FINAL CLINICAL STUDY REPORT

Study Title:	Single-agent Idelalisib for Previously Treated Low-grade Lymphoma: A Phase 1/2 Study of Safety, Efficacy, and Flow-cytometric Assessment of Tumor-cell Signaling Events
Name of Test Drug:	Idelalisib (Zydelig®; GS-1101)
Dose and Formulation:	Idelalisib 75-,100-, and 150-mg tablets
Indication:	Previously treated low-grade indolent non-Hodgkin lymphoma (iNHL)
Sponsor:	Gilead Sciences, Inc. 199 East Blaine Street Seattle, WA 98102 USA
Study No.:	101-10
Phase of Development:	Phase 1/2
IND No.:	101254
EudraCT No.:	Not Applicable
ClinicalTrials.gov Identifier:	NCT01306643
Study Start Date:	22 February 2011 (First Subject Screened)
Study End Date:	24 August 2015 (Last Subject Observation)
Principal or Coordinating Investigator:	Name: Joshua Brody, MD Affiliation: PPD
Gilead Responsible Medical Monitor:	Name: Henry Adewoye, MD Telephone: PPD Fax: PPD
Report Date:	18 April 2017
Previous Report Date(s):	09 August 2013 (Interim)

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 101-10
Gilead Sciences, Inc.
199 East Blaine Street
Seattle, WA 98102
USA

Title of Study: Single-agent Idelalisib for Previously Treated Low-grade Lymphoma: A Phase 1/2 Study of Safety, Efficacy, and Flow-cytometric Assessment of Tumor-cell Signaling Events

Investigators: Joshua Brody, MD, PPD

Study Centers: Subjects were enrolled at 2 study sites in the United States (US)

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

Study Period:

22 February 2011 (First Subject Screened)
24 August 2015 (Last Subject Observation)

Phase of Development: Phase 1/2

Objectives:

The primary objectives of this study were as follows:

- To investigate the safety of idelalisib (IDL) in subjects with previously treated iNHL
- To investigate the efficacy of IDL in subjects with previously treated iNHL
- To investigate the efficacy of IDL 300 mg twice daily in subjects with previously treated iNHL who were tolerating therapy but experienced disease progression while receiving ≤ 150 mg twice daily

The secondary objectives of this study were as follows:

- To determine whether differential phosphatidylinositol 3-kinase p110δ isoform (PI3Kδ) inhibition could be observed amongst B-cell receptor (BCR)-sensitive and BCR-insensitive cells within primary lymphoma samples or among subjects with different proportions of these cell subsets
- To determine whether the proportion of tumoral BCR-insensitive cells predicted clinical efficacy of IDL monotherapy
- To determine whether the degree of 'upstream' PI3Kδ inhibition (based on phosphorylated serine/threonine protein kinase [pAkt]/ serine/threonine protein kinase [Akt] ratio) or 'downstream' PI3Kδ inhibition (per pS6/S6 ratio) in tumor B-cells (BCR-stimulated or un-stimulated cells) predicted the clinical efficacy of IDL monotherapy

- To assess the effects of PI3Kδ inhibition on the signaling and in vitro functionality of intra-tumoral and peripheral T-cells and natural killer cells (intra-tumoral and peripheral), given the lack of cytotoxicity of PI3Kδ inhibition on these additional cell subsets
- To assess the pharmacodynamic effects of IDL treatment on peripheral blood chemokines and cytokines
- To evaluate the effects of IDL on gadoxetic acid (Gd-EOB-DTPA) uptake in liver as assessed by magnetic resonance imaging (MRI)

Methodology: This was a Phase 1/2, open-label, single-arm, safety, efficacy, and flow-cytometric assessment of tumor-cell signaling events study of IDL in subjects with previously treated low-grade iNHL.

