were excluded from the analysis.

The main reason for end of treatment in the CLL cohort was inacceptable toxicity in 47% of subjects. This underlines the importance of therapy management and management of ADRs in patients treated with idelalisib.

No new safety signals were observed in the NIS. The most frequently reported ADRs (PT) were diarrhoea, nausea, pneumonia, rash, fatigue, increased liver enzymes (Aspartate Transaminase (AST) and Alanine Transaminase (ALT)) and leukopenia, which corresponds to previously published data.

The results of the quality of life questionnaires do not indicate a significant worsening of health-related quality of life during idelalisib treatment. However, since many subjects dropped out of the study for various reasons, their quality of life was also not further assessed.

Marketing Authorization Holder
The Marketing Authorization Holder for Zydelig® is Gilead Sciences Ireland UC, Carrigtohill, County Cork, T45 DP77, Ireland.

Names and affiliations of principal investigators
A list with all the participating investigators in this study is provided as a stand-alone document in Appendix 1.

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