FINAL CLINICAL STUDY REPORT

Study Title:	A Phase 2 Single Arm Study to Investigate the Safety and Clinical Activity of Idelalisib Alone and in Combination with Rituximab in Elderly Subjects with Previously Untreated Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma
Name of Test Drug:	Idelalisib (Zydelig®; IDL, GS-1101)
Dose and Formulation:	Idelalisib 150-mg tablets twice daily
Indication:	Chronic Lymphocytic Leukemia (CLL) and Small Lymphocytic Lymphoma (SLL)
Sponsor:	Gilead Sciences, Inc. 199 East Blaine Street Seattle, WA 98102 USA
Study No.:	101-08
Phase of Development:	Phase 2
IND No.:	101254
EudraCT No.:	Not Applicable
ClinicalTrials.gov Identifier:	NCT01203930
Study Start Date:	28 September 2010 (First Subject Screened)
Study End Date:	07 June 2016 (Last Subject Observation)
Principal or Coordinating Investigator:	Name: Andrew Zelenetz, MD Affiliation: PPD
Gilead Responsible Medical Monitor:	Name: Ronald Dubowy, MD Telephone: PPD Fax: PPD
Report Date:	17 November 2016
Previous Report Dates:	01 April 2015 (Interim 2) 19 July 2013 (Interim 1)

STUDY SYNOPSIS

Study 101-08
Gilead Sciences, Inc.
199 East Blaine Street
Seattle, WA 98102
USA

Title of Study: A Phase 2 Single Arm Study to Investigate the Safety and Clinical Activity of Idelalisib Alone and in Combination with Rituximab in Elderly Subjects with Previously Untreated Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma

Investigators: Multicenter study (see Appendix 16.1.4)

Study Centers: A total of 6 sites in the United States (US) participated in this study.

Publications:

Zelenetz AD, Lamanna N, Kipps TJ, Coutre SE, O'Brien SM, Graves J, et al. A Phase 2 Study of Idelalisib Monotherapy in Previously Untreated Patients ≥65 Years With Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma [Presentation]. 16th International Workshop on Chronic Lymphocytic Leukemia (IWCLL); 2015 07-09 September; Sydney, Australia.

O'Brien SM, Lamanna N, Kipps TJ, Flinn I, Zelenetz AD, Burger JA, et al. A phase 2 study of idelalisib plus rituximab in treatment-naive older patients with chronic lymphocytic leukemia. Blood 2015;126 (25):2686-94.

O'Brien SM, Lamanna N, Kipps TJ, et al. Update on a Phase 2 Study of Idelalisib in Combination with Rituximab in Treatment-Naive Patients ≥ 65 Years with Chronic Lymphocytic Leukemia (CLL) or Small Lymphocytic Lymphoma (SLL). American Society of Hematology (ASH) 2014 Annual Meeting, 6 to 9 December 2014; San Francisco, CA, USA. Abstract 7564.

Zelenetz AD, Lamanna N, Kipps TJ, et al. A phase 2 study of idelalisib monotherapy in previously untreated patients ≥ 65 years with chronic lymphocytic leukemia or small lymphocytic lymphoma. ASH 2014 Annual Meeting, 6 to 9 December 2014; San Francisco, CA, USA. Abstract 1986.

O'Brien SM, Lamanna N, Kipps TJ, et al. A phase II study of the selective phosphatidylinositol 3-kinase delta (PI3Kδ) inhibitor idelalisib (GS 1101) in combination with rituximab (R) in treatment-naive patients (pts) ≥ 65 years with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL). American Society of Clinical Oncology (ASCO) 2013 Annual Meeting, 31 May to 4 June, 2013; Chicago, IL, USA. Abstract 7005.