Eligible subjects initiated oral IDL therapy at a dose of 150 mg twice daily for 28 days (1 cycle) for up to 12 cycles. Subjects who experienced disease progression while receiving ≤ 150 mg study drug twice daily were eligible to receive an escalated-dose of IDL, up to a maximum of 300 mg twice daily. Subjects were followed in clinic at 2-week intervals during the first 28-day cycle of treatment, and every 4-weeks for cycles 2 through 12. Subjects were assessed for clinical response by appropriate imaging (eg, computed tomography [CT] scans of neck, chest, abdomen, and pelvis) at the end of cycles 3, 6, 9, and 12. Responding subjects or subjects with stable disease continued to receive treatment for a maximum of 12 cycles.

Number of Subjects (Planned and Analyzed):
Planned: 15 evaluable subjects with previously treated iNHL
Analyzed: 18 subjects (Intent-to-treat [ITT] Analysis Set)

Diagnosis and Main Criteria for Inclusion:

- Histologically confirmed diagnosis of low-grade B-cell iNHL as defined by the World Health Organization (WHO) Lymphoma Classification (Grade 1, 2, 3A follicular lymphoma [FL], marginal zone lymphoma [MZL], or small lymphocytic lymphoma [SLL])
- At least one prior systemic therapy for iNHL
- Previously treated relapsed or refractory B-cell iNHL (refractory defined as not responding to previous therapy or progressing within 6 months of the last dose of previous therapy)
- Measurable disease by CT scan defined as at least 2 lesions measuring ≥ 1.5 cm in a single dimension (one of which was superficial and easily accessible for biopsy)
- WHO performance status of ≤ 2

Duration of Treatment: 48 weeks (12 cycles). Subjects were to be withdrawn from the study if they developed progressive disease while receiving IDL at the 300 mg twice daily escalated-dose, if they experienced unacceptable toxicity, or if they no longer derived clinical benefit in the opinion of the investigator. Subjects who completed the 12 cycles of treatment in this protocol were eligible to enroll to a long-term safety extension protocol (Gilead Sciences Study 101-99).

Test Product, Dose, Mode of Administration, and Batch No.: Idelalisib formulated as 150-mg tablets was administered at 150 mg twice daily at approximately 12-hour intervals. Higher and lower dose levels were provided in the event that the subject would benefit from a dose modification:

Dose level +2: 300 mg twice daily
Dose level +1: 200 mg twice daily
Dose level −1: 100 mg twice daily
Dose level −2: 75 mg twice daily

Batch numbers for 75-mg tablets: B100653, CV1103B1

Batch numbers for 100-mg tablets: CV1107B2, CV1110C1, CV1205C1-a, B100172, CV1106B1

Batch numbers for 150-mg tablets: CV1107D2, CV1110D2-A, CV1205D1-a, CV1205D1-A-a

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

Criteria for Evaluation:

Efficacy:

Primary Endpoint

- Overall response rate (ORR) defined as the proportion of subjects who achieved a complete response (CR) or partial response (PR) based on investigator assessment after the start of IDL treatment until progression or the end of study drug treatment.

Secondary Endpoints

- Duration of response (DOR), defined as the interval from the first documentation of CR or PR to the earlier of the first documentation of disease progression or death from any cause
- Lymph node response rate (LNR), defined as the proportion of subjects who achieve a ≥ 50% decrease from baseline in the sum of the products of the greatest perpendicular diameters (SPD) of measurable lesions
- Time to response (TTR), defined as the interval from the start of study drug to the first documentation of CR or PR
- Progression-free survival (PFS), defined as the interval from the start of study drug to the earlier of the first documentation of disease progression or death from any cause

Pharmacokinetics/Pharmacodynamics: No pharmacokinetic (PK) or pharmacodynamic analyses were performed for this report.

