FINAL SYNOPTIC CLINICAL STUDY REPORT

Study Title:	An Expanded Access Protocol for Idelalisib in Combination with Rituximab for Relapsed, Previously Treated Subjects with Chronic Lymphocytic Leukemia
Name of Test Drug:	Idelalisib (Zydelig®)
Dose and Formulation:	150-mg tablets twice daily 100-mg tablets for subjects requiring dose reduction
Indication:	Chronic Lymphocytic Leukemia
Sponsor:	Gilead Sciences, Inc. 199 East Blaine Street Seattle, WA 98102 USA Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404 USA
Study No.:	GS-US-312-1325
Phase of Development:	Phase 3
IND No.: **EudraCT No.:**	101254 2013-005343-82
ClinicalTrials.gov Identifier:	NCT02136511
Study Start Date:	19 May 2014 (First Subject Screened)
Study End Date:	15 August 2017 (Last Subject Last Observation for the Primary Endpoint)
Principal or Coordinating Investigator:	Name: Donald MacDonald, MB, MD, PhD Affiliation: PPD
Gilead Responsible Medical Monitor:	Name: Pankaj Bhargava, MD Telephone: PPD Fax: PPD
Report Date:	13 July 2018

STUDY SYNOPSIS

Study GS-US-312-1325

Gilead Sciences, Inc.
199 East Blaine Street
Seattle, WA 98102
USA

Gilead Sciences, Inc.
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Foster City, CA 94404
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Title of Study: An Expanded Access Protocol for Idelalisib in Combination with Rituximab for Relapsed, Previously Treated Subjects with Chronic Lymphocytic Leukemia

Investigators: PPD PPD PPD PPD PPD PPD PPD Donald MacDonald, MB, MD, PhD; and PPD PPD

Study Centers: Six sites in Ireland, Italy, the United Kingdom, and the United States

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

Study Period:

19 May 2014 (First Subject Screened)
15 August 2017 (Last Subject Last Observation for the Primary Endpoint)

Phase of Development: Phase 3

Objectives:

The primary objective of this study was as follows:

- To provide idelalisib in an open-label format to eligible subjects with relapsed chronic lymphocytic leukemia (CLL) who had limited treatment options. Once other options to receive idelalisib were available, this study would close to enrollment.

Methodology: This was an open-label, multisite, expanded-access protocol of idelalisib in combination with rituximab.

All subjects were to receive idelalisib 150 mg taken orally, twice per day continuously. Subjects were administered 8 infusions of rituximab (every 2 weeks for 5 infusions and every 4 weeks for a further 3 infusions). Subjects underwent disease assessments and received medical care per institutional standards of care.

This study was closed to enrollment by Gilead Sciences, Inc. (Gilead) when idelalisib received regulatory approval and was made commercially available. Subjects receiving idelalisib could subsequently choose to continue to receive treatment with commercially-available idelalisib, and the study was closed once all subjects were transitioned off study.

Number of Subjects (Planned and Analyzed):
Planned: Approximately 150 subjects
Analyzed: Full Analysis Set: 31 subjects

Diagnosis and Main Criteria for Inclusion: Eligible subjects were male or nonpregnant, nonlactating female subjects ≥ 18 years of age with relapsed, previously-treated CLL who required therapy, had experienced disease progression < 24 months since the completion of the last prior therapy, and were not sufficiently fit to receive cytotoxic therapy due to chemotherapy-induced bone marrow damage, renal dysfunction, and/or comorbidities. Subjects were excluded if they had ongoing and/or uncontrolled intercurrent illness (ie, ongoing drug-induced pneumonitis, ongoing inflammatory bowel disease, ongoing systemic bacterial, fungal, or viral infection).

Duration of Treatment: Subjects were to be treated until progressive disease or intolerable toxicity. Idelalisib administration continued in responders with a positive risk-benefit profile, per the treating physician.

Test Product, Dose, Mode of Administration, and Batch Nos.:

- Idelalisib 150 mg twice daily (1 × 150-mg oral tablet twice daily, batch Nos. THSP and CV1308B1)
- Idelalisib 100 mg (100-mg oral tablet for subjects requiring dose reduction, batch Nos. NSZP, CV1302C1, and PCZC)

Reference Therapy, Dose, Mode of Administration, and Batch No.:

- Rituximab 375 mg/m^2 intravenously on Week 0; thereafter 500 mg/m^2 intravenously on Weeks 2, 4, 6, 8, 12, 16, and 20 for a total of 8 infusions.

Criteria for Evaluation:

Efficacy: Efficacy was assessed using progression-free survival (PFS), which was defined as the interval from the initial study dosing date to the first documentation of disease progression or death from any cause. Disease progression was defined as CLL progression based on investigator assessment of standard criteria (including radiologic scans), excluding lymphocytosis alone.

Pharmacokinetics: No pharmacokinetic (PK) assessments were performed for this report.

Safety: The overall safety profile was characterized by the type, frequency, severity, timing of onset, duration, and relationship to study therapy of Grade ≥ 3 adverse events (AEs) and serious adverse events (SAEs).

