FINAL CLINICAL STUDY REPORT

Study Title:	A Phase 3, Double-Blind Extension Study Evaluating the Efficacy and Safety of Two Different Dose Levels of Single-Agent Idelalisib (GS-1101) for Previously Treated Chronic Lymphocytic Leukemia *A Companion Trial to Study GS-US-312-0116: A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Efficacy and Safety of Idelalisib (GS-1101) in Combination with Rituximab for Previously Treated Chronic Lymphocytic Leukemia*
Name of Test Drug:	Idelalisib (IDL, Zydelig®, GS-1101)
Dose and Formulation:	Idelalisib 150 mg or 300 mg, twice daily
Indication:	Chronic lymphocytic leukemia
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404, USA
Study No.:	GS-US-312-0117
Phase of Development:	Phase 3
IND No.:	101254
EudraCT No.:	2011-006293-72
ClinicalTrials.gov Identifier:	NCT01539291
Study Start Date:	03 October 2012 (First Subject Screened)
Study End Date:	29 June 2018 (Last Subject Last Observation for this Report) 21 June 2018 (for Independent Review Committee)
Principal or Coordinating Investigator:	Name: Jeff Sharman Affiliation: PPD
Gilead Responsible Medical Monitor:	Name: Theo Sarif, MD Telephone: PPD Fax: PPD
Report Date:	05 November 2018
Previous Report Date:	28 November 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-312-0117
Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404
USA

Title of Study: A Phase 3, Double-Blind Extension Study Evaluating the Efficacy and Safety of Two Different Dose Levels of Single-Agent Idelalisib (GS-1101) for Previously Treated Chronic Lymphocytic Leukemia

A Companion Trial to Study GS-US-312-0116: A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Efficacy and Safety of Idelalisib (GS-1101) in Combination with Rituximab for Previously Treated Chronic Lymphocytic Leukemia

Investigators: This study was a multicenter study.

Study Centers: A total of 53 sites in the United States (US), Germany, Italy, the United Kingdom, and France randomized at least 1 subject in Study GS-US-312-0116; 45 sites enrolled subjects in Study GS-US-312-0117.

Publications:

Coutre SE, Furman RR, Sharman, JP, Cheson BD, Pagel JM, Hillmen P, et al. Second Interim Analysis of a Phase 3 Study of Idelalisib (Zydelig®) Plus Rituximab for Relapsed Chronic Lymphocytic Leukemia: Efficacy Analysis in Patient Subpopulations with Del(17p) and Other Adverse Prognostic Factors. Blood 2014; 124 (21):330

Sharman JP, Coutre SE, Furman RR, Cheson BD, Pagel JM, Hillmen P, et al. Efficacy of Idelalisib in CLL Subpopulations Harboring Del(17p) and Other Adverse Prognostic Factors: Results from a Phase 3, Randomized, Double-blind, Placebo-controlled Trial [Poster 7011]. American Society of Clinical Oncology (ASCO) 50th Annual Meeting; 2014 May 30-June 3; Chicago, IL. J Clin Oncol 32:5s, 2014 (suppl; abstr 7011)

Study Period:

03 October 2012 (First Subject Screened)
29 June 2018 (Last Subject Last Observation for this Report)

Phase of Development: Phase 3

Objectives:

- To evaluate the effect of idelalisib (IDL, Zydelig®, GS-1101) on the onset, magnitude, and duration of tumor control
- To compare tumor control in subjects receiving rituximab alone in Study GS-US-312-0116 to that observed in the same subjects when receiving the standard dose of IDL alone in Study GS-US-312-0117
- To assess the effect of IDL on measures of subject well-being, including overall survival (OS), health-related quality of life (HRQL), and performance status

- To assess the effects of IDL on disease-associated biomarkers and to evaluate potential mechanisms of resistance to IDL
- To characterize exposure to IDL as determined by treatment administration and evaluation of IDL plasma concentrations over time
- To describe the safety profile observed with IDL
- To estimate health resource utilization associated with administration of IDL

Methodology: Study GS-US-312-0116 was a Phase 3, multicenter, 2-arm, randomized, double-blind, placebo-controlled, parallel-group study. Study GS-US-312-0117 is a separate, multicenter, 2-arm, double-blind, parallel-group extension study that was a companion study to Study GS-US-312-0116. Compliant subjects from Study GS-US-312-0116 who tolerated primary study therapy but experienced definitive chronic lymphocytic leukemia (CLL) progression were eligible to receive active blinded IDL therapy at the standard dose or a higher dose, with allocation based on the original primary study randomization. Study GS-US-312-0116 was stopped due to efficacy on 08 November 2013; subjects remaining on Study GS-US-312-0116 at that time transitioned to Study GS-US-312-0117 and could receive open-label standard dose IDL.

In 2017, following a review of ongoing IDL clinical development studies, Gilead determined that a number of legacy studies, including Study GS-US-312-0117, had few remaining active subjects and limited additional safety data to be generated even if the studies were to continue. Both the United States Food and Drug Administration (FDA) and the European Medicines Agency (EMA) agreed with Gilead's proposal to transition ongoing subjects to commercial Zydelig® and close Study GS-US-312-0117 that was being conducted in part to fulfill an FDA postmarketing requirement and an EMA post-authorization measure. On 29 June 2018, Gilead transitioned the last remaining subject in Study GS-US-312-0117 to commercial Zydelig® and closed the study.

Number of Subjects (Planned and Analyzed):
Planned: Up to 180 subjects, assuming a 10% dropout rate during Study GS-US-312-0116 and a further 10% dropout rate in the transition from Study GS-US-312-0116 to Study GS-US-312-0117

Analyzed: 220 subjects (110 subjects each: IDL+rituximab [R] and placebo+R) enrolled in Study GS-US-312-0116; 161 subjects subsequently enrolled in Study GS-US-312-0117

Diagnosis and Main Criteria for Inclusion: The target population included subjects in Study GS-US-312-0116 who were compliant, tolerated primary study therapy, and 1) had definitive progression of CLL while receiving study drug therapy (IDL/placebo) or 2) were actively participating in Study GS-US-312-0116 at the time the study was stopped on 08 November 2013.

Subjects met all of the following criteria to enroll in the blinded portion of this study:

1) Participation in Study GS-US-312-0116
2) Occurrence of confirmed, definitive CLL progression while receiving study drug therapy (IDL/placebo) in Study GS-US-312-0116

3) Presence of measurable lymphadenopathy (defined as the presence of ≥ 1 nodal lesion that measured ≥ 2.0 cm in the longest diameter and ≥ 1.0 cm in the longest perpendicular diameter as assessed by computed tomography or magnetic resonance imaging

4) Permanent cessation of Study GS-US-312-0116 treatment (rituximab and/or IDL/placebo) and no intervening or continuing therapy (including radiotherapy, chemotherapy, immunotherapy, or investigational therapy) for the treatment of CLL

5) The time from permanent cessation of Study GS-US-312-0116 treatment (rituximab and/or IDL/placebo) and the initiation of Study GS-US-312-0117 therapy was ≤ 12 weeks.