Study Period:

28 September 2010 (First Subject Screened)
07 June 2016 (Last Subject Observation) 21 April 2016 (Last Subject Observation for the Primary Endpoint)

Phase of Development: Phase 2

Objectives:

The primary objective of this study was as follows:

- To evaluate the overall response rate (ORR) of idelalisib (IDL, GS-1101, Zydelig®) alone and when combined with rituximab in elderly subjects with previously untreated chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL)

The secondary objectives of this study were as follows:

- To assess the duration of response (DOR) and progression-free survival (PFS) of IDL alone and when combined with rituximab in elderly subjects with previously untreated CLL or SLL
- To evaluate the safety of IDL alone and combined with rituximab in elderly subjects with previously untreated CLL or SLL
- To determine plasma exposures of IDL alone and when combined with rituximab in elderly subjects with previously untreated CLL or SLL
- To investigate the pharmacodynamic effects and potential mechanisms of resistance to study therapy

Methodology: This was a Phase 2, single-arm study of IDL alone or combined with rituximab in elderly subjects with previously untreated CLL or SLL.

In Cohort 1, eligible subjects received IDL 150 mg orally twice daily on Days 1 through 28 of each 28-day cycle for 12 cycles and rituximab 375 mg/m^2 intravenously once weekly for 8 doses (Cycles 1 and 2). Subjects were evaluated for response after Cycles 2, 4, 6, 9, and 12 according to standard criteria. In Cohort 1, treatment with IDL and rituximab continued until disease progression or unacceptable toxicity, up to a maximum of 12 cycles of IDL. Subjects in Cohort 1 completing 48 weeks were eligible to continue IDL treatment in the long-term extension Study 101-99. All of the results for Cohort 1 were previously reported in the Study 101-08 Interim 1 Clinical Study Report (CSR) dated 19 July 2013; therefore, this Final CSR does not include any data from Cohort 1, as all subjects had previously either completed the study or continued into the extension Study 101-99. Data for subjects in Cohort 1 who continued into the extension Study 101-99 were reported in the Study 101-99 Interim CSR dated 30 July 2013 and the Study 101-99 Interim 2 CSR dated 09 February 2015. Data for subjects in Study 101-08 Cohort 1 that were ongoing at the time that the 101-99 Interim 2 CSR was finalized are reported in the 101-99 Interim 3 CSR.

In Cohort 2, eligible subjects received IDL 150 mg orally twice daily on Days 1 through 28 of each 28-day cycle. Subjects were evaluated for response after Weeks 8, 16, 24, and every 12 weeks thereafter according to standard criteria, as specifically modified to reflect current recommendations which consider the mechanism of action of IDL and similar drugs. In Cohort 2, treatment with IDL was to continue until disease progression or unacceptable toxicity. However, Cohort 2 was terminated early in March 2016 due to a safety signal demonstrating increased rates of deaths and serious adverse events (SAEs), generally due to infections, in a pooled analysis conducted by an independent Data Monitoring Committee (DMC) during regular review of 3 Phase 3 studies (GS-US-312-0123, GS-US-313-0124, and GS-US-313-0125) evaluating the addition of IDL to standard therapies in first-line CLL or early-line relapsed indolent non-Hodgkin lymphoma (iNHL). Subsequently, a decision was made to terminate all ongoing studies treating first-line CLL and early-line iNHL populations, which included Cohort 2 of Study 101-08.

Interim results for Cohort 2 were presented in the Study 101-08 Interim 2 CSR dated 01 April 2015. This Final CSR describes the final results for Cohort 2.

Safety parameters were evaluated throughout the study.

Number of Subjects (Planned and Analyzed):
Planned: 40 subjects (Cohort 2)
Enrolled: 41 subjects (Cohort 2)
Analyzed: 41 subjects in the Intent-to-Treat (ITT) Analysis Set (Cohort 2)

Diagnosis and Main Criteria for Inclusion: Eligible subjects were males and females ≥ 65 years of age with histologically or cytologically confirmed CLL or SLL who had received no prior therapy for CLL or SLL with the exception of corticosteroids for relief of symptoms, had measurable lymphadenopathy, and had a World Health Organization (WHO) performance status ≤ 2.

In addition, subjects with CLL had Binet Stage C or Rai Stage III or IV or active disease.

Subjects with SLL were required to have active disease.

Duration of Treatment: In Cohort 2, subjects received continuous IDL 150 mg orally twice daily until disease progression, unacceptable toxicity, or early study termination by the sponsor.

