ABBREVIATED FINAL CLINICAL STUDY REPORT

Study Title:	A Phase 2, Single Arm Study Evaluating the Safety and Efficacy of Idelalisib in Combination with Rituximab for Previously Untreated Follicular Lymphoma and Small Lymphocytic Lymphoma
Name of Test Drug:	Idelalisib (Zydelig®, GS-1101)
Dose and Formulation:	150-mg tablet taken orally twice daily
Indication:	Follicular Lymphoma Small Lymphocytic Lymphoma
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404 USA
Study No.:	GS-US-313-1414
Phase of Development:	Phase 2
IND No.:	101254
EudraCT No.:	Not Applicable
ClinicalTrials.gov Identifier:	NCT02258529
Study Start Date:	14 September 2015 (First Subject Screened)
Study End Date:	03 May 2016 (Last Subject Observation)
Principal or Coordinating Investigator:	Name: Ian Flinn, MD Affiliation: PPD
Gilead Responsible Medical Monitor:	Name: Siddhartha Mitra, MD, PhD Telephone: PPD Fax: PPD
Report Date:	25 April 2017

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-313-1414
Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404
USA

Title of Study: A Phase 2, Single Arm Study Evaluating the Safety and Efficacy of Idelalisib in Combination with Rituximab for Previously Untreated Follicular Lymphoma and Small Lymphocytic Lymphoma

Investigators: Multicenter study

Study Centers: A total of 7 sites in the United States

Publications: There were no publications at the time of this clinical study report (CSR).

Study Period:

First Subject Screened: 14 September 2015

Last Subject Observation: 03 May 2016

Phase of Development: Phase 2

Objectives:

The primary objective of this study was as follows:

- To evaluate the ORR and complete response (CR) rate to treatment with idelalisib (IDL) combined with rituximab

The secondary objectives of this study were:

- To evaluate the overall safety profile of IDL combined with rituximab
- To assess the rate of ≥ Grade 3 transaminase elevations observed after treatment with IDL combined with rituximab
- To estimate progression-free survival (PFS) and duration of response (DOR)

The exploratory objectives of this study were:

- To assess the effects of IDL/rituximab therapy on disease-associated biomarkers and to evaluate correlates of sensitivity and resistance
- To evaluate biomarkers associated with adverse events (AE)

Methodology: Study GS-US-313-1414 was a Phase 2, multicenter, single-arm study of adult subjects with untreated follicular lymphoma (FL) or small lymphocytic lymphoma (SLL).

All subjects received both IDL and rituximab. Idelalisib 150 mg was taken orally twice daily starting on Day 1 and was to be administered continuously for up to 104 weeks. Rituximab 375 mg/m^2 was to be administered intravenously weekly for 4 doses over the first 4 weeks. Thereafter, subjects were to receive maintenance rituximab every 8 weeks up to Week 100.

Laboratory/clinic visits occurred every week through Week 6, every 2 weeks from Week 6 to Week 12, every 4 weeks to Week 28, and then every 8 weeks through Week 104. Subjects were assessed for safety at every visit.

Subjects were assessed for lymphoma disease status by computed tomography (CT) or magnetic resonance imaging (MRI). Long-term follow-up was to be conducted at annual intervals for 5 years, starting at the end-of-study (EOS) visit.

After a 4-week screening period, subjects were expected to start and remain on treatment for up to 104 weeks, and then were followed annually for disease status and survival. The overall duration of the trial was expected to be approximately 7 years including survival follow-up. Subjects with stable disease or objective response could remain on study treatment for 104 weeks. Subjects were to remain on treatment until subject withdrawal from study, definitive progression of lymphoma, intolerable toxicity, death, pregnancy, noncompliance with study procedures, or study discontinuation. If permanent discontinuation of study drug occurred prior to definitive progression of lymphoma, subjects remained on study until definitive progression of lymphoma or withdrawal from the study.