6) Karnofsky performance score of ≥ 40

7) Required baseline laboratory data (within 4 weeks prior to initiation of study treatment) as shown in the following table:

Required Screening Laboratory Values

Organ System	Parameter	Required Value
Hepatic	Serum total bilirubin	≤ 1.5 × ULN (unless elevated due to Gilbert's syndrome)
	Serum alanine amino transferase	≤ 2.5 × ULN
	Serum aspartate amino transferase	
Renal	eCL_{cr}[a]	> 30 mL/min
Pregnancy	β-HCG[b]	Negative

β-HCG = beta human chorionic gonadotropin; eCL_{cr} = estimated creatinine clearance; ULN = upper limit of normal
a As calculated by the Cockcroft-Gault formula {Cockcroft 1976}
b For women of childbearing potential only; serum β-HCG must have been negative during screening and serum β-HCG or urine dipstick pregnancy test must have been negative at randomization (Visit 2)

When Study GS-US-312-0116 was stopped at first interim analysis, subjects who were participating in Study GS-US-312-0116 became eligible for Study GS-US-312-0117, provided the following inclusion criteria were met:

1) Participation in Study GS-US-312-0116 within 12 weeks of enrollment onto Study GS-US-312-0117

2) For female subjects of childbearing potential, willingness to use a protocol-recommended method of contraception from the screening visit (Visit 1) throughout the study and for 30 days from the last dose of study drug

3) For male subjects of childbearing potential having intercourse with females of childbearing potential, willingness to use a protocol-recommended method of contraception from the start of study drug (Visit 2) throughout the study and for 90 days following the last dose of study drug and to refrain from sperm donation from the start of study drug (Visit 2) throughout the study and for 90 days following the last dose of study drug

4) 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

5) Willingness and ability to comply with scheduled visits, drug administration plan, imaging studies, laboratory tests, other study procedures, and study restrictions. Note: psychological, social, familial, or geographical factors that might preclude adequate study participation should be considered
6) Evidence of a personally signed informed consent indicating that the subject was aware of the neoplastic nature of the disease and was 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: Study drug was taken continuously until the earliest of subject withdrawal from study drug, definitive progression of CLL, intolerable study drug-related toxicity, pregnancy, substantial noncompliance with study procedures, or study discontinuation.

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

Blinded Portion

- IDL 300 mg/dose twice daily: study drug was provided as 2 tablets of active IDL for oral administration, lot no. CV1104D2, CV1204B2, CV1206B2, CV1305B1, and CV1308B1.
- IDL 150 mg/dose twice daily: study drug was provided as 1 tablet of active IDL and 1 tablet of placebo for oral administration, lot no. CV1108D2 and CV1203B2.

Open-Label Extension Portion (following unblinding)

- Subjects in the IDL 300 mg group prior to unblinding continued to receive two 150-mg tablets of IDL twice daily, lot no. CV1104D2, CV1204B2, CV1206B2, CV1305B1, and CV1308B1.
- All other subjects received one 150-mg tablet of IDL twice daily, lot no. CV1104D2, CV1204B2, CV1205C1, CV1206B2, CV1305B1, CV1308B1, CV1308B1-A, and THSP.

Following dose interruption, some subjects were rechallenged (per protocol) with a modified dose of 100mg, lot no. CV1104C2, CV1110C3, CY1201B2, CV1205C1, CV1302C1, and CV1304D1.

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

Criteria for Evaluation:

Efficacy:

Tumor Control

- Progression-free survival (PFS) – defined as the interval from the start of study therapy to the earlier of the first documentation of definitive disease progression or death from any cause; definitive disease progression is CLL progression based on standard criteria other than lymphocytosis alone
- Overall response rate (ORR) – defined as the proportion of subjects who achieved a complete response (CR) or partial response (PR)
- Lymph node response rate (LNR) – defined as the proportion of subjects who achieved a ≥ 50% decrease from baseline in the sum of the products of the greatest perpendicular diameters (SPD) of index lymph nodes
- CR rate – defined as the proportion of subjects who achieved a CR

- Time to response (TTR) – defined as the interval from start of study therapy to the first documentation of CR or PR
- Duration of response (DOR) – defined as the interval from the first documentation of CR or PR to the earlier of the first documentation of definitive disease progression or death from any cause
- Percent change in lymph node area – defined as the percent change from baseline in the SPD of index lymph nodes
- Splenomegaly response rate – defined as the proportion of subjects with baseline splenomegaly who achieve normalization or a 50% decrease (minimum 2 cm) from baseline in the enlargement of the splenic longest vertical dimension (LVD) (by imaging)
- Hepatomegaly response rate – defined as the proportion of subjects with baseline hepatomegaly who achieve an on-study normalization or a 50% decrease (minimum 2 cm) from baseline in the hepatic LVD (by imaging)
- Absolute lymphocyte count (ALC) response rate – defined as the proportion of subjects with baseline lymphocytosis (ALC $\geq 4 \times 10^9$/L) who achieved an on-study ALC $< 4 \times 10^9$/L or demonstrated a $\geq$ 50% decrease in ALC from baseline. ALC values within 4 weeks postbaseline were excluded from the ALC response rate evaluation
- Platelet response rate – defined as the proportion of subjects with baseline thrombocytopenia (platelet count $< 100 \times 10^9$/L) who achieved an on-study platelet count $\geq 100 \times 10^9$/L or demonstrated a $\geq$ 50% increase in platelet count from baseline. Platelet values within 4 weeks postbaseline or after 8 days posttransfusion were excluded from the platelet response rate evaluation
- Hemoglobin response rate – defined as the proportion of subjects with baseline anemia (hemoglobin < 110 g/L [11.0 g/dL]) who achieved an on-study hemoglobin $\geq$ 110 g/L (11.0 g/dL) or demonstrated a $\geq$ 50% increase in hemoglobin from baseline; hemoglobin values within 4 weeks postbaseline, after 4 weeks of receiving packed cell/whole blood transfusion, or after 6 weeks of receiving exogenous growth factors (eg, darbepoetin alfa) were excluded from the hemoglobin response evaluation
- Neutrophil response rate – defined as the proportion of subjects with baseline neutropenia (absolute neutrophil count [ANC] $\leq 1.5 \times 10^9$/L) who achieve an ANC $> 1.5 \times 10^9$/L or demonstrate a $\geq$ 50% increase in ANC from baseline; ANC values within 4 weeks of postbaseline, or after 2 weeks of receiving granulocyte-colony stimulating factor (G-CSF) or other exogenous growth factors (eg, filgrastim, granulocyte colony-stimulating factor, lenograstim), or after 4 weeks of receiving Neulasta® were excluded from response evaluation

<u>Patient Well-Being</u>

- OS – defined as the interval from the date of randomization in Study GS-US-312-0116 to death from any cause during the study or long-term follow-up
- Change in HRQL domain and symptom scores based on the Functional Assessment of Cancer Therapy: Leukemia (FACT-Leu)
- Changes in Karnofsky performance status – defined as the change from baseline in the performance status

Pharmacodynamics:

Pharmacodynamic Markers of Drug Activity and Resistance

- Changes from baseline in phosphatidylinositol 3-kinase (PI3K)/serine/threonine protein kinase/mammalian target of rapamycin pathway activation as a measure of PI3Kδ pathway activity
- Changes from baseline in the plasma concentrations of disease-associated chemokines and cytokines

Exposure:

- Study drug administration as assessed by prescribing records and compliance as assessed by quantification of used and unused drug
- Trough (predose) and peak (1.5-hour postdose samples) of IDL plasma concentrations as assessed by a validated bioanalytical method

Safety:

- Overall safety profile of each regimen characterized by the type, frequency, severity, timing of onset, duration, and relationship to study therapy of any adverse events (AEs) or abnormalities of laboratory tests; serious adverse events (SAEs); or AEs leading to discontinuation of study drug

Other: Pharmacoeconomics:

- Change in health status – defined as the change from baseline in overall health and single-item dimension scores as assessed using the EuroQoL Five-Dimension (EQ-5D) utility measure
- Health resource measures, including resource utilization, total costs, and measures of cost per unit of benefit (eg, cost per additional progression-free month and cost per quality-adjusted life-year)

Statistical Methods:

Various analysis sets were defined for this study. The Intent-to-Treat (ITT) Analysis Set includes data from all subjects who were randomized in Study GS-US-312-0116 regardless of whether subjects received any study drug(s) or received a different regimen from the regimen to which they were randomized. Treatment assignment was designated according to randomization. This analysis set was used for OS analyses. The Full Analysis Set (FAS) includes all subjects in the ITT Analysis Set who received ≥ 1 dose of IDL, with treatment assignments designated according to randomization. Because all the subjects received the correct treatment as randomized, this analysis set was used for both the efficacy and safety analyses.

Other analysis sets (Pharmacokinetic [PK]/Pharmacodynamic Analysis Sets) were used for certain analyses as well. The PK/Pharmacodynamic Analysis Sets include data from subjects in the FAS who had the necessary baseline and on-study measurements to provide interpretable results for the specific parameters of interest.

Subject characteristics and study results were described and summarized by treatment group and assessment for the relevant analysis sets. Descriptive summaries were prepared to show sample

size, mean, standard deviation, 95% confidence intervals (CIs) on the mean, median, minimum, and maximum for continuous variables and counts, percentages, and 95% CIs on the percentage for categorical variables.

An independent review committee (IRC) reviewed radiographic data and pertinent clinical data in order to provide expert evaluation of tumor status. The findings of the IRC were considered primary for analyses of PFS and other tumor control endpoints.

For endpoints relating to tumor control, patient well-being, and biomarkers, analyses were done based on the FAS or PK/Pharmacodynamic Analysis Sets, as appropriate. The blinded portion of the study analyses are presented for the following 2 groups:

- **IDL+R (progressive disease [PD])/IDL:** Subjects in Group A (IDL+ R) in Study GS-US-312-0116 who had PD per IRC confirmation and subsequently enrolled in Study GS-US-312-0117 to receive IDL 300 mg twice daily during the double-blind portion of the study
- **Placebo+R (PD)/IDL:** Subjects in Group B of Study GS-US-312-0116 who had PD per IRC confirmation and subsequently enrolled in Study GS-US-312-0117 to receive IDL 150 mg twice daily during the double-blind portion of the study

After unblinding, open-label extension study analyses are presented for the following 4 groups:

- **IDL+R/IDL:** Subjects in Group A in Study GS-US-312-0116 who transitioned to Study GS-US-312-0117 during the open-label portion of the study to continue IDL 150 mg twice daily
- **Placebo+R/IDL:** Subjects in Group B in Study GS-US-312-0116 who transitioned to Study GS-US-312-0117 during the open-label portion of the study to receive IDL 150 mg twice daily
- **IDL+R (PD)/IDL:** Subjects in Group A of Study GS-US-312-0116 who had PD per IRC confirmation and subsequently enrolled in Study GS-US-312-0117 to receive IDL 300 mg twice daily during the double-blind portion of the study
- **Placebo+R (PD)/IDL:** Subjects in Group B of Study GS-US-312-0116 who had PD per IRC confirmation and subsequently enrolled in Study GS-US-312-0117 to receive IDL 150 mg twice daily during the double-blind portion of the study

Analyses focused on evaluation of outcomes within each treatment group and were descriptive in nature; formal comparisons of outcomes between arms were not planned. Time-to-event endpoints were summarized using Kaplan-Meier methods; medians and the corresponding 95% CIs were presented. Continuous and categorical variables were also summarized as appropriate. Changes from baseline in categorical variables and changes from baseline in continuous endpoints were analyzed using appropriate methods.

Efficacy outcomes among subjects receiving rituximab alone in Study GS-US-312-0116 were evaluated relative to those same outcomes among the same subjects (placebo+R [PD]/IDL) receiving standard-dose IDL alone in Study GS-US-312-0117.

Based on the Safety Analysis Set, information regarding study drug administration, study drug compliance, safety variables, and poststudy therapies was described and summarized. Using data from the PK/Pharmacodynamic Analysis Set, IDL plasma concentrations were also described and summarized.

Sample Size Calculation

The sample size for this extension study was not based upon a formal statistical hypothesis. The upper bound of the sample size in this study was determined by the sample size of the preceding primary clinical Study GS-US-312-0116 in which approximately 180 subjects (90 per arm) were expected to be enrolled. Assuming a 10% dropout rate during Study GS-US-312-0116 and a further 10% dropout rate in the transition from the primary study to the extension study, 180 subjects were expected to be enrolled into Study GS-US-312-0117.

SUMMARY OF RESULTS:

On 08 November 2013, the Data Monitoring Committee (DMC) reviewed interim safety and efficacy data and recommended that Study GS-US-312-0116 be stopped due to efficacy. Following consultation with the United States Food and Drug Administration (FDA), Gilead stopped Study GS-US-312-0116, and subjects who were on Study GS-US-312-0116 at that time were offered the option of transitioning to Study GS-US-312-0117, which became an open-label study. Except for the 4 subjects in the IDL+R [PD]/IDL group who began receiving 300 mg IDL during the blinded portion of Study GS-US-312-0117 and remained on this dose, all of the subjects who transitioned into Study GS-US-312-0117 during the open-label portion received 150 mg IDL twice daily.

On 29 June 2018, Gilead transitioned the last remaining subject in Study GS-US-312-0117 to commercial Zydelig® and closed the study.

Subject Disposition and Demographics:

Of the 164 eligible subjects (including 55 subjects who had disease progression as determined by the investigator and 109 subjects who completed Study-GS-US-312-0116), 161 enrolled in Study GS-US-312-0117, and 35 subjects completed or discontinued Study GS-US-312-0116 and did not enroll in Study GS-US-312-0117. The IDL+R (PD)/IDL group of Study GS-US-312-0117 consisted of 4 subjects who received 150 mg of IDL+R in Study GS-US-312-0116 and met the primary endpoint of PD (confirmed by IRC) and were transitioned to 300 mg of IDL during the blinded portion of Study GS-US-312-0117. These 4 subjects continued to receive 300 mg throughout the open-label portion of the study. Due to the small number of subjects in this group, these subjects are included in the IDL+R/IDL group for most of the analyses.