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

Idelalisib formulated as 150-mg tablets was administered at 150 mg twice daily at approximately 12-hour intervals. Idelalisib formulated as 100-mg tablets was administered at 100 mg twice daily at approximately 12-hour intervals if a subject experienced an IDL-related adverse event (AE) requiring dose reduction.

Lot numbers for 100-mg tablets (plain-faced): CV1110C1 and CY1201B1

Lot numbers for 100-mg tablets (debossed): CV1205C1, CV1205C1-A, and CV1302C1

Lot numbers for 150-mg tablets (debossed): CV1205D1, CV1205D1-A, and CV1305B1

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

Criteria for Evaluation:

Efficacy: Tumor response was assessed by the investigator according to modified International Workshop on Chronic Lymphocytic Leukemia Working Group (IWCLL) criteria and was defined as the proportion of subjects who achieved a complete response (CR) or partial response (PR). Lymph node response rate was assessed and defined as the proportion of subjects with a ≥ 50% decrease in the sum of the products of the greatest perpendicular diameters (SPD) of index lymph nodes. Duration of response from the first documentation of CR or PR to the earlier of the first documentation of disease progression or death from any cause, and PFS from the date of the first dose to the date of death or classification of progressive disease (PD) (whichever occurred first), were evaluated. The change from baseline in the SPD of index lymph nodes and response rates for splenomegaly, hepatomegaly, absolute lymphocyte count (ALC), platelets, hemoglobin, absolute neutrophil count (ANC), and B symptoms were also summarized.

Pharmacokinetics: Concentrations of IDL and its metabolite GS-563117 in plasma were determined.

Safety: Safety was assessed by monitoring of physical examination, vital signs, clinical laboratory tests (hematology, serum chemistry, coagulation, and urinalysis), electrocardiogram (ECG), and AEs. Toxicity of AEs was graded according to the Common Terminology Criteria for Adverse Events (CTCAE), Version 4.02 or 4.03 depending on the protocol version implemented when the AE was reported.

Statistical Methods:

Efficacy: The proportions (and 95% confidence intervals [CIs]) of subjects with overall and other response rates were computed. The exact 95% binomial CIs of the response rates were computed based on the value for the observed response rates.

Duration of response and PFS were computed using Kaplan-Meier (KM) methods. Data from surviving, nonprogressing subjects were censored at the last time that lack of definitive progression was objectively documented. For KM estimates, the 95% CIs were calculated using the Greenwood's formula with (complementary) log-log transformation.

Summary tables for continuous variables contained the following statistics: N (number in analysis set), n (number with data), mean, standard deviation (StD), 95% CI, median, first quartile (Q1), third quartile (Q3), minimum, and maximum. For data summaries of categorical variables, the following were presented: N, n, and percentage.

Pharmacokinetics: Individual subject concentration data and summary statistics at each time point for IDL and GS-563117 were tabulated for the PK Analysis Set. Plots of mean (StD) and median (Q1, Q3) IDL and GS-563117 concentration values versus time were provided.

Safety: Subject incidence of treatment-emergent adverse events (TEAEs), TEAEs assessed by the investigators as related to IDL, SAEs, TEAEs leading to deaths, and TEAEs leading to IDL dose discontinuation are presented. For TEAEs presented by severity, the worst severity during the study is presented for each subject. The incidence of TEAEs is summarized by system organ class (SOC), high-level term (HLT), and preferred term (PT) using Medical Dictionary for Regulatory Activities (MedDRA), Version 19.0. The incidence of AEs assessed by the investigators as related to IDL and CTCAE toxicity grade were summarized by SOC, HLT, and PT.

Adverse events of interest (AEI) for IDL were any grade bowel perforation, ≥ Grade 3 diarrhea and/or colitis, any grade pneumonitis, ≥ Grade 3 rash by medical search term (MST), and any grade progressive multifocal leukoencephalopathy (PML). 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 cytomegalovirus [CMV] infection, and any grade *Pneumocystis jirovecii* pneumonia [PJP]). The treatment-emergent AEI were summarized descriptively. Summaries of the incidence and prevalence of AEI by 12-week time intervals were provided. Time to first onset of AEI and time to resolution of AEI were summarized using descriptive statistics and KM estimates.