Early Study Termination: In March 2016, an increased rate of deaths and serious adverse events (SAEs) among subjects with early-line indolent non-Hodgkin lymphoma (iNHL) and front-line chronic lymphocytic leukemia (CLL) treated with IDL in combination with standard therapies compared with the control groups was observed by the independent data monitoring committee (DMC) in a pooled analysis of 3 Phase 3 placebo-controlled studies (Studies GS-US-312-0123, GS-US-313-0124, and GS-US-313-0125). Gilead Sciences reviewed the unblinded data, and terminated the 3 Phase 3 placebo-controlled studies, in agreement with the DMC recommendation and in consultation with the US Food and Drug Administration (FDA). Because the factors contributing to the imbalance in SAEs and deaths were not well understood and the study population and treatment were similar, the decision was made to terminate the current study as well. A letter to investigators was issued globally on 11 March 2016 providing notification of the safety findings and decision to terminate the study. The last patient last visit (LPLV) occurred on 03 May 2016.

Number of Subjects (Planned and Analyzed):
Planned: approximately 50 subjects

Analyzed:

ITT Analysis Set: 10 subjects

PK Analysis Set: 9 subjects

Diagnosis and Main Criteria for Inclusion:
The study population consisted of adults with histologically confirmed diagnosis of FL Grade 1, 2, or 3a, or SLL with absolute B lymphocyte count $< 5 \times 10^9$/L at the time of diagnosis.

Key inclusion criteria were as follows:

- Histologically confirmed diagnosis of B-cell lymphoma, with histological subtype limited to the following based on criteria established by the World Health Organization (WHO) 2008 classification of tumors of hematopoietic and lymphoid tissues:
  a) FL Grade 1, 2, or 3a
  b) SLL with absolute B lymphocyte count $< 5 \times 10^9$/L at the time of original
- No previous systemic treatment for lymphoma. Subjects may have had a single course of radiation therapy to a limited field (ie, not exceeding 2 adjacent lymph node regions)
- Subject demonstrated need for treatment for lymphoma, as indicated by the presence of ≥ 1 of the following:
  a) B symptoms
  b) tumor mass (characterized by lymphomas with a diameter > 3 cm in 3 or more regions or by a lymphoma with a diameter > 7 cm in 1 region)
  c) presence of lymphoma-related complications
- Histologically confirmed $CD20^+$ FL or SLL
- Ann-Arbor Stage 2 (noncontiguous), 3, or 4 disease
- Radiographically measurable lymphadenopathy or extranodal lymphoid malignancy as determined by independent review committee (IRC), (defined as the presence of ≥ 1 lesion that measures ≥ 2.0 cm in the longest dimension [LD] and ≥ 1.0 cm in the longest perpendicular dimension [LPD] as assessed by CT or magnetic resonance imaging [MRI])
- An Eastern Cooperative Oncology Group (ECOG) Performance Status of ≤ 2 or an equivalent Karnofsky score of ≥ 60

Key exclusion criteria were as follows:

- Known history of transformed lymphoma or diffuse large cell lymphoid malignancy. Biopsy documentation of the absence or presence of high-grade lymphoma was not required.
- Known history of, or clinically apparent, central nervous system (CNS) lymphoma or leptomeningeal lymphoma. Imaging documentation of the absence or presence of central disease was not required.
- Candidate for stem cell transplantation
- Candidate for potentially curative radiotherapy

Duration of Treatment:

Idelalisib 150 mg was taken orally twice daily starting on Day 1 and administered continuously for up to 104 weeks. Rituximab 375 mg/m^2 was administered intravenously weekly for 4 doses over the first 4 weeks. Thereafter, subjects received maintenance rituximab every 8 weeks up to Week 100. Subjects with stable disease or objective response remained on study treatment for up to 104 weeks.

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

Idelalisib: 150 mg taken orally twice daily starting on Day 1 and taken continuously thereafter

150 mg Lot No.: CV1308B1

Dose reductions to 50-mg and 100-mg tablets taken orally twice daily

50 mg Lot No.: CV1404C1

100 mg Lot No.: CV1302C1

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

Rituximab was administered as part of the regimen intravenously in the clinic. Dosing was based on body surface area at baseline (375 mg/m^2). Rituximab was administered weekly for 4 doses over the first 4 weeks. Thereafter, subjects received maintenance rituximab every 8 weeks. Commercial product was used at all sites.