Statistical Methods:

Both safety and efficacy were assessed using data collected from subjects who received at least 1 dose of study drug. All the analyses were limited to descriptive summaries.

Efficacy: The Full Analysis Set (FAS) includes all subjects who took at least 1 dose of study drug. The primary analysis of PFS by investigator assessment was performed using the Kaplan-Meier (KM) method for the FAS. Medians, Q1, and Q3 of the PFS, the proportion of subjects who were progression-free at 24 and 48 weeks, and corresponding 95% CIs were presented. The KM curve was provided.

Pharmacokinetics: No PK assessments were performed for this report.

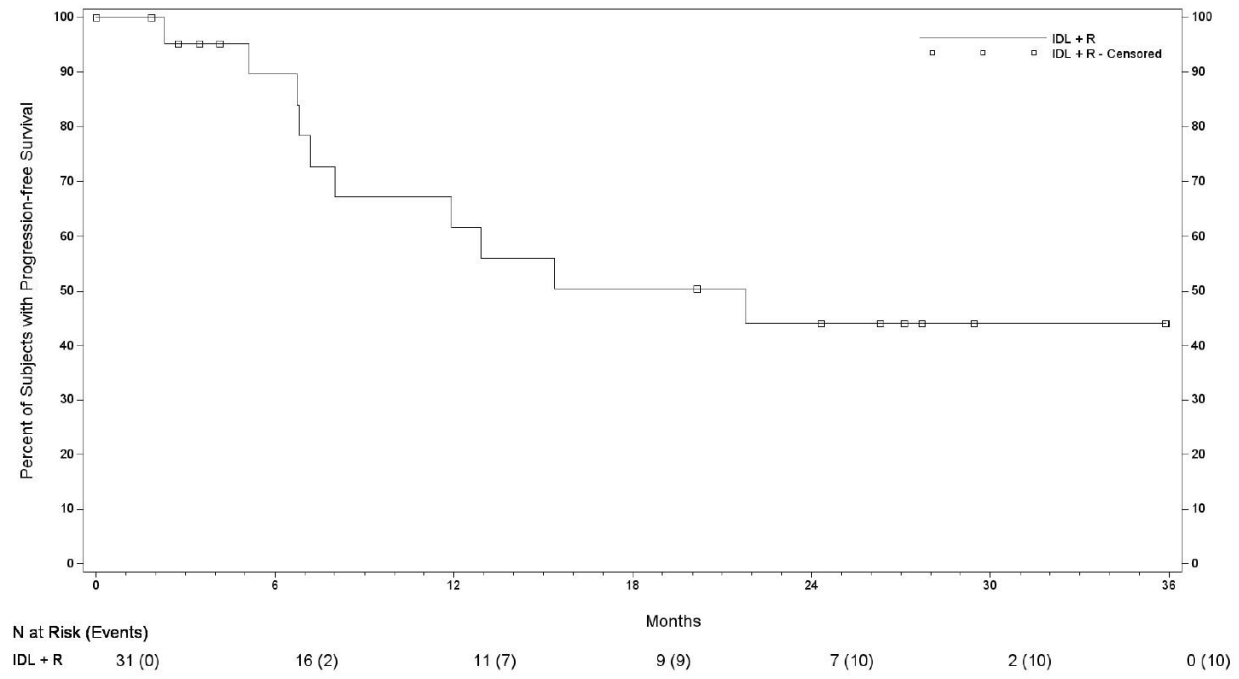
Safety: The focus of AE summarization was on treatment-emergent AEs (TEAEs). All AEs and laboratory abnormalities presented in this report were treatment emergent and are referred to as AEs and laboratory abnormalities throughout this report. Additionally, the relationships of AEs to study drug were investigator assigned. All AEs and deaths reported on study were summarized based on the FAS. All AEs were listed in detail based on the FAS. The AEs of interest (AEIs) were summarized similarly to AEs. The AEIs included any Grade pneumonitis, bowel perforation, progressive multifocal leukoencephalopathy, *Pneumocystis jirovecii* pneumonia (PJP), cytomegalovirus (CMV) infection, and organizing pneumonia (OP), and Grade ≥ 3 diarrhea/colitis, rash, infection, febrile neutropenia, and transaminase, ALT, or AST increased. Adverse events were graded by the investigator as Grade 1, 2, 3, 4, or 5 according to Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03.

SUMMARY OF RESULTS:

Subject Disposition and Demographics: A total of 31 subjects were screened for study participation; all were enrolled and received study drug treatment. All subjects have discontinued study drug: 15 due to AEs, 6 due to progressive disease, 3 due to death, and 1 due to protocol violation. The remaining 6 subjects discontinued study drug following Gilead's decision to terminate the study. All 31 subjects have discontinued the study (9 due to death, 6 each due to AEs, progressive disease, and study termination by the sponsor, and 1 each due to investigator's discretion, protocol violation, loss to follow up, and unacceptable toxicity). The median age of subjects was 63 years (range 45 to 80); 21 subjects (67.7%) were male, 30 subjects (96.8%) were white, and none were of Hispanic or Latino ethnicity.