Safety:

- Overall safety profile of IDL as characterized by the type, frequency, severity, timing, and relationship to study drug of any adverse events (AEs) or abnormalities of physical findings or laboratory tests; drug discontinuation due to AEs or serious AEs (SAEs)

Statistical Methods:

Efficacy:

The primary endpoint, ORR, was defined as the proportion of subjects who achieved a CR or PR after the start of IDL treatment until progression or the end of study drug treatment. The ORR and 95% CI were presented in the ITT Analysis Set. The number and proportion of subjects who were evaluated as CR, PR, stable disease (SD), progressive disease (PD), and not evaluable (NE) was tabulated.

Secondary endpoints DOR (based on responding subjects) and PFS were summarized using the Kaplan-Meier (KM) method. The date of definitive progression was the time point at which progression was first identified by relevant radiographic data. Death that occurred ≤ 30 days following discontinuation of study drug was considered as an event for the DOR and PFS calculation. Data were censored on the date of the last tumor assessment (including assessments with a NE outcome) for subjects who did not have disease progression or die within 30 days after discontinuation of the study drug, or subjects who started new anti-tumor therapy prior to documented disease progression. Data were censored on the date of last tumor assessment (including assessments of NE) prior to ≥ 2 consecutive missing tumor assessments for subjects who had 2 or more consecutive missing tumor assessments before disease progression or death.

The LNR was summarized with 95% CI based on the exact binomial distribution. The SPD and percent change in SPD from baseline to each subsequent assessment was summarized. The best percent change from baseline during the study was also summarized. A waterfall plot of best on-treatment percent change in SPD was provided. Individual records for measurable and non-measurable lesions were listed in detail.

Time to response was evaluated for subjects who achieved a CR or PR and listed.

Pharmacokinetics/Pharmacodynamics: No PK or pharmacodynamic analyses were performed for this report.

Safety: The Safety Analysis Set included all subjects who received at least 1 dose of study drug. The primary safety endpoint for this study was the frequency of AEs. Adverse events were classified by System Organ Class (SOC) and Preferred Term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA), Version 18.1. An overview of treatment-emergent AEs (TEAEs), which includes incidence of AEs, TEAEs, AEs by severity, SAEs, deaths, and AEs leading to discontinuation are presented using descriptive statistics. In addition, an evaluation of clinical laboratory results and duration of exposure are presented using descriptive statistics, and vital signs were listed. Applicable hematological and serum biochemistry laboratory data were programmatically graded according to Common Toxicity Criteria for Adverse Events (CTCAE) Version 4.03.

SUMMARY OF RESULTS:

Subject Disposition and Demographics: Eighteen subjects were enrolled in the study and all 18 subjects (100%) received study drug (IDL). Five subjects (27.8%) completed the study and 13 subjects (72.2%) prematurely discontinued the study. Reasons for study discontinuation included AE (5 subjects, 27.8%), disease progression (7 subjects, 38.9%), and other (change in eligibility status) (1 subject, 5.6%).

Subjects ranged in age from 31 to 84 years, with a median age of 58 years. Most subjects were male (10 subjects, 55.6%) and white (12 subjects, 66.7%). Median (range) BMI was 26.1 (18.1 to 51.1) kg/m^2.

At baseline, a total of 10 subjects (55.6%) had a diagnosis of FL, 4 subjects (22.2%) had SLL, 3 subjects (16.7%) had MZL, and 1 subject (5.6%) had a missing diagnosis. The median (range) time since diagnosis was 3.9 (0.2 to 16.9) years. Ten subjects (55.6%) had a WHO performance score of 0 and 8 subjects (44.4%) had a WHO performance score of 1. All 18 subjects (100.0%) had a lymph node biopsy sample that was tumor-positive.

Efficacy Results:

Overall Response Rate: The ORR (95% CI) for all subjects (N = 18) was 44.4% (21.5, 69.2). One subject (5.6%) had a CR, 7 subjects (38.9%) had a PR, 3 subjects (16.7%) had SD, 3 subjects (16.7%) had PD, and 4 subjects (22.2%) were not evaluated.

Duration of Response: Eight subjects achieved a CR or PR and were evaluated for DOR. The KM estimate of median (95% CI) DOR (months) was not reached (7.6, NR).