Criteria for Evaluation:

Efficacy: Due to early termination of the study, no prespecified efficacy analyses were conducted.

Pharmacokinetics: Serial plasma samples were collected for analysis of IDL/metabolite plasma concentration. The plasma samples were analyzed for concentration of IDL (and/or its primary metabolite, GS-563117) at trough (pre-dose) and peak (1.5-hour samples) as assessed by a validated bioanalytical method.

Pharmacodynamics: Serial plasma samples were collected for analysis of association with response or lack of response, and optional exploratory pharmacodynamic measures. In addition, the samples were to be used to assess changes in the plasma concentrations of disease-associated and AE-associated chemokines and cytokines.

Safety: Safety was assessed via physical examination, vital signs, clinical laboratory tests (hematology, serum chemistry, coagulation, and urinalysis), and adverse events (AEs). Toxicity of AEs was graded according to the Common Terminology Criteria for Adverse Events (CTCAE), Version 4.03.

Statistical Methods:

Efficacy: Due to early termination of the study, no prespecified efficacy analyses were performed.

Pharmacokinetics: The IDL (and/or its primary metabolite, GS-563117) plasma concentrations immediately prior to dosing and at 1.5 hours after administration of the dose of study drug at each relevant clinic visit were summarized by treatment group and visit using descriptive statistics.

Safety: The number and percentage of subjects with the following types of treatment-emergent AEs (TEAEs) were summarized by system organ class (SOC) and preferred term (PT): all TEAEs, Grade ≥ 3 TEAEs (by maximum severity), all IDL-related TEAEs, Grade ≥ 3 IDL-related TEAEs, all rituximab-related TEAEs, and Grade ≥ 3 rituximab-related TEAEs. In addition, the number and percentage of subjects with treatment-emergent SAEs, IDL-related treatment-emergent SAEs, and treatment-emergent rituximab-related SAEs were summarized. The number and percentage of subjects with TEAEs leading to premature discontinuation of study drug, study drug interruption, study drug dose reduction, or death were also summarized.

Adverse events of interest (AEIs) for IDL included any grade bowel perforation by MST, ≥ Grade 3 diarrhea and/or colitis, and any grade progressive multifocal leukoencephalopathy (PML), any grade pneumonitis, and ≥ Grade 3 rash by MST. Following from safety findings identified in March 2016, the AEI list was expanded to include infection (specifically, ≥ Grade 3 infection, ≥ Grade 3 febrile neutropenia, any grade CMV infection, and any grade *Pneumocystis jirovecii* pneumonia [PJP]). Adverse events of interest were summarized in a similar manner to all TEAEs. Time to first onset of AEIs and time to resolution were summarized using descriptive statistics for continuous variables.

Laboratory data collected during the study were analyzed and summarized using both quantitative and qualitative methods. Summaries of laboratory data (including hematology, serum chemistry, and urinalysis [baseline urine pH only]) were provided for the ITT Analysis Set. No formal statistical testing was conducted. Descriptive statistics were provided by treatment group for each laboratory test specified in the study protocol (baseline values, values at each postbaseline visit, and change from baseline at each postbaseline visit).

Analyses of transaminase elevations were based on laboratory values using the ITT Analysis Set. The number and percentage of subjects were summarized for subjects with: Grade 3 or 4 treatment-emergent alanine aminotransferase/aspartate aminotransferase (ALT/AST) elevation, and for subjects with Grade 3 or 4 treatment-emergent ALT/AST elevation that resolved to both ALT/AST of Grade 1 or less. Descriptive statistics were provided for time to onset of first Grade 3 or 4 treatment-emergent ALT/AST elevations. For subjects with at least 1 episode of Grade 3 or 4 ALT/AST elevation, time to resolution of first episode of treatment-emergent Grade 3 or 4 ALT/AST elevation to Grade 1 or less was summarized using descriptive statistics for continuous variables.

