STATISTICAL ANALYSIS PLAN

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*
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TABLE OF CONTENTS

TABLE OF CONTENTS 2
LIST OF IN-TEXT TABLES 3
LIST OF ABBREVIATIONS 4
1. INTRODUCTION 6
1.1. Study Objectives 6
1.2. Study Design 6
1.3. Sample Size and Power 11
2. TYPE OF PLANNED ANALYSIS 12
3. GENERAL CONSIDERATIONS FOR DATA ANALYSES 13
3.1. Analysis Sets 13
3.1.1. Intent-to-Treat Analysis Set 13
3.1.2. Full Analysis Set 13
3.1.3. Pharmacokinetic/Pharmacodynamic Analysis Sets 13
3.2. Strata and Covariates 13
3.3. Examination of Subject Subsets 13
3.4. Missing Data and Outliers 14
3.5. Data Handling Conventions and Transformations 14
3.5.1. Data Handling for Treatment Groups 15
3.5.2. Data Handling for Efficacy and Safety Endpoints 19
3.5.3. Data Handling for Laboratory data 19
3.6. Visit Windows 19
3.6.1. Analysis Windows 19
3.6.2. Selection of Data in the Event of Multiple Records in a Window 20
4. SUBJECT DISPOSITION 21
4.1. Subject Enrollment 21
4.2. Disposition of Subjects 21
4.3. Extent of Exposure 22
4.3.1. Duration of Exposure to Study Drugs 22
4.4. Protocol Deviations 22
5. BASELINE DATA 23
5.1. Demographics and Baseline Characteristics 23
5.2. Medical History 23
6. EFFICACY ANALYSES 24
6.1. Efficacy Endpoints 24
6.1.1. Definition of Efficacy Endpoints 24
6.1.2. Analysis Methods for Efficacy Endpoints 25
6.1.3. Between-Study Comparisons 30
6.2. Changes From Protocol-Specified Efficacy Analyses 30
7. SAFETY ANALYSES 31
7.1. Adverse Events and Deaths 31
7.1.1. Adverse Event Dictionary 31
7.1.2. Adverse Event Severity 31
7.1.3. Relationship of Adverse Events to Study Drug 31
7.1.4. Serious Adverse Events 31

7.1.5. Treatment-Emergent Adverse Events 32
7.1.6. Summaries of Adverse Events and Deaths 32
7.1.7. Treatment-Emergent Adverse Events of Interest 33
7.1.8. Exposure-adjusted TEAE Rate 35
7.2. Laboratory Evaluations 35
7.2.1. Summaries of Numeric Laboratory Results 35
7.2.2. Summaries of Categorical Laboratory Results 35
7.2.3. Graded Laboratory Values 36
7.2.4. Shift in CTCAE Grade Relative to Baseline 36
7.2.5. Transaminase Elevations 37
7.2.6. Liver-Related Laboratory Tests 37
7.3. Prior Therapy 38
7.4. Concomitant Medications 38
7.5. Other Safety Measures 39
7.6. Changes From Protocol-Specified Safety Analyses 39
8. PHARMACOKINETIC ANALYSES 40
9. PHARMACODYNAMIC ANALYSES 41
10. REFERENCES 42
11. SOFTWARE 43
12. SAP REVISION 44
13. APPENDICES 45

Appendix 1. Table of Contents for Statistical Tables, Figures, and Listings 46
Appendix 2. Schedule of Study Procedures 58

LIST OF IN-TEXT TABLES

Table 3-1. Baseline for Data Summaries by Treatment Group 18
Table 3-2. Analysis Visit Window 20