The placebo+R (PD)/IDL group of Study GS-US-312-0117 consisted of 42 subjects who received placebo+R and met the primary endpoint of PD (confirmed by IRC) in Study GS-US-312-0116 and were transitioned to 150 mg of IDL twice daily during the blinded portion of Study GS-US-312-0117.

The Interim 1 clinical study report (CSR) for Study GS-US-312-0117 examined data up to 02 December 2014. At the time of the first interim report, 76 subjects were ongoing in Study GS-US-312-0117.

For the Interim 2 CSR, data up to 02 May 2016 were examined. At the time of the second interim report, 23 subjects were ongoing in Study GS-US-312-0117.

For the Interim 3 CSR, data up to 02 May 2017 were examined. At the time of the third interim report, 14 subjects were ongoing in Study GS-US-312-0117.

For this final report, of the 71 subjects in the IDL+R/IDL group, 30 subjects (28.3%) met the primary endpoint as determined by investigator, including 20 subjects (18.9%) who had PD and 10 subjects (9.4%) who died. Forty-one subjects (38.7%) in the IDL+R/IDL group discontinued Study GS-US-312-0117 for reasons other than PD or death: 22 subjects (20.8%) discontinued due to an AE, 9 subjects (8.5%) were withdrawn by physician decision, 5 subjects (4.7%) withdrew consent, 2 subjects (1.9%) listed "other" as the reason, and 3 subjects (2.8%) discontinued because the study was terminated by the sponsor.

Of the 4 subjects in the IDL+R (PD)/IDL group, 2 subjects (50.0%) died, meeting the primary endpoint. Of the remaining 2 subjects, 1 subject (25.0%) listed "other" as the reason for discontinuation; this subject discontinued due to PD, and was classified as a subject with an event of PD by investigator assessment; this subject had "worsening of the disease" as the cause of death. One subject (25.0%) discontinued due to an AE of diarrhea.

Of the 42 subjects in the placebo+R (PD)/IDL group, 20 (47.6%) met the primary endpoint: 5 (11.9%) had PD and 15 (35.7%) died. Of the 22 subjects (52.4%) in the placebo+R (PD)/IDL group who discontinued for reasons other than PD or death, 9 (21.4%) discontinued due to an AE, 6 (14.3%) withdrew consent, 6 (14.3%) were withdrawn by physician decision, and 1 subject (2.4%) listed "other" as the reason for discontinuation.

Of the 44 subjects in the placebo+R/IDL group, 18 subjects (40.9%) met the primary endpoint: 10 (22.7%) had PD and 8 (18.2%) died. Of the 26 subjects (59.1%) who discontinued for reasons other than PD or death, 12 (27.3%) discontinued due to an AE, 4 (9.1%) were withdrawn by physician decision, 4 (9.1%) withdrew consent, 1 (2.3%) listed "other" as the reason for discontinuation, and 5 subjects (11.4%) discontinued because the study was terminated by the sponsor.

Subject disposition is summarized in the following table:

Subject Disposition, n (%)	**IDL+R/IDL (N = 106)**	**IDL + R (PD)/IDL (N = 4)**	**Placebo+ R (PD)/IDL (N = 42)**	**Placebo+R/IDL (N = 44)**
Completed Study GS-US-312-0116 and Enrolled in Study GS-US-312-0117	71 (67.0)	4 (100.0)	42 (100.0)	44 (100.0)
Completed/Discontinued Study GS-US-312-0117[a]				
Met Primary Endpoint in Study GS-US-312-0117[a]	30 (28.3)	2 (50.0)	20 (47.6)	18 (40.9)
PD	20 (18.9)	0	5 (11.9)	10 (22.7)
Death	10 (9.4)	2 (50.0)	15 (35.7)	8 (18.2)
Discontinued Study GS-US-312-0117[a]	41 (38.7)	2 (50.0)	22 (52.4)	26 (59.1)
AE	22 (20.8)	1 (25.0)	9 (21.4)	12 (27.3)
Other	2 (1.9)	1 (25.0)	1 (2.4)	1 (2.3)
Physician Decision	9 (8.5)	0	6 (14.3)	4 (9.1)
Study Terminated by Sponsor	3 (2.8)	0	0	5 (11.4)
Withdrawal by Subject	5 (4.7)	0	6 (14.3)	4 (9.1)

a. Reason as determined by investigator
The FAS includes subjects who were randomized in Study GS-US-312-0116 and received at least 1 dose of IDL in either Study GS-US-312-0116 or Study GS-US-312-0117, with treatment assignments designated according to randomization in Study GS-US-312-0116.

Data outputs for baseline characteristics (demographics and disease) were reported in the Interim 1 CSR (dated 08 April 2015) and remain the same for this Final CSR. Consistent with the advanced age typical of the general CLL population, most subjects in the IDL+R/IDL group (80.9%) were ≥ 65 years of age, with a median (first quartile [Q1], third quartile [Q3]), age of 71 (66, 76) years and range of 48 to 90 years. Most subjects in the IDL+R/IDL group (69.1%) were male and most (90.9%) were white. Black/African American subjects comprised 2.7% of subjects, and 6.4% of subjects were classified with race "Other" or "Not Permitted" (ie, not permitted to report). The median (Q1, Q3) baseline body mass index (BMI) was 25.5 (22.7, 29.5) kg/m^2 in the IDL+R/IDL group. Almost all subjects in the IDL+R/IDL group (95 subjects; 89.6%) had a reduced Karnofsky Performance Status (KPS) at study entry: 59.1% had modest reduction (ie, KPS score 80 to 90), 23.6% had significant reduction (ie, KPS score 60 to 70), and approximately 3.6% had severe impact (ie, KPS score ≤ 50). The subject population in the IDL+R/IDL group had longstanding disease: the median (Q1, Q3) time since CLL diagnosis was 7.8 years (5.8, 11.8), with a range of 0.6 to 26.6 years. At study screening, most subjects in the IDL+R/IDL group had advanced disease with 63.6% Rai Stage III or IV and 57.3% Binet Stage C.

The study population as a whole had high rates of adverse CLL genetics that are prognostic for a poor outcome. Of the 110 study subjects in the IDL+R/IDL group, 41.8% had 17p deletion and/or TP53 mutation and most subjects in the IDL+R/IDL had unmutated immunoglobulin heavy chain variable region ([IGHV] status [91 subjects, 82.7%]). The group of subjects that did not have disease progression while receiving placebo+R in Study GS-US-312-0116 (placebo+R/IDL) had a somewhat more favorable genetic profile than those who had PD while receiving placebo+R in Study GS-US-312-0116 (placebo+R [PD]/IDL), with fewer subjects having either 17p deletion or TP53 mutation.

The study population had been heavily pretreated for CLL. The median (Q1, Q3) number of prior CLL regimens was 3.0 (2.0, 5.0), with a range of 1 to 12 prior regimens received.