Descriptive statistics were provided for body weight and vital signs (baseline values, values at each postbaseline visit, and change from baseline at each postbaseline visit. Use of concomitant medications was summarized by preferred name using the number and percentage of subjects for each treatment group. No formal statistical testing was conducted.

SUMMARY OF RESULTS:

Subject Disposition and Demographics: At the time the study was terminated, 10 subjects had been enrolled and treated. Due to early termination of the study by the sponsor, no subjects completed the study. Prior to termination of the study, 1 subject discontinued study drug and discontinued the study due to an AE (Grade 1 musculoskeletal chest pain).

The median (Q1, Q3) age was 67 (59, 78) years with an age range of 52 to 87 years; half of the subjects were ≥ 65 years of age. Overall, 40% of the subjects (4 of 10) were male; all of the subjects were white and identified as not Hispanic or Latino. The median (Q1, Q3) baseline BMI was 28.8 (26.4, 34.5) kg/m^2. At baseline, half of the subjects had an ECOG performance status score of 0 and half had an ECOG performance status score of 1.

Eight of the 10 subjects (80%) were diagnosed with FL, and 2 of the 10 subjects (20%) were diagnosed with SLL. Median (Q1, Q3) time since diagnosis was 0.2 (0.1, 1.8) years. Half of the subjects had a current Follicular Lymphoma International Prognostic Index (FLIPI) score of 3, and the remaining 3 subjects (30%) with baseline data had a FLIPI score of 2. Half of the subjects reported disease-related constitutional symptoms, and 3 of the 10 subjects (30%) reported complication of lymphoma.

Efficacy Results: Due to the study's early termination, no efficacy analyses were conducted.

Pharmacokinetics/Pharmacodynamics Results: In general, IDL and GS-563117 plasma concentrations were comparable at predose or 1.5 hours postdose at Weeks 2, 4, and 12. Trough concentrations of IDL were similar to those observed in other monotherapy studies (eg, Study 101-02) and to population pharmacokinetics (PK) modeling estimates following IDL 150 mg twice daily monotherapy. These results suggest that there is no significant change in the PK of IDL or its primary metabolite when IDL is coadministered with rituximab.

Safety Results: All 10 subjects in the ITT Analysis Set received at least 1 dose of IDL and at least 1 dose of rituximab and were evaluable for study drug (IDL/rituximab) exposure. The median (Q1, Q3) duration of exposure to IDL was 11.0 (7.1, 18.4) weeks, with a range of 1.7 to 24.1 weeks. The median (Q1, Q3) duration of exposure to rituximab was 11.1 (3.1, 11.6) weeks, with a range of 0.1 to 21.1 weeks.

The key safety findings are as follows:

Adverse Events: All AEs were treatment emergent unless otherwise specified. Nine subjects (90%) experienced at least 1 AE during the study. The 3 most commonly reported AEs by PT were as follows:

- ALT increased (50%, 5 subjects)
- AST increased (50%, 5 subjects)
- Infusion-related reaction (40%, 4 subjects)

The ALT and AST increased AEs occurred in the same 5 subjects. A total of 9 subjects (90%) experienced IDL-related AEs based on investigator assessment, with 7 subjects experiencing IDL-related AEs of Grade 3 or higher severity. A total of 9 subjects (90%) experienced rituximab-related AEs, with 4 subjects (40%) experiencing rituximab-related AEs of Grade 3 or higher severity.

Adverse Events of Interest: A total of 4 subjects (40%) experienced 5 AEIs during the study (rash maculopapular [3 events in 3 subjects], pneumonitis [2 events in 1 subject], and sepsis [1 event]). No subjects discontinued IDL treatment due to these AEIs. No subjects experienced ≥ Grade 3 diarrhea/colitis, bowel perforation (by MST), ≥ Grade 3 febrile neutropenia; any grade PML, or PJP or CMV infection.

Deaths: There were no deaths during the study.

Serious Adverse Events: A total of 3 subjects experienced 5 SAEs during the study (Grade 3 pneumonitis in 1 subject, Grade 3 sepsis and Grade 3 peripheral edema in 1 subject, and Grade 3 musculoskeletal chest pain and Grade 3 trigeminal neuralgia in 1 subject). Two of these SAEs (Grade 3 pneumonitis and Grade 3 sepsis) were AEIs.