The severity of laboratory abnormalities was programmatically graded using the CTCAE, Version 4.03 whenever possible. Shifts from baseline laboratory values (to worst toxicity grade per subject) were tabulated.

SUMMARY OF RESULTS:

A safety signal demonstrating increased rates of deaths and SAEs, generally due to infections, was observed with IDL in combination with standard therapies in a pooled analysis of 3 Phase 3 studies in front-line CLL and early-line relapsed iNHL (GS-US-312-0123, GS-US-313-0124, and GS-US-313-0125). As a result, all Gilead-sponsored studies in front-line CLL and iNHL, including the present study, were terminated early as the risk:benefit profile was deemed unlikely to be favorable. Final results for Cohort 2 of this study are summarized below.

Subject Disposition and Demographics: A total of 41 subjects were enrolled in Cohort 2 of the study. All 41 subjects (100%) received at least 1 dose of study drug. Twenty-nine subjects discontinued study drug for reasons other than study termination by the sponsor, including AEs (20 subjects, 48.8%), consent withdrawn (5 subjects, 12.2%), investigator request (1 subject, 2.4%), subject noncompliance (1 subject, 2.4%), disease progression (1 subject, 2.4%), and death (1 subject, 2.4%). The remaining 12 subjects (29.3%) discontinued due to study termination by the sponsor.

At baseline, subjects ranged in age from 65 to 84 years (median: 71 years) in Cohort 2. Most subjects were male (32 subjects, 78.0%) and white (40 subjects, 97.6%). At screening, 26 subjects (63.4%) had a WHO performance status score of 1; 14 subjects (34.1%) had a score of 0; and 1 subject (2.4%) had a score of 2. Most subjects (38, 92.7%) were diagnosed with CLL; 3 subjects (7.3%) were diagnosed with SLL. The median time since diagnosis was 4.0 years (range 0.1 to 19.5 years). In total, 19 subjects (46.3%) had at least 1 B symptom at baseline, and the most common B symptoms were extreme fatigue (16 subjects, 39.0%) and unexplained night sweats (12 subjects, 29.3%). The following cytogenic mutations were reported based on samples collected at screening: immunoglobulin heavy chain variable gene (IGHV) mutations (17 subjects, 41.5%), 13q deletion (15 subjects, 36.6%), a gain of chromosome 12 (11 subjects, 26.8%), 11q deletion (9 subjects, 22.0%), 17p deletion/TP53 mutation (6 subjects, 14.6%), TP53 mutation (6 subjects, 14.6%), 17p deletion (4 subjects, 9.8%), and 8p deletion (3 subjects, 7.3%). No subjects were determined as having a NOTCH1 or SF3B1 mutation.

Efficacy Results: Final efficacy results for Cohort 2 are summarized below.

Overall Response Rates: The ORR for all subjects in Cohort 2 (N = 41) was 87.8% (95% CI, 73.8, 95.9). No CRs were documented; 36 subjects (87.8%) had a PR as the best overall response, 2 subjects (4.9%) had SD as the best overall response, and 3 subjects (7.3%) were not evaluated due to discontinuation prior to the first efficacy evaluation. Although numerically higher, the ORR in the group with neither 17p deletion nor TP53 mutation (90.3%) was similar to that in the group with either of these mutations (83.3%). It should be noted that the number of subjects who had either 17p deletion or TP53 mutation was small (6 subjects). Although numerically higher, the ORR in those with IGHV mutation (16 subjects, 94.1%) was similar to that in the group without IGHV mutation (17 subjects, 89.5%).

Additional Response Rates: Clinically meaningful improvement was observed in all the individual components of ORR: 33 of 38 subjects (86.8%) had lymph node response, 22 of 24 subjects (91.7%) had splenomegaly response, 4 of 5 subjects (80.0%) had hepatomegaly response, 32 of 39 subjects (82.1%) had ALC response, 12 of 13 subjects (92.3%) had platelet response, 16 of 23 subjects (69.6%) had hemoglobin response, and 10 of 10 subjects (100.0%) had neutrophil response. Sixteen of the 19 subjects (84.2%) who had at least 1 B symptom at baseline became asymptomatic at a time point(s) postbaseline.

