# FINAL SYNOPTIC CLINICAL STUDY REPORT

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| **Study Title:** | A Phase 1b/2 Study of Idelalisib in Combination with BI 836826 in Subjects with Chronic Lymphocytic Leukemia |
| **Name of Test Drug:** | Idelalisib (IDL, Zydelig®, GS-1101) |
| **Dose and Formulation:** | 50 mg IDL twice daily<br>50-mg tablets |
| **Indication:** | Chronic Lymphocytic Leukemia (CLL) |
| **Sponsor:** | Gilead Sciences, Inc.<br>333 Lakeside Drive<br>Foster City, CA 94404 USA |
| **Study No.:** | GS-US-312-1579 |
| **Phase of Development:** | Phase 1b/2 |
| **IND No.:**<br>**EudraCT No.:** | 101254<br>Not applicable |
| **ClinicalTrials.gov Identifier:** | NCT02538614 |
| **Study Start Date:** | 29 December 2015 (First Subject Screened) |
| **Study End Date:** | 05 July 2017 (Last Subject Last Observation for the Primary Endpoint) |
| **Principal or Coordinating Investigator:** | Name: Farrukh Anwan, MD<br>Affiliation: PPD |
| **Gilead Responsible Medical Monitor:** | Name: Ronald Dubowy, MD<br>Telephone: PPD<br>Fax: PPD |
| **Report Date:** | 09 April 2018 |

**CONFIDENTIAL AND PROPRIETARY INFORMATION**

This study was conducted in accordance with the guidelines of Good Clinical Practice, including archiving of essential documents.

# STUDY SYNOPSIS

**Study GS-US-312-1579**
**Gilead Sciences, Inc.**
**333 Lakeside Drive**
**Foster City, CA 94404**
**US**

**Title of Study:** A Phase 1b/2 Study of Idelalisib in Combination with BI 836826 in Subjects with Chronic Lymphocytic Leukemia

**Investigators:** Awan, F and PPD

**Study Centers:** 2 sites in the United States (US, USA)

**Publications:** There were no publications at the time of this CSR

**Study Period:**

29 December 2015 (First Subject Screened)
05 July 2017 (Last Subject Last Observation for the Primary Endpoint)

**Phase of Development**: Phase 1b/2

**Objectives:**

The primary objectives of this study were as follows:

- Phase 1b: To determine the safety and tolerability of the combination of idelalisib (IDL) with BI 836826 in subjects with relapsed/refractory (R/R) chronic lymphocytic leukemia (CLL), and to establish the maximum recommended Phase 2 combination dose (highRP2D) as well as an alternate lower recommended Phase 2 combination dose (lowRP2D)
- Phase 2: To determine the rates of complete response (CR) and of minimal residual disease (MRD) negativity with the combination at the highRP2D and lowRP2D

The secondary objectives of this study were as follows:

- Phase 1b and 2: To evaluate overall response rate (ORR), progression-free survival (PFS), duration of complete response (DCR), duration of response (DOR), and overall survival (OS)
- Phase 2: To further characterize the safety and tolerability of the combination using the highRP2D and the lowRP2D

The exploratory objectives of this study were as follows:

- To evaluate the pharmacokinetics (PK) of IDL and BI 836826 in combination
- To evaluate biomarkers and their association with response to therapy

**Methodology:**

The Phase 1b portion of the study was designed to evaluate various dose combinations of IDL and BI 836826 in sequential cohorts following an initial 7-day IDL monotherapy run-in period. However, enrollment to this study was closed during Phase 1b following an updated feasibility assessment in relation to changes in standard of care. Due to the early study termination, only the 50-mg IDL twice daily dose was administered.