Adverse Events Leading to Discontinuation of Study Drug: IDL dosing was permanently discontinued for 1 subject due to a Grade 1 AE of musculoskeletal chest pain.

Laboratory Evaluations of Interest: Laboratory evaluations of interest for IDL include decreased neutrophil counts and transaminase elevations, both of which have been commonly reported in prior studies with IDL.

Six subjects (60%) had a decreased neutrophil count of any grade: 2 subjects (20%) had decreased neutrophil count of Grade 3 severity, and 2 subjects (20%) had decreased neutrophil count of Grade 4 severity. Median change from baseline at Week 24 in neutrophil count was 0.54 GI/L (0.43, 0.64). One subject had a Grade 3 AE of neutrophil count decreased that was assessed by the investigator as related to both IDL and to rituximab. The AE resolved after treatment with filgrastim.

No subject experienced a Grade 4 elevation in serum ALT or AST. Grade 3 treatment-emergent elevations in serum ALT occurred in 4 subjects (40%), and Grade 3 treatment-emergent elevation in AST also occurred in 1 of these subjects (10%). The Grade 3 transaminase elevations resolved to Grade 0 for all 4 subjects except 1 subject for whom the ALT value resolved to Grade 1. The Grade 3 ALT or AST elevations typically occurred within the first 3 months of therapy. The median time to onset for Grade 3 elevations in ALT or AST was 5.57 weeks (range: 2.1 to 7.1 weeks), and the median time to resolution of the Grade 3 elevations in ALT or AST was 2.14 weeks (range: 1.1 to 6.7 weeks).

Overall, 5 subjects (50%) had AEs of transaminase elevations (terms included increased ALT and/or AST and liver function test increased) that led to IDL dose interruption. One subject had an AE of ALT increased that led to IDL dose reduction.

Other Clinical Laboratory Evaluations: In addition to neutropenia, decreased lymphocytes was the other most common hematologic abnormality, occurring in 6 subjects (60%). Grade 3-4 decreased lymphocytes occurred in 2 subjects (20%).

The most common treatment-emergent serum chemistry abnormalities (all grades) were observed in the following parameters: ALT increased, creatinine clearance, and triglycerides increased (70%, 7 subjects each); AST increased (60%, 6 subjects); and hyperglycemia (50%, 5 subjects). Except for ALT, most of the abnormalities were < Grade 3 in severity.

Other: No other evaluations were performed for this study.

CONCLUSIONS: This study was terminated early due to a safety signal observed by an independent DMC in a pooled analysis of 3 Phase 3 clinical studies in first-line CLL and early-line iNHL (Studies GS-US-312-0123, GS-US-313-0124, and GS-US-313-0125). The potential risks of IDL treatment in combination with standard therapies shown in the pooled analysis of safety data from other Phase 3 studies outweighed the potential disease progression and survival benefits in the current study. Because the factors contributing to the imbalance in SAEs and deaths in the pooled analysis of the other Phase 3 studies were not completely understood, the decision was made to terminate the current study as well.

Due to early termination of this study, the prespecified efficacy analyses were not conducted.

The safety conclusions from this study are as follows:

- No subjects died during the study.
- Three subjects experienced SAEs during the study (1 subject each: Grade 3 pneumonitis; Grade 3 sepsis and Grade 3 peripheral edema; and Grade 3 musculoskeletal chest pain and Grade 3 trigeminal neuralgia).
- IDL dosing was permanently discontinued for 1 subject due to an AE (Grade 1 musculoskeletal chest pain).
- Four subjects (40%) experienced 5 AEIs during the study (rash maculopapular [3 events in 3 subjects], pneumonitis [2 events in 1 subject], and sepsis [1 event]).
- The 2 most commonly reported AEs were ALT or AST increased (50%, 5 subjects in each); and infusion-related reaction (40%, 4 subjects).
- Six subjects (60%) had a decreased neutrophil count of any grade; 2 subjects with Grade 3 and 2 subjects with Grade 4 severity.