Efficacy Results:

Primary efficacy analyses were performed on the FAS, with the exception of OS, which was performed based on the ITT Analysis Set. Key efficacy findings from Study GS-US-312-0117 were as follows:

Tumor Control

Progression-Free Survival:

A total of 64 subjects (58.2%) in the IDL+R/IDL group, 32 subjects (76.2%) in the placebo+R (PD)/IDL, and 29 subjects (65.9%) in the placebo+R/IDL group experienced a PFS event. The median (95% CI) PFS was 20.3 (17.3, 26.3) months for subjects in the IDL+R/IDL group, 6.9 (4.1, 10.7) months for subjects in the placebo+R (PD)/IDL group, and 16.2 (8.8, 26.2) months for subjects in the placebo+R/IDL group.

Overall Response Rate:

The ORR (95% CI) was 85.5% (77.5, 91.5) for subjects in the IDL+R/IDL group, 47.6% (32.0, 63.6) for subjects in the placebo+R (PD)/IDL group, and 68.2% (52.4, 81.4) for subjects in the placebo+R/IDL group. One response was CR in the IDL+R/IDL group, and all other responses were PR.

Lymph Node Response Rate:

The LNR rate (95% CI) was 97.2% (92.0, 99.4) for subjects in the IDL+R/IDL group, 77.8% (60.8, 89.9) for subjects in the placebo+R (PD)/IDL group, and 83.7% (69.3, 93.2) for subjects in the placebo+R/IDL group.

Time to Response:

For subjects who were responders in the IDL+R/IDL group (N = 94), the median (Q1, Q3) TTR was 2.1 (1.9, 3.8) months with a range of 1.5 to 13.9 months. For subjects in the placebo+R (PD)/IDL group (N = 20), the median (Q1, Q3) TTR was 3.6 (1.9, 4.0) months with a range of 1.7 to 11.0 months. For subjects in the placebo+R/IDL group (N = 30), the median (Q1, Q3) TTR was 2.8 (1.9, 4.2) months with a range of 1.0 to 16.5 months.

Duration of Response:

The median (95% CI) DOR in the IDL+R/IDL group (N = 94) was 21.4 (16.6, 26.1) months. For subjects in the placebo+R (PD)/IDL group (N = 20), the median (95% CI) DOR was 11.0 (3.3, not reached) months, while for subjects in the placebo+R/IDL group (N = 30), the median (95% CI) DOR was 17.6 (13.2, 37.7) months.

Best Percent Change in SPD:

The median (Q1, Q3) best percent change in SPD was −80.1% (−86.1, −70.5) in the IDL+R/IDL treatment group, −69.7% (−79.5, −53.7) in the placebo+R (PD)/IDL treatment group, and −71.4% (−80.4, −62.7) in the placebo+R/IDL group.

Splenomegaly and Hepatomegaly Response Rates:

The splenomegaly response rate (95% CI) was 80.3% (69.5, 88.5) for subjects in the IDL+R/IDL group, 47.8% (26.8, 69.4) for the subjects in the placebo+R (PD)/IDL group, and 66.7% (44.7, 84.4) for subjects in the placebo+R/IDL group.

The hepatomegaly response rate (95% CI) was 63.0% (48.7, 75.7) for subjects in the IDL+R/IDL group, 36.4% (17.2, 59.3) for subjects in the placebo+R (PD)/IDL group, and 30.0% (11.9, 54.3) for subjects in the placebo+R/IDL group.

ALC, Platelet, Hemoglobin, and ANC Response Rates:

The ALC response rate was 94.3% in the IDL+R/IDL group, 66.7% in the placebo+R (PD)/IDL group, and 64.7% in the placebo+R/IDL group.

Platelet response rates were 98.0% in the IDL+R/IDL group, 73.9% in the placebo+R (PD)/IDL group, and 100% in the placebo+R/IDL group.

Hemoglobin response rates were 83.1% in the IDL+R/IDL group, 45.8% in the placebo+R (PD)/IDL group, and 81.8% in the placebo+R/IDL group.

The ANC response rates in the IDL+R/IDL, placebo+R (PD)/IDL, and placebo+R/IDL were 96.3%, 90.9%, and 100%, respectively.

Patient Well-Being

Overall Survival:

The primary OS analysis was performed using the ITT Analysis Set (according to the original randomization), which included all available survival information from Study GS-US-312-0116 (including data in long-term follow up) and Study GS-US-312-0117 (including any data in

long-term follow up) up to the database finalization dates of 16 August 2018 (CRF data) and 21 June 2018 (IRC data). Data from surviving subjects were censored at the last time that the subject was known to be alive on study or long-term follow up.

The median OS (95% CI) in the IDL+R group was 40.6 (28.5, 57.3) months. In the placebo+R group, the median (95% CI) OS was 34.6 (16.0, not reached) months. During Study GS-US-312-0116/ Study GS-US-312-0117, a total of 106 subjects had died (IDL + R, 50 subjects, 45.5%; placebo + R, 56 subjects, 50.9%). The adjusted hazard ratio (95% CI) for OS was 0.75 (0.51, 1.1), which favored IDL + R compared with placebo+R.

HRQL: FACT-Leu Questionnaire Results:

Results were not updated for this Final CSR.

Karnofsky Performance Status Results:

Results were not updated for this Final CSR.

Change in EQ-5D Score

Results were not updated for this Final CSR.

Efficacy in Subjects with 17p Deletion and/or TP53 Mutation

PFS:

Median (95% CI) PFS for subjects in the subgroups was as follows:

- IDL+R/IDL group without 17p deletion was 22.1 (17.3, 28.9) months
- IDL+R/IDL group with 17p deletion was 18.2 (12.3, 47.8) months
- IDL+R/IDL group with neither 17p deletion/TP53 mutation was 20.8 (16.4, 28.9) months
- IDL+R/IDL group with either 17p deletion/TP53 mutation was 18.7 (16.6, 32.4) months

ORR:

The ORR (95% CI) for subjects in the subgroups was as follows:

- IDL+R/IDL group without 17p deletion was 86.9% (77.8, 93.3)
- IDL+R/IDL group with 17p deletion was 80.8% (60.6, 93.4)
- IDL+R/IDL group with neither 17p deletion/TP53 mutation was 85.9% (75.0, 93.4)
- IDL+R/IDL group with either 17p deletion/TP53 mutation was 84.8% (71.1, 93.7)

LNR:

The LNR rate (95% CI) for subjects in the subgroups was as follows:

- IDL+R/IDL group without 17p deletion was 96.3% (89.6, 99.2)
- IDL+R/IDL group with 17p deletion was 100% (86.3, 100)
- IDL+R/IDL group with neither 17p deletion/TP53 mutation was 95.2% (86.5, 99.0)
- IDL+R/IDL group with either 17p deletion/TP53 mutation was 100% (92.0, 100)

DOR:

The median (95% CI) DOR for subjects in the subgroups was as follows:

- IDL+R/IDL group without 17p deletion was 22.8 (17.0, 28.4) months
- IDL+R/IDL group with 17p deletion was 17.5 (12.6, 41.9) months
- IDL+R/IDL group with neither 17p deletion/TP53 mutation was 22.8 (13.8, 28.4) months
- IDL+R/IDL group with either 17p deletion/TP53 mutation was 19.1 (15.0, 41.9) months

OS:

The median OS for subjects in the subgroups was as follows:

- IDL+R group without 17p deletion was 50.9 (34.8, not reached) months
- IDL+R group with 17p deletion was 25.4 (17.0, 48.2) months
- IDL+R group with neither 17p deletion/TP53 mutation was 50.9 (32.7, not reached) months
- IDL+R group with either 17p deletion/TP53 mutation was 28.5 (24.8, 50.1) months

During Study GS-US-312-0116/ Study GS-US-312-0117, a total of 50 subjects in the IDL+R group died.