**Number of Subjects (Planned and Analyzed):**

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| Planned: | Approximately 42 subjects | |
| Analyzed: | All Enrolled Analysis Set: | 2 subjects |
| | Safety Analysis Set | 2 subjects |

**Diagnosis and Main Criteria for Inclusion**:

Diagnosis: R/R B-cell CLL

Main Criteria for Inclusion: subjects must have met the following inclusion criteria to be eligible for participation in the study:

- Male or female ≥ 18 years of age
- Diagnosis of B-cell CLL, with diagnosis established according to modified International Workshop on Chronic Lymphocytic Leukemia (IWCLL) criteria and documented within medical records
- Chronic lymphocytic leukemia that warranted treatment (consistent with accepted IWCLL criteria for initiation of therapy). Any of the following conditions constitute CLL that warranted treatment:
  - Evidence of progressive marrow failure as manifested by the onset or worsening of anemia and/or thrombocytopenia
  - Massive (ie, lower edge of spleen ≥ 6 cm below the left costal margin), progressive, or symptomatic splenomegaly
  - Massive (ie, ≥ 10 cm in the longest diameter), progressive, or symptomatic lymphadenopathy
  - Progressive lymphocytosis in the absence of infection, with an increase in blood absolute lymphocyte count (ALC) ≥ 50% over a 2-month period or lymphocyte doubling time of < 6 months (as long as initial ALC was ≥ 30,000/L)
  - Autoimmune anemia and/or thrombocytopenia that was poorly responsive to corticosteroids or other standard therapy
  - Constitutional symptoms, defined as any 1 or more of the following disease-related symptoms or signs occurring in the absence of evidence of infection:
    - Unintentional weight loss of ≥ 10% within the previous 6 months
    - Significant fatigue (≥ Grade 2)

  - Fevers > 100.5°F or 38.0°C for ≥ 2 weeks
  - Night sweats for > 1 month
- Clinically quantifiable disease burden defined as ALC > 5000/µl in peripheral blood

- Discontinuation of all cytotoxic chemotherapy and anti-CD20 antibody therapy for ≥ 4 weeks, alemtuzumab for ≥ 8 weeks, targeted therapy for ≥ 2 weeks, and investigational therapy for ≥ 3 weeks before enrollment (Phase 1b) or randomization (Phase 2). For subjects with relapsed CLL most recently treated with B-cell receptor (BCR) pathway inhibitors who, in the opinion of the investigator, would not tolerate waiting 3 weeks, a washout period of > 5 half-lives was allowed. If on a systemic corticosteroid, the dose must have been stable for the previous 4 weeks.
- All acute non-hematologic toxic effects of any prior antitumor therapy resolved to Grade ≤ 1 before enrollment with the exception of alopecia or neurotoxicity (Grade 1 or 2 neurotoxicity permitted)
- Eastern Cooperative Oncology Group (ECOG) score of 0, 1, or 2
- Required baseline laboratory data (within 4 weeks prior to enrollment) as specified in the protocol
- For female subjects of child-bearing potential, willingness to use a protocol-recommended method of contraception from the Screening visit (Visit 1) throughout the study, and for 30 days after the last dose of IDL or 12 months from the last dose of BI 836826 (whichever was later)
- For male subjects of reproductive potential having intercourse with females of child-bearing potential, willingness to use a protocol-recommended method of contraception from enrollment (Day 1) throughout the study and for 90 days following the last dose of IDL or 12 months following the last dose of BI 836826 (whichever was later), and to refrain from sperm donation from enrollment (Day 1) throughout the study and for 90 days following the last dose of IDL or 12 months following the last dose of BI 836826 (whichever was later).
- In the judgment of the investigator, participation in the protocol offered an acceptable benefit-to-risk ratio when considering current CLL disease status, medical condition, and the potential benefits and risks of alternative treatments for CLL
- Willingness and ability to comply with scheduled visits, drug administration plan, imaging studies, laboratory tests, other study procedures, and study restrictions, including mandatory prophylaxis for *Pneumocystic jirovecii* pneumonia
- Evidence of a personally signed informed consent indicating that the subject was aware of the neoplastic nature of the disease and had been informed of the procedures to be followed, the experimental nature of the therapy, alternatives, potential benefits, possible side effects, potential risks and discomforts, and other pertinent aspects of study participation

**Duration of Treatment:** IDL was planned to be administered twice daily from Study Day 1 until disease progression, intolerable toxicity, of if peripheral blood and bone marrow were negative at or after Week 50. BI 836826 was planned to be administered as 18 doses from Week 2 through Week 46.