Efficacy Results:

Ten subjects (32.2%) experienced a PFS event during study participation. The KM estimate of median PFS (95% CI) was 21.8 (7.2, not reached) months. The KM estimate of PFS rate at 24 and 48 weeks was 89.6% and 67.2%, respectively. The KM curve of PFS by investigator assessment is displayed below.



IDL = idelalisib; R = rituximab

Pharmacokinetics Results: No PK assessments were performed for this report.

Safety Results:

Exposure: Exposure to idelalisib ranged from 2.6 to 156.1 weeks, with a median of 39.7 weeks. Thirteen subjects (41.9%) had a cumulative exposure to idelalisib of ≥ 12 months. Twenty-three subjects (74.2%) had at least 1 dose modification, and for all of these subjects the dose was interrupted and rechallenged; of these, 12 subjects were rechallenged with idelalisib 150 mg twice daily and 11 subjects were rechallenged with idelalisib at a reduced dose of 100 mg twice daily. No subjects had a dose reduction without an interruption.

Adverse Events: Thirty-one subjects (100%) experienced at least 1 AE during the study. The most frequently reported AEs were pyrexia (21 subjects, 67.7%), diarrhea (19 subjects, 61.3%), and neutropenia (13 subjects, 41.9%). Thirty subjects (96.8%) had at least 1 Grade ≥ 3 AE. Grade 3, 4, and 5 AEs were experienced by 13 (41.9%), 9 (29.0%), and 8 (25.8%) subjects, respectively. The most common Grade ≥ 3 events were neutropenia (13 subjects, 41.9%), anemia (7 subjects, 22.6%), and febrile neutropenia (6 subjects, 19.4%).

Twenty-four subjects (77.4%) experienced AEs assessed by the investigator as related to idelalisib and 18 subjects (58.1%) had Grade ≥ 3 AEs assessed as related to idelalisib. Eight subjects (25.8%) experienced AEs assessed by the investigator as related to rituximab and 1 subject (3.2%) had 1 or more Grade ≥ 3 AEs assessed as related to rituximab. Twenty-two subjects (71.0%) experienced at least 1 SAE; 9 (29.0%) subjects had SAEs assessed as related to idelalisib by the investigator and 4 (12.9%) subjects had SAEs assessed as related to rituximab by the investigator. The most common SAEs were pneumonia (5 subjects, 16.1%), and diarrhea, febrile neutropenia, and sepsis (4 subjects, 12.9% each). In addition, 20 (64.5%) subjects experienced an AE leading to idelalisib interruption and 16 subjects (51.6%) experienced an AE leading to permanent discontinuation of idelalisib. Eight subjects (25.8%) experienced 1 or more

AEs leading to death, and there were 10 subject deaths in total (32.2%). Adverse events leading to death included pneumonia (occurring in 2 subjects), and progressive multifocal leukoencephalopathy (PML), large intestinal obstruction sepsis, *Escherichia* sepsis, febrile neutropenia, septic shock, respiratory failure, and shock (each occurring in 1 subject). For the subject with fatal PML, the onset of PML occurred 7 months after starting idelalisib, and 3 months after completing 11 months of rituximab. The investigator assessed the PML event as related to rituximab and not related to idelalisib.

The most common AEIs were Grade ≥ 3 infection (16 subjects, 51.6%), Grade ≥ 3 febrile neutropenia (6 subjects, 19.4%), and Grade ≥ 3 diarrhea/colitis (5 subjects, 16.1%). Other AEIs included 1 subject each (3.2% each) with Grade ≥ 3 rash, any Grade CMV infection, any Grade PJP, and any Grade PML. Adverse events of interest leading to idelalisib discontinuation included Grade ≥ 3 infection (4 subjects, 12.9%), and Grade ≥ 3 diarrhea/colitis, and Grade ≥ 3 febrile neutropenia (2 subjects, 6.5% each), and Grade ≥ 3 rash and any Grade PML (1 subject, 3.2% each).

Three subjects had Grade ≥ 3 transaminase, ALT, or AST increased AEs (2 subjects with Grade 3 transaminases increased and 1 subject with Grade 3 ALT increased and Grade 3 AST increased). Liver-related laboratory abnormalities occurred in 17 subjects (56.7%), among which 4 (12.9%) had a Grade 3 or 4 alanine aminotransferase (ALT) or aspartate aminotransferase (AST) elevation. The remaining subjects had Grade 1 or 2 liver-related laboratory abnormalities. The median (min, max) time to onset of the first Grade 3 or 4 ALT or AST elevation was 16.5 (6.0, 70.9) weeks. There was no ALT or AST > 3 × ULN with total bilirubin > 1.5 × ULN.

CONCLUSIONS:

- The KM estimate of median PFS (95% CI) was 21.8 (7.2, not reached) months. The KM estimate of PFS rate at 24 and 48 weeks was 89.6% and 67.2%, respectively.
- No changes to the safety profile of idelalisib were identified in this study.