Pharmacokinetics/Pharmacodynamics Results:

Results were not updated for this CSR.

Safety Results:

All safety analyses were performed using the FAS. Key safety findings revealed no new safety signals, were consistent with the previous reports, and are as follows:

Exposure

Study drug exposure (IDL) is summarized in Table 37. Of the 220 subjects initially randomized in Study GS-US-312-0116, 196 received at least 1 dose of IDL (either in Study GS-US-312-0116 or Study GS-US-312-0117), and were evaluable for safety. The median (Q1, Q3) duration of exposure to study drug in the IDL+R/IDL group was 16.2 (8.2, 25.8) months, with a range of 0.3 to 67.3 months. The median (Q1, Q3) duration of exposure to study drug in the placebo+R (PD)/IDL group was 5.7 (3.1, 11.9) months, with a range of 0.4 to 40.8 months. The median (Q1, Q3) duration of exposure to study drug in the placebo+R/IDL group was 9.5 (5.3, 26.5) months, with a range of 0.2 to 52.5 months.

Of the 110 subjects in the IDL+R/IDL group, 4 subjects received 300 mg of IDL twice daily in Study GS-US-312-0117.

AEs

AEs were consistent for a heavily pretreated, relapsed CLL population receiving immunochemotherapeutic agents and with the established safety profile of IDL. Treatment-emergent AEs were common in all treatment groups, occurring in 108 subjects (98.2%) in the IDL+R/IDL group, 42 subjects (100%) in the placebo+R (PD)/IDL group, and

43 subjects (97.7%) in the placebo+R/IDL group. Diarrhea was the most common event overall, occurring in 51 subjects (46.4%) in the IDL+R/IDL group, 19 subjects (45.2%) in the placebo+R (PD)/IDL group, and 29 subjects (65.9%) in the placebo+R/IDL group.

The most commonly reported AEs by treatment group were as follows:

- **IDL+R/IDL:** pyrexia (52 subjects, 47.3%), diarrhea (51 subjects, 46.4%), and fatigue (42 subjects, 38.2%)
- **Placebo+R (PD)/IDL:** diarrhea (19 subjects, 45.2%), pneumonia (17 subjects, 40.5%), and fatigue (13 subjects, 31.0%)
- **Placebo+R/IDL:** diarrhea (29 subjects, 65.9%), pyrexia (20 subjects, 45.5%), and cough (16 subjects, 36.4%)

The most commonly reported ≥ Grade 3 AEs by treatment group were as follows:

- **IDL+R/IDL:** neutropenia (31 subjects, 28.2%), diarrhea (18 subjects, 16.4%), and pneumonia (17 subjects, 14.5%)
- **Placebo+R (PD)/IDL:** pneumonia (11 subjects, 26.2%), neutropenia (9 subjects, 21.4%), and diarrhea (6 subjects, 15.5%)
- **Placebo+R/IDL:** diarrhea (11 subjects, 25.0%), colitis (6 subjects, 13.6%), and neutropenia (5 subjects, 11.4%)

AEs related to IDL

The most frequently reported treatment-emergent adverse events (TEAEs) assessed by the investigator as related to IDL were as follows:

- **IDL+R/IDL:** diarrhea (30 subjects, 27.3%), neutropenia (17 subjects, 15.5%), and fatigue (16 subjects, 14.5%)
- **Placebo+R (PD)/IDL:** diarrhea (13 subjects, 31.0%), pneumonia (5 subjects, 11.9%), and colitis (5 subjects, 11.9%)
- **Placebo+R/IDL:** diarrhea (13 subjects, 29.5%), colitis (7 subjects, 15.9%), and fatigue (5 subjects, 11.4%)

The most frequently reported ≥ Grade 3 AEs assessed by the investigator as related to IDL were as follows:

- **IDL+R/IDL:** diarrhea (15 subjects, 13.6%), neutropenia (14 subjects, 12.7%), and colitis (8 subjects, 7.3%)
- **Placebo+R (PD)/IDL:** diarrhea (5 subjects, 11.9%) and colitis, neutropenia, and pneumonia (each 3 subjects, 7.1%)
- **Placebo+R/IDL:** diarrhea (9 subjects, 20.5%), colitis (5 subjects, 11.4%), and neutropenia (3 subjects, 6.8%)

AEs of Interest

AEs of interest for IDL were any grade bowel perforation, ≥ Grade 3 diarrhea and/or colitis, any grade pneumonitis, any grade progressive multifocal leukoencephalopathy (PML), and ≥ Grade 3 rash by medical search term (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 cytomegalovirus [CMV] infection, and any grade *Pneumocystis jirovecii* pneumonia [PJP]). Gilead Sciences' (Gilead) ongoing pharmacovigilance and signal detection practices for Zydelig (idelalisib) prompted the addition of organizing pneumonia (OP) as of 01 September 2017.

Bowel perforation:

No subjects in any group had bowel perforation.

Diarrhea/colitis:

In the IDL+R/IDL group, 22 subjects (20.0%) had diarrhea/colitis events that were ≥ Grade 3 in severity (21 subjects with Grade 3 and 1 subject with Grade 4). Thirteen subjects (11.8%) in the IDL+R/IDL group discontinued study drug due to ≥ Grade 3 diarrhea or colitis.

In the placebo+R (PD)/IDL group, 9 subjects (21.4%) had diarrhea/colitis events that were ≥ Grade 3 in severity (8 subjects with Grade 3 and 1 subject with Grade 4). Five subjects (11.9%) in the placebo+R (PD)/IDL group discontinued study drug due to ≥ Grade 3 diarrhea or colitis.

In the placebo+R/IDL group, 13 subjects (29.5%) had diarrhea/colitis events that were ≥ Grade 3 in severity (all 13 were Grade 3). Six subjects (13.6%) in the placebo+R/IDL group discontinued study drug due to ≥ Grade 3 diarrhea or colitis.

Pneumonitis:

Eleven subjects (10.0%) in the IDL+R/IDL group had pneumonitis of any grade, and 7 subjects (6.4%) had pneumonitis of ≥ Grade 3; 1 subject (0.9%) had fatal pneumonitis of Grade 5 reported in the Interim 2 CSR. Five subjects (4.5%) in the IDL+R/IDL group discontinued study drug due to pneumonitis, and 1 event was Grade 5 as reported in the Interim 2 CSR. In the IDL+R/IDL group, the incidence and prevalence of pneumonitis appeared to remain relatively stable across time intervals, although the numbers of subjects experiencing these events within each time interval were small.