Enrollment to this study was closed on 26 April 2017 following an updated feasibility assessment in relation to changes in standard of care. The 2 subjects enrolled as of that date were allowed to remain on study.

**Test Product, Dose, Mode of Administration, and Lot No.:**

Idelalisib tablets were taken orally twice daily at approximately the same time each day until end of treatment. Ideally, doses were taken at approximately 12-hour intervals. IDL was supplied as round, pink, film-coated 50-mg tablets with lot numbers CV1404C1 and CV1604B1.

BI 836826 was administered intravenously as a rate-controlled infusion. An initial dose of 10 mg was administered on Day 8. Doses of 50 mg were administered on Day 9 and Day 15. The full assigned dose of 100 mg was administered on Day 22, every 2 weeks thereafter through Week 18, and every 4 weeks thereafter through Week 46. BI 836826 was provided as a concentrate for solution for infusion (10 mg/mL), each vial contained 100 mg active ingredients (10 mg/mL) with lot number E3688F01.

**Reference Therapy, Dose, Mode of Administration, and Batch No.:** None.

**Criteria for Evaluation:**

**Efficacy:** No efficacy analyses were conducted for this report. The investigator's assessment of overall response was collected and is presented in Appendix 16.2, Listing 16.2.5.

**Pharmacokinetics**: No pharmacokinetic analyses were conducted for this report.

**Safety:** Safety was evaluated by assessment of clinical laboratory tests, physical examinations, 12-lead electrocardiograms (ECGs), vital sign measurements, and documentation of AEs.

**Statistical Methods:**

**Efficacy:** No efficacy analyses were conducted for this report.

**Pharmacokinetics:** No pharmacokinetic analyses were conducted for this report.

**Safety:** Clinical and laboratory AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 20.0. System organ class, preferred term (PT), and reported term were provided in the AE listings.

Adverse events were graded by the investigator as Grade 1, 2, 3, 4, or 5 according to the National Cancer Institutes' Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 4.03. The severity grade of events for which the investigator did not record severity will be categorized as "missing" for data listings.

A serious adverse event (SAE) was defined as an event that, at any dose, resulted in any of the following:

- Death
- Life-threatening (an event in which the subject was at risk of death at the time of the event)
- In-patient hospitalization or prolongation of existing hospitalization

- Persistent or significant disability/incapacity
- A congenital anomaly/birth defect
- A medically important event or reaction: such events may not have been immediately life-threatening or resulted in death or hospitalization but may have jeopardized the subject or may have required intervention to prevent 1 of the other outcomes constituting SAEs. Medical and scientific judgment was exercised to determine whether such an event was reportable under expedited reporting rules.

A treatment-emergent adverse event (TEAE) was defined as any of the following:

- Any AE with an onset date on or after the study drug start date and no later than 30 days after permanent discontinuation of study drug
- Any AE leading to premature discontinuation of study drug

All AEs presented in this report were treatment emergent and are referred to as AEs in this report.

All AEs and SAEs were listed based on the Safety Analysis Set.

**T**oxicity grades (Grade 0 to Grade 4) were assigned to laboratory results for analysis. Grade 0 included all values that did not meet the criteria for an abnormality of at least Grade 1. For laboratory tests with criteria for both increased and decreased levels, analyses for each direction (ie, increased, decreased) were presented separately.