Duration of Response: The median DOR from the KM method (based on subjects achieving a PR) was 22.5 months.

Progression-Free Survival: The median PFS from the KM method was 26.2 months. Eleven subjects (26.8%) progressed while on study. One subject PPD died due to sepsis secondary to healthcare associated pneumonia. Another subject PPD died during long-term follow-up. His PFS was censored at the first dosing date because of missing postbaseline tumor assessment.

Time to Response (TTR): Among the 36 responding subjects (ie, subjects with a best overall response of PR) out of 41 ITT subjects in Cohort 2, the median (range) TTR was 1.9 (1.8 to 11.1) months. Median (range) TTR was 5.3 (1.9 to 7.4) months for those with either 17p deletion or TP53 mutation (5 subjects) versus 1.9 (1.8 to 11.1) months for subjects with neither 17p deletion nor TP53 mutation. Median (range) TTR was 2.8 (1.8 to 11.1) months for those with IGHV mutation who responded (16 subjects) versus 1.9 (1.9 to 3.9) months for those without IGHV mutation who responded (17 subjects).

Best Percent Change from Baseline in SPD: Of the 38 subjects with lymph node enlargement at baseline who had at least 1 postbaseline efficacy assessment, median (range) best percent change in SPD compared to baseline was −81.1% (−100.0% to 0.0%) ($p < 0.001$).

Pharmacokinetics Results: In general, both IDL and GS-563117 plasma concentrations were comparable to other studies (eg, Study 101-02) following 150 mg twice daily dosing and were greater than the 50% effective concentration (EC_{50}) for inhibition of PI3Kδ activity (39 nM geometric mean EC_{50} data).

Safety Results: In Cohort 2, a total of 41 subjects received IDL for a median of 9.3 months (range: 1.4 to 26.8 months).

Adverse Events, Overall: The most common AEs were diarrhea (28 subjects, 68.3%); nausea, pyrexia, and rash (14 subjects, 34.1%, each); and fatigue (13 subjects, 31.7%).

Adverse Events, Severity: The most common AEs of ≥ Grade 3 severity were diarrhea (11 subjects, 26.8%), ALT increased (9 subjects, 22.0%), and AST increased (7 subjects, 17.1%).

Adverse Events, Relationship to IDL as Reported by Investigators, Severity: Overall, AEs of ≥ Grade 3 severity considered related to IDL were reported for 28 subjects (68.3%) in Cohort 2. The most common AEs of ≥ Grade 3 severity considered related to IDL were diarrhea (10 subjects, 24.4%), ALT increased (9 subjects, 22.0%), and AST increased (7 subjects, 17.1%).

Adverse Events of Interest: AEI for IDL were any grade bowel perforation, ≥ Grade 3 diarrhea and/or colitis, any grade pneumonitis, ≥ Grade 3 rash by MST, and any grade PML. 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 PJP). The incidence and prevalence of AEI was generally highest during the early intervals after treatment initiation, and declined over the duration of the study. No events of bowel perforation, PML, or ≥ Grade 3 febrile neutropenia occurred during this study through 132 weeks of follow-up.

≥ Grade 3 Diarrhea and/or Colitis

In Cohort 2, 15 subjects (36.6%) had ≥ Grade 3 AEs of diarrhea/colitis (14 subjects with Grade 3 and 1 subject with Grade 4 events), with an exposure-adjusted incidence rate of 0.352 events/subject-year. The median time to onset of the first ≥ Grade 3 event of diarrhea/colitis (n = 15) was 33.4 weeks (range: 6.1 to 92 weeks), and the median time to resolution of any ≥ Grade 3 diarrhea/colitis (n = 14) was 1.5 weeks (range: 0.9 to 9.0 weeks). Nine subjects (22.0%) permanently discontinued IDL due to ≥ Grade 3 diarrhea or colitis. No deaths due to diarrhea or colitis were reported.