In the placebo+R (PD)/IDL group, 2 subjects (4.8%) had pneumonitis, and 1 event was of Grade 4 severity. Both of these subjects discontinued study drug due to pneumonitis as reported in the Interim 2 CSR.

In the placebo+R/IDL group, 4 subjects (9.1%) had pneumonitis of any grade, and 1 event was Grade 3. One subject (2.3%) in the placebo+R/IDL group discontinued study drug due to pneumonitis as reported in the Interim 2 CSR.

No additional subjects in any treatment group developed pneumonitis since the Interim 2 CSR.

Progressive multifocal leukoencephalopathy:

One subject (0.9%) in the IDL+R/IDL group had PML of Grade 5. This subject discontinued study drug due to PML and ultimately died due to PML, as reported in the Interim 2 CSR.

No subjects in the placebo+R (PD)/IDL group or the placebo+R/IDL group had PML.

No additional subjects in any treatment group developed PML since the Interim 2 CSR.

Rash by MST:

Thirty-three subjects (30.0%) in the IDL+R/IDL group had an event within the MST rash classification. This included 7 subjects (6.4%) in the IDL+R/IDL group with rash by MST events that were Grade 3. In the IDL+R/IDL group, 3 subjects (2.7%) discontinued due to a rash MST terms.

In the placebo+R (PD)/IDL group, 5 subjects (11.9%) had an event within the MST rash classification, no subjects with ≥ Grade 3 events, and no subjects discontinued.

In the placebo+R/IDL, 16 subjects (36.4%) had an event within the MST rash classification. This included 2 subjects (4.5%) in the placebo+R/IDL group with rash by MST events that were Grade 3, and 1 subject (2.3%) with a rash by MST event that was Grade 4. In the placebo+R/IDL group, 1 subject (2.3%) discontinued due to a rash MST terms

The incidence and prevalence of all grade rashes by MST and of Grade ≥ 3 rash by MST in the IDL+R/IDL group remained mostly stable after Week 12.

There were no cases of Stevens-Johnson syndrome or toxic epidermal necrolysis in this study.

No subjects in the placebo+R/IDL group treatment group developed events classified as rash by MST since the Interim 2 CSR.

Infections:

In the IDL+R/IDL group, 59 subjects (53.6%) had infections of ≥ Grade 3. Twelve subjects (10.9%) in the IDL+R/IDL group discontinued study drug due to infections. This reflects one additional discontinuation due to infection since the Interim 3 CSR.

In the placebo+R (PD)/IDL group, 23 subjects (54.8%) had infections of ≥ Grade 3, reflecting no change since the Interim 3 CSR. Nine subjects (21.4%) in the placebo+R (PD)/IDL group discontinued study drug.

In the placebo+R/IDL group, 16 subjects (36.4%) had infections of ≥ Grade 3, reflecting no change since the Interim 3 CSR. Three subjects (6.8%) in the placebo+R/IDL group discontinued study drug due to infections.

Febrile Neutropenia:

Seven subjects (6.4%) in the IDL+R/IDL group had febrile neutropenia of any grade, and 7 subjects (6.4%) had febrile neutropenia of ≥ Grade 3. Two subjects (1.8%) in the IDL+R/IDL group discontinued study drug due to ≥ Grade 3 febrile neutropenia.

In the placebo+R (PD)/IDL group, 5 subjects (11.9%) had febrile neutropenia of any grade, and 5 subjects (11.9%) had febrile neutropenia of ≥ Grade 3. In the placebo+R/IDL group, 2 subjects (4.5%) had febrile neutropenia of any grade, and 2 subjects (4.5%) had febrile neutropenia of ≥ Grade 3. One subject (2.4%) in the placebo+R (PD)/IDL group and no subjects in the placebo+R/IDL group discontinued study drug due to ≥ Grade 3 febrile neutropenia.

No additional subjects in any treatment group developed febrile neutropenia since the Interim 2 CSR.

Cytomegalovirus:

In Study GS-US-312-0117, CMV infection of any grade in the IDL+R/IDL group occurred in 2 subjects (1.8%), and no subjects had events that were ≥ Grade 3 in severity, reflecting no additional subjects since the Interim 3 CSR.

In the placebo+R (PD)/IDL group, 1 subject (2.4%) had CMV infection of any grade, and no subjects had events that were ≥ Grade 3 in severity. In the placebo+R/IDL group, no subjects had CMV infection of any grade.

No subjects in any treatment group discontinued study drug due to CMV infection.

***Pneumocystis jirovecii* pneumonia:**

Five subjects (4.5%) in the IDL+R/IDL group had PJP of any grade, and 4 subjects (3.6%) had PJP of ≥ Grade 3, this represents no change since the Interim 3 CSR. Two subjects (1.8%) in the IDL+R/IDL group discontinued study drug due to PJP, and both of these subjects subsequently died (both events were Grade 5) as of 02 May 2016, the Interim 2 CSR. Neither of these subjects was receiving PJP prophylactic treatment at the time of Grade 5 event (Study GS-US-312-0117, Interim 2 CSR, Listing 3.6).

In the placebo+R (PD)/IDL group and the placebo+R/IDL group, no subjects had PJP.

No new subjects in any treatment group developed PJP since the Interim 2 CSR.

Organizing Pneumonia

No subjects in any group had organizing pneumonia.

Deaths

From the beginning of Study GS-US-312-0116 through the end of Study GS-US-312-0117, a total of 91 subjects died. Among subjects in the IDL+R/IDL group, 47 subjects (44.3%) died. In the IDL+R (PD)/IDL group, 3 subjects (75.0%) died. In the placebo + R (PD)/IDL group, 25 subjects (59.5%) died. In the placebo+R/IDL group, 16 subjects (36.4%) died. Of these deaths, 46 occurred in Study GS-US-312-0117 and 33 occurred more than 30 days from the end of treatment in Study GS-US-312-0117.

Causes of death were largely consistent with advanced CLL and the underlying frailty, age, and poor prognosis of the study population and were unchanged from the Interim 3 CSR. AEs leading to the death of more than 1 subject in any treatment group were acute respiratory failure, respiratory failure, PJP, cardio-respiratory arrest, and pneumonia (Table 48). Acute respiratory failure led to death in 4 subjects: 2 subjects (1.8%) in the IDL+R/IDL group and 2 subjects (4.8%) in the placebo+R (PD)/IDL group (2 of the 4 deaths occurred in association with serious infections). Respiratory failure led to death in 3 subjects: 2 subjects (4.8%) in the placebo+R (PD)/IDL group and 1 subject (2.3%) in the placebo+R/IDL group (2 of the 3 deaths occurred in association with serious infections). *Pneumocystis jirovecii* pneumonia led to death in 2 subjects (1.8%), both in the IDL+R/IDL group. Cardio-respiratory arrest led to death in 2 subjects (4.8%), both in the placebo+R (PD)/IDL group. Pneumonia led to death in 3 subjects (7.1%) in the placebo+R (PD)/IDL group.