Treatment-emergent laboratory abnormalities were defined as values that increased at least 1 toxicity grade from Baseline at any postbaseline time point, up to and including the date of last dose of study drug plus 30 days for subjects who permanently discontinued study drug. If the relevant baseline laboratory value was missing, any abnormality of at least Grade 1 observed within the time frame specified above will be considered treatment emergent.

Liver-related abnormalities after initial study drug dosing were examined using the following laboratory test values for postbaseline measurements:

- Aspartate aminotransferase (AST): > 3 times the upper limit of normal (ULN)
- Alanine aminotransferase (ALT): > 3 × ULN
- Total bilirubin: > 1.5 × ULN
- Alkaline phosphatase (ALP): > 1.5 × ULN
- ALP < 2 × ULN and total bilirubin > 2 × ULN

The listings included laboratory data from all postbaseline visits up to 30 days after the last dose of study drug. For individual laboratory tests, subjects were counted once based on the most severe postbaseline value. For the composite endpoint, subjects were counted once when the criteria were met at the same postbaseline visit date.

Due to the early study termination, only safety-related endpoints were listed for the subjects enrolled in the study.

**SUMMARY OF RESULTS:**

Enrollment to this study was closed on 26 April 2017 during Phase 1b following an updated feasibility assessment in relation to changes in standard of care. The 2 subjects enrolled as of that date remained on study with a modified schedule of assessments. Due to the early study termination, the study objectives were not met and subjects were assessed for safety only.

**Subject Disposition and Demographics:** Two subjects were enrolled in the study before it was terminated early; both subjects received at least 1 dose of study drug and were included in the Safety Analysis Set. Both subjects discontinued the study due to progressive disease:

- PPD
- PPD

One subject was 65 years of age and one subject was 68 years of age. One subject was male and 1 subject was female. Both subjects were PPD Neither subject was of Hispanic or Latino ethnicity (Appendix 16.2, Listing 16.2.4.1). Subject baseline characteristics, medical history, prior and concomitant medications, prior anticancer therapy, prior radiation therapy, and prior surgical and medical procedures are presented in Appendix 16.2.

**Efficacy:** The investigator's assessment of overall response is presented in Appendix 16.2, Listing 16.2.5.

**Pharmacokinetics:** No pharmacokinetic analyses were conducted for this report.

**Safety Results:** The 2 enrolled subjects experienced a total of 49 AEs during the study (Appendix 16.2, Listing 16.2.7.1). The majority of AEs were Grade 1 or Grade 2 in severity. Both subjects experienced AEs Grade 3 or higher, which included the following: anemia, blood lactate dehydrogenase increased, thrombocytopenia, and upper respiratory tract infection (1 subject each). Both subjects experienced SAEs, which included the following: AST increased, edema peripheral, and upper respiratory tract infection (1 subject each) (Appendix 16.2, Listing 16.2.7.3). Subject PPD experienced AEs assessed by the investigator as related to IDL, which included the following: diarrhea and platelet count decreased (Appendix 16.2, Listing 16.2.7.1). Subject PPD experienced an AE that led to IDL and BI 836826 dose interruption (Grade 2 AST increased). In addition, the subject experienced 2 AEs that led to BI 836826 dose interruption (Grade 1 nausea and Grade 1 cold sweat) (Appendix 16.2, Listing 16.2.7.1). No deaths were reported (Appendix 16.2, Listing 16.2.7.2.1).

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| Both subjects had treatment-emergent laboratory abnormalities (Appendix 16.2, Listing 16.2.8.1.4). Both subjects had liver-related laboratory abnormalities of AST > 3 × ULN, ALT > 3 × ULN, and ALP > 1.5 × ULN. Neither subject had total bilirubin > 1.5 × ULN, total bilirubin > 2 × ULN, or total bilirubin > 2 × ULN and ALP < 2 × ULN (Appendix 16.2, Listing 16.2.8.1.6). |
| **CONCLUSIONS:** No efficacy or dosing conclusions could be drawn given the limited number of subjects in the study. There were no new safety issues identified. |