Any Grade Pneumonitis

In Cohort 2, 3 subjects (7.3%) had pneumonitis of any grade (1 subject had a Grade 2 AE of pneumonitis and 2 subjects had Grade 3 AEs of pneumonitis). The exposure-adjusted incidence rate for pneumonitis was 0.064 events/subject-year. The median time to onset of the first ≥ Grade 3 pneumonitis event (n = 3) was 8.1 weeks (range: 6.9 to 15.0 weeks), and the median time to resolution of pneumonitis (n = 3) was 1.7 weeks (range: 1.4 to 11.1 weeks). Two subjects (4.9%) discontinued IDL due to pneumonitis.

≥ Grade 3 Rash by MST

In Cohort 2, 4 subjects (9.8%) experienced ≥ Grade 3 AEs of rash; all were Grade 3 events. The exposure-adjusted incidence rate for ≥ Grade 3 AEs of rash was 0.089 events/subject-year. The median time to onset of the first ≥ Grade 3 rash (n = 4) was 8.9 weeks (range: 1.6 to 42.9 weeks), and the median time to resolution of rash (n = 4) was 4.1 weeks (range: 1.6 to 10.3 weeks). Idelalisib dosing was interrupted and then reduced for 1 subject with an AE of rash, and IDL dosing was discontinued for 1 subject with an AE of rash.

≥ Grade 3 Infection

In Cohort 2, 8 subjects (19.5%) had ≥ Grade 3 infections, with an exposure-adjusted incidence rate of 0.187 events/subject-year. The median time to onset of the first ≥ Grade 3 infection (n = 8) was 24.8 weeks (range: 4.9 to 35.7 weeks), and the median time to resolution of any ≥ Grade 3 infection (n = 7) was 1.4 weeks (range: 0.4 to 5.0 weeks). Three subjects permanently discontinued IDL due to infections, including Grade 3 cellulitis (2 subjects) and Grade 5 pneumonia (1 subject; this event led to the subject's death).

≥ Grade 3 Febrile Neutropenia

In Cohort 2, no subject had a ≥ Grade 3 AE of febrile neutropenia during the study.

Any Grade CMV Infection

In Cohort 2, CMV of any grade occurred in 2 subjects (4.9%), including 1 subject who had a Grade 1 AE of CMV infection and 1 subject who had a Grade 3 AE of CMV esophagitis. The exposure-adjusted incidence rate for CMV was 0.043 events/subject-year. The time to onset for the events of CMV infection and CMV esophagitis was 15.0 and 31.9 weeks, respectively. The CMV esophagitis resolved during the study and the time to resolution was 5.0 weeks; the CMV infection was ongoing at the time of final database lock.

The Grade 3 AE of CMV esophagitis led to interruption of IDL dosing. No subject permanently discontinued IDL or died due to CMV during the study.

Any Grade PJP

In Cohort 2, 1 subject had PJP (Grade 2) during the study; this subject was not receiving PJP prophylaxis. The exposure-adjusted incidence rate for PJP was 0.022 events/subject-year. The time to onset of this event was 49.1 weeks, and the time to resolution was 1.4 weeks. Idelalisib dosing was not interrupted or discontinued due to this event.

Deaths: Two subjects in Cohort 2 died during the study. One subject died due to sepsis secondary to healthcare-associated pneumonia. The investigator assessed the subject's death as not related to IDL. The other subject died 371 days after discontinuation of IDL; the cause of this subject's death was unknown.

Serious Adverse Events: Overall, SAEs were reported for 28 subjects (68.3%) in Cohort 2. The most common SAEs (≥ 5% of subjects) were diarrhea (7 subjects, 17.1%), pneumonia (5 subjects, 12.2%), colitis (4 subjects, 9.8%), and pyrexia (3 subjects, 7.3%); most of these events were considered by the investigator to be related to IDL.