SAEs

SAEs were common in all treatment groups, reported for the majority of subjects in each group (IDL+R/IDL: 89 subjects, 80.9%; placebo+R (PD)/IDL: 34 subjects, 81.0%; and placebo+R/IDL: 32 subjects, 72.7%).

IDL-related SAEs were reported for 39 subjects (35.5%) in the IDL+R/IDL group, 11 subjects (26.2%) in the placebo+R (PD)/IDL group, and 13 subjects (29.5%) in the placebo+R/IDL group.

Frequently reported SAEs by preferred term (PT) (Table 50) were as follows:

- **IDL+R/IDL:** pneumonia (17 subjects, 15.5%), diarrhea (14 subjects, 12.7%), and pyrexia (13 subjects, 11.8%)
- **Placebo+R (PD)/IDL:** pneumonia (10 subjects, 23.8%), febrile neutropenia (5 subjects, 11.9%), and diarrhea (4 subjects, 9.5%)
- **Placebo+R/IDL:** diarrhea (8 subjects, 18.2%), and pyrexia and cellulitis (each 4 subjects, 9.1%)

IDL Discontinuations Due to AEs

A total of 101 subjects (IDL+R/IDL: 52 subjects, 47.3%; placebo+R [PD]/IDL: 27 subjects, 64.3%; placebo+R/IDL: 22 subjects, 50.0%) discontinued IDL due to an AE.

- In the IDL+R/IDL group, the most common AEs that led to discontinuation were diarrhea (12 subjects, 10.9%), colitis (6 subjects, 5.5%), and pneumonitis (5 subjects, 4.5%).
- In the placebo+R (PD)/IDL group, the most common AEs that led to discontinuation were pneumonia (4 subjects, 9.5%), diarrhea and colitis (each 3 subjects, 7.1%), and pneumonitis, and acute respiratory failure (each 2 subjects, 4.8%).
- In the placebo+R/IDL group, the most common AEs that led to discontinuation were diarrhea (9 subjects 20.5%), and colitis, nausea, and dyspnea (each 2 subjects, 4.5%).

Laboratory Evaluations of Interest

Based on laboratory assessments, 77 subjects (70.0%) in the IDL+R/IDL group had decreased neutrophil count of any grade; 23 subjects (20.9%) had decreased neutrophil count of Grade 3 and 27 subjects (24.5%) of Grade 4. In the placebo+R (PD)/IDL group, 23 subjects (54.8%) had decreased neutrophil count of any grade; 8 subjects (19.0%) each had decreased neutrophil count of Grade 3 and Grade 4.

In the IDL+R/IDL group, alanine aminotransferase (ALT) elevations (all grades) occurred in 51 subjects (46.4%) with Grade 3 or 4 events observed in 10 subjects (9.1%). Aspartate aminotransferase (AST) elevations (all grades) occurred in 40 subjects (36.4%), with Grade 3 or 4 events observed in 6 subjects (5.5%). All 6 subjects with Grade 3 or 4 AST elevations also had Grade 3 or 4 ALT elevations.

In the placebo+R (PD)/IDL group, ALT elevations (all grades) occurred in 16 subjects (38.1%) with Grade 3 or 4 events observed in 2 subjects (4.8%). Aspartate aminotransferase elevations (all grades) occurred in 14 subjects (33.3%) with Grade 3 or 4 events observed in 2 subjects (4.8%). Both subjects with Grade 3 or 4 AST elevations also had Grade 3 or 4 ALT elevations.

In the placebo+R/IDL group, ALT elevations (all grades) occurred in 21 subjects (47.7%) with Grade 3 or 4 events observed in 4 subjects (9.1%). AST elevations (all grades) occurred in 19 subjects (43.2%) with Grade 3 or 4 events observed in 2 subjects (4.5%). Both subjects with Grade 3 or 4 AST elevations also had Grade 3 or 4 ALT elevations. Adjustment for rates of transaminase elevations by study drug exposure did not alter the overall trend or conclusions, and the findings in this study were consistent with previous observations with IDL treatment.

Clinical Laboratory Evaluations

Hematologic abnormalities were common among subjects in all treatment groups. Hemoglobin concentrations and platelet counts trended upward with time for both the IDL+R/IDL and the placebo+R/IDL treatment groups.

CONCLUSIONS:

Study GS-US-312-0117 was a multicenter, 2-arm, parallel-group extension study to the primary study, GS-US-312-0116. The study was amended at the time of Study GS-US-312-0116 closure to transition all patients over with the option to receive open-label IDL and/or be included in long-term follow up. Key findings were consistent with those previously reported for this study and are summarized as follows:

- The median (95% CI) PFS was 20.3 (17.3, 26.3) months for subjects in the IDL+R/IDL group, 6.9 (4.1, 10.7) months for subjects in the placebo+R (PD)/IDL group, and 16.2 (8.8, 26.2) months for subjects in the placebo+R/IDL group.
- OS continued to favor the IDL+R group, which includes all subjects randomized into the IDL+R group in Study GS-US-312-0116. The median OS (95% CI) in the IDL+R group was 40.6 (28.5, 57.3) months. The placebo+R group includes all subjects randomized into the placebo+R group in Study GS-US-312-0116. In the placebo+R group, the median (95% CI) OS was 34.6 (16.0, not reached) months. During this study, a total of 106 subjects had died (IDL + R: 50 subjects, 45.5%; placebo + R, 56 subjects, 50.9%). The adjusted hazard ratio (95% CI) for OS was 0.75 (0.51, 1.1), which favored IDL + R compared with placebo+R.
- In subjects without 17p deletion, the median (95% CI) PFS in the IDL+R/IDL group was 22.1 (17.3, 28.9) months, compared with 18.2 (12.3, 47.8) months in subjects with 17p deletion. The median (95% CI) OS in subjects without 17p deletion in the IDL+R/IDL group was 50.9 (34.8, not reached) months, compared with 25.4 (17.0, 48.2) months in subjects with 17p deletion.
- The median (95% CI) PFS for subjects with neither 17p deletion/TP53 mutation in the IDL+R/IDL group was 20.8 (16.4, 28.9) months. The median (95% CI) PFS for subjects with either 17p deletion/TP53 mutation in the IDL+R/IDL group was 18.7 (16.6, 32.4) months. The median OS in subjects with neither 17p deletion/TP53 mutation in the IDL+R/IDL group was 50.9 (32.7, not reached) months. The median (95% CI) OS in subjects with either 17p deletion/TP53 mutation in the IDL+R/IDL group was 28.5 (24.8, 50.1) months.

IDL was generally well tolerated and had a manageable safety profile consistent with the known safety profile of IDL. Most AEs were as expected for a heavily pretreated, relapsed/refractory CLL population.

- Diarrhea was the most common AE overall, occurring in 51 subjects (46.4%) in the IDL+R/IDL group, 19 subjects (45.2%) in the placebo+R (PD)/IDL group, and 29 subjects (65.9%) in the placebo+R/IDL group.
- Other common AEs included pyrexia, fatigue, pneumonia, and cough.

The efficacy and safety findings from the final analysis of this study continue to confirm the positive benefit:risk evaluation established for the use of IDL in the relapsed/refractory CLL population.