Lymph Node Response and Best Percent Change From Baseline in SPD: Nine of 13 subjects with postbaseline assessments had a ≥ 50% decrease from baseline SPD for a LNR (95% CI) of 69.2% (38.6, 90.9).

Time to Response: Median (range) TTR for the 8 subjects who achieved a CR or PR was 2.7 months (2.4 to 9.1).

Progression-Free Survival: The KM estimate of median PFS (95% CI) was 10.2 months (2.8, NR). Seven subjects (38.9%) experienced disease progression and data for 11 subjects (61.1%) were censored.

Pharmacokinetics/Pharmacodynamics Results: No PK or pharmacodynamic analyses were performed for this report.

Safety Results:

Exposure: Exposure to IDL ranged from 0.0 to 11.5 months, with a median exposure of 4.3 months. Eleven subjects (61.1%) had a modification from the starting dose. One subject (5.6%) had a dose elevation to Dose level +2 (300 mg, twice daily). Ten subjects (55.6%) had a dose reduction to Dose level −1 (100 mg, twice daily), of which 1 subject (5.6%) had a further dose reduction to Dose level −2 (75 mg, twice daily).

Adverse Events: A total of 16 subjects (88.9%) experienced an AE. The most commonly reported AEs were increased alanine aminotransferase (ALT) and increased aspartate aminotransferase (AST) (9 subjects, 50.0%, each); diarrhea and fatigue (8 subjects, 44.4%, each); and nausea (7 subjects, 38.9%).

Ten subjects (55.6%) experienced at least 1 AE ≥ Grade 3. The most common AEs ≥ Grade 3 were increased ALT (5 subjects, 27.8%), increased AST (4 subjects, 22.2%), and increased transaminase, neutropenia, and renal failure (3 subjects, 16.7%, each).

A total of 15 subjects (83.3%) experienced at least 1 AE assessed by the investigator as related to IDL. The most common IDL-related AEs were increased ALT and increased AST (9 subjects, 50.0%, each); diarrhea, nausea, and fatigue (6 subjects, 33.3%, each); and rash (5 subjects, 27.8%).

Adverse Events of Interest: Adverse events of interest (AEIs) for IDL were any grade bowel perforation, ≥ Grade 3 diarrhea and/or colitis, any grade progressive multifocal leukoencephalopathy (PML), any grade pneumonitis, and ≥ Grade 3 rash per medical search term (MST). Following from the safety findings identified in March 2016, AEIs of infection (specifically ≥ Grade 3 infection, ≥ Grade 3 febrile neutropenia, any grade cytomegalovirus [CMV] infection, and any grade *Pneumocystis jirovecii* pneumonia [PJP]) were added.

No subjects reported any grade bowel perforation, ≥ Grade 3 diarrhea and/or colitis, any grade PML, ≥ Grade 3 febrile neutropenia, any grade CMV infection, or any grade PJP. Five subjects (27.8%) experienced an AEI. Three subjects (16.7%) reported any grade pneumonitis, 2 subjects (11.1%) reported a ≥ Grade 3 infection, and 1 subject reported a ≥ Grade 3 rash per MST.

For the 3 subjects (16.7%) who reported pneumonitis of any grade during this study, the median (Q1, Q3) time to onset of the first event of any grade pneumonitis (N = 3) was 25.7 (12.1, 34.0) weeks, and the median (Q1, Q3) time to resolution (N = 2) was 8.7 (4.1, 13.3) weeks. Three subjects (16.7%) had an interruption of IDL due to pneumonitis. No deaths due to pneumonitis were reported.

Two subjects (11.1%) experienced a ≥ Grade 3 infection during this study. The median (Q1, Q3) time to onset of the first event of ≥ Grade 3 infection was 23.7 (4.1, 43.3) weeks, none of these events resolved. One subject (5.6%) had an interruption of IDL due to ≥ Grade 3 infection. Subject PPD had an infectious event (sepsis) leading to death and Subject PPD had an infectious event (left thigh cellulitis) ongoing at the time of death.