Dose Reductions, Interruptions, and Discontinuations due to Adverse Events: Fourteen subjects (34.1%) had 1 or more AEs leading to IDL dose reductions and 25 subjects (61.0%) had 1 or more AEs leading to IDL dose interruptions (note that a subject may have had multiple dose modifications). Twenty-three subjects (56.1%) had 1 or more AEs leading to permanent discontinuation of IDL. The most common AEs leading to discontinuation of IDL were diarrhea in 9 subjects (22.0%); colitis in 3 subjects (7.3%); and cellulitis, pneumonitis, and rash in 2 subjects (4.9%) each.

Clinical Laboratory Evaluations: A clinically favorable change in hemoglobin level was observed with continuous administration of IDL. A clinically favorable change in platelets was also observed with continuous administration of IDL through Week 84, with more variable results thereafter. Among the 41 treatment-naive subjects in this present study, 7 subjects (17.1%) had ≥ Grade 3 neutropenia. The neutropenia observed was often transient, with single observations of ≥ Grade 3 neutropenia being reported in 3 of the 4 subjects with ≥ Grade 3 neutropenia who had normal baseline values. One subject with normal baseline values had more persistent neutropenia. Lymphocytosis was evident in the early months of treatment with IDL monotherapy in Cohort 2. By laboratory evaluation, 9 subjects (22.0%) had ≥ Grade 3 ALT/AST elevations, all of which resolved to Grade 1 or less. Four of these subjects were rechallenged with IDL after a dose interruption due to their ≥ Grade 3 ALT/AST elevation. After rechallenge, 1 of the 4 subjects had recurrence of a ≥ Grade 3 ALT/AST elevation, which subsequently resolved to Grade 1 during a dose interruption. This subject subsequently restarted IDL 100 mg twice daily and had Grade 2 ALT/AST elevation. The median time to onset for ≥ Grade 3 ALT/AST elevation was 7.9 weeks (range: 6.1, 24.1 weeks), and the median time to resolution of the first ≥ Grade 3 ALT/AST elevation was 3.6 weeks (range: 1.1, 6.1 weeks). One additional subject had ≥ Grade 3 elevations in ALT/AST that were reported as AEs based on local laboratory evaluations that were not captured in the central laboratory data. In Cohort 2, by laboratory evaluation, no subject experienced AST or ALT > 3 × ULN with concurrent elevation of bilirubin > 2 × ULN and elevated alkaline phosphatase (> 1.5 × ULN).

Vital Signs: Overall, there were no clinically meaningful changes in temperature, blood pressure, or heart rate during the study. For 1 subject in Cohort 2, the corrected QT intervals by Bazett and Fridericia methods were increased by > 60 msec from baseline at Week 36.

CONCLUSIONS:

- Single-agent IDL was clinically active in this population of elderly subjects with previously untreated CLL (38 subjects) or SLL (3 subjects) who, due to their advanced age, were not able to receive cytotoxic agents. The ORR in these subjects was 87.8% (95% CI, 73.8%, 95.9%). Partial response or SD was seen in all 38 evaluable subjects. Partial responses were seen in 36 subjects (87.8%) in Cohort 2, including 5 of 6 subjects with 17p deletion and/or TP53 mutation. The KM estimate of median DOR was 22.5 months.
- The KM estimate of median PFS was 26.2 months. Eleven subjects (26.8%) experienced PD and 1 subject (2.4%) died (cause of death: sepsis secondary to healthcare associated pneumonia). Improvements were noted in hematologic parameters such as platelet response (92.3%), ANC response (100.0%), ALC response (82.1%), and hemoglobin response (69.6%). Improvements were also noted in other clinical manifestations of disease including lymphadenopathy (86.8%), splenomegaly (91.7%), and hepatomegaly (80.0%).
- In general, both IDL and GS-563117 plasma concentrations were comparable to other clinical studies of IDL (eg, Study 101-02) following 150 mg twice daily dosing and were greater than the EC_{50} for inhibition of PI3Kδ activity (39 nM geometric mean EC_{50} data).
- No new safety events were identified in Cohort 2 of this study. The relatively high incidence of Grade 3 diarrhea/colitis (36.6%) is consistent with that observed in subjects enrolled in Cohort 1, who received IDL + rituximab.