The time to onset of the first event of ≥ Grade 3 rash (1 subject, 5.6%) was 1.4 weeks, and time to resolution was 1.9 weeks. One subject (5.6%) had an interruption of IDL due to ≥ Grade 3 rash. No deaths due to ≥ Grade 3 rash were reported.

Deaths: Two subjects (11.1%) died during the study treatment period or within 30 days following the last dose of study drug. Subject PPD an PPD male with FL, died on Study Day 30 (22 days after last dose of IDL). No cause of death was provided. Serious adverse events of gastrointestinal (GI) bleed and sepsis were ongoing when this subject died. Neither SAE was assessed by the investigator as related to IDL.

Subject PPD a 62-year-old male with SLL, died on Study Day 314 (13 days after last dose of IDL). According to the investigator, the cause of death was progression of disease. Cellulitis was assessed as ongoing at the time of death, serious, and possibly related to IDL. Tumor lysis syndrome and renal failure were reported as continuing at the time of death, fatal, and not related to IDL.

Serious Adverse Events: Overall, SAEs were reported for 5 subjects (27.8%). Two subjects (11.1%, each) experienced SAEs of renal failure and tumor lysis syndrome. All other SAEs were reported for 1 subject (5.6%, each).

Four subjects (22.2%) experienced SAEs considered by the investigator as related to IDL. All SAEs considered to be related to IDL were reported for 1 subject (5.6%, each), and included increased ALT, increased AST, increased transaminases, cellulitis, and pneumonitis.

Discontinuations Due to Adverse Events: Five subjects (27.8%) discontinued treatment with IDL due to AEs. Adverse events leading to IDL discontinuation included increased AST and increased transaminases (2 subjects, each), as well as increased ALT and increased hepatic enzyme (1 subject, each).

Dose Reductions Due to Adverse Events: Eleven subjects (61.1%) reported an AE that led to IDL dose reduction or interruption. Ten subjects (55.6%) had a dose reduction to from the starting dose of IDL (150 mg, twice daily) to Dose level −1 (100 mg, twice daily), of which 1 subject (5.6%) had a further dose reduction to Dose level −2 (75 mg, twice daily). The most common AEs leading to IDL dose reduction or interruption were increased ALT (5 subjects, 27.8%), increased AST (4 subjects, 22.2%), and increased transaminase and pneumonitis (3 subjects, 16.7%, each). All AEs leading to IDL dose reduction or interruption were considered related to study drug by the investigator.

Clinical Laboratory Evaluations: Two subjects (11.1%, each) experienced ≥ Grade 3 postbaseline hematologic laboratory abnormalities for hemoglobin, decreased lymphocytes, and platelets. All other ≥ Grade 3 postbaseline hematologic laboratory abnormalities occurred in 1 subject each. The most common ≥ Grade 3 postbaseline serum chemistry laboratory abnormalities were increased ALT (9 subjects, 50.0%), increased AST (7 subjects, 38.9%), and increased urate (2 subjects, 11.1%).

Nine subjects (50.0%) experienced a ≥ Grade 3 laboratory elevation in AST or ALT, all of which resolved to Grade 1 or less. Six subjects were rechallenged with IDL after a dose interruption due to ≥ Grade 3 elevated AST/ALT. Of these, 3 subjects experienced another ≥ Grade 3 AST/ALT elevation which subsequently resolved to Grade 1 or less.

Vital Signs: There were no trends of clinically significant changes in blood pressure, pulse, or body temperature during the study.

Treatment with IDL 150 mg twice daily was adequately tolerated.

CONCLUSIONS:

Key conclusions from the final analysis of Study 101-10 were as follows:

- Idelalisib had moderate activity in this population of previously treated subjects with low-grade iNHL (ORR of 44.4% for the ITT Analysis Set).
- Treatment with IDL 150 mg twice daily was adequately tolerated and had a manageable safety profile.