LIST OF ABBREVIATIONS

AE	adverse event
AEI	adverse event of interest
ALC	absolute lymphocyte count
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
ATC	Anatomical-Therapeutic-Chemical classification
BID	twice per day
BMI	body mass index
CDF	cumulative distribution function
CI	confidence interval
CIRS	Cumulative Illness Rating Scale
CLL	chronic lymphocytic leukemia
CR	complete response
CSR	clinical study report
CT	computerized tomography
CTC	Common Terminology Criteria
CTCAE	Common Terminology Criteria for Adverse Events
DMC	Data Monitoring Committee
DOR	duration of response
DSPH	Gilead Sciences Drug Safety and Public Health
eCRF	electronic case report form
ECG	electrocardiogram
EOT	end of treatment
EQ-5D	EuroQoL Five-Dimension utility measure
EWB	emotional well-being
FACT-Leu	Functional Assessment of Cancer Therapy: Leukemia
FAS	full analysis set
FWB	functional well-being
HLGT	high-level group term
HLT	high-level term
HRQL	health-related quality of life
IRC	Independent Review Committee
ITT	intent-to-treat
IWCLL	International Workshop on CLL
IWRS	interactive web response system
LeuS	leukemia-specific subscale
LD	longest diameter

LIST OF ABBREVIATIONS (CONTINUED)

LLT	low level term
LNR	lymph node response
LPD	longest perpendicular diameter
LVD	longest vertical dimension
MedDRA	Medical Dictionary for Regulatory Activities
MID	minimally important difference
MRI	magnetic resonance imaging
ND	no disease
NE	not evaluable
ORR	overall response rate
OS	overall survival
PD	progressive disease
PK	pharmacokinetic
PK/PD	pharmacokinetic/pharmacodynamic
PFS	progression-free survival
PR	partial response
PT	preferred term
PWB	physical well-being
RPSFT	rank-preserving structural failure time
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
SOC	system organ class
SPD	sum of the products of the perpendicular diameters
StD	standard deviation
SWB	social/family well-being
TEAE	treatment-emergent adverse event
TFL	table, figure, listing
TOI	trial outcome index
TTR	time to response
ULN	upper limit normal
VAS	visual analogue scale
WHODRUG	World Health Organization Drug Dictionary

1. INTRODUCTION

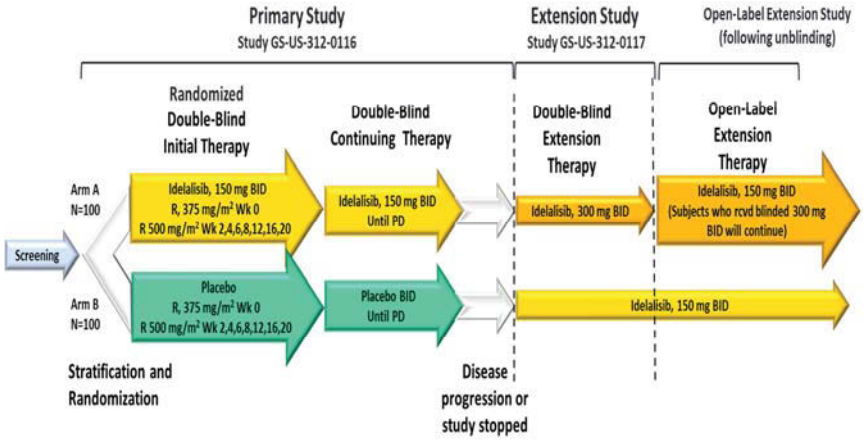
This document details the planned interim and final analyses for the open-label portion of Study GS-US-312-0117, a Phase 3, double-blind extension study evaluating the efficacy and safety of 2 different dose levels of single-agent idelalisib (IDELA) for previously treated chronic lymphocytic leukemia (CLL). Related documents are the study protocol and electronic case report form (eCRF).

1.1. Study Objectives

Study Objectives	• To evaluate the effect of idelalisib 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 idelalisib alone in Study GS-US-312-0117 • To assess the effect of idelalisib on measures of subject well-being, including overall survival (OS), health-related quality of life (HRQL), and performance status • To assess the effects of idelalisib on disease-associated biomarkers and to evaluate potential mechanisms of resistance to idelalisib • To characterize exposure to idelalisib as determined by treatment administration and evaluation of idelalisib plasma concentrations over time • To describe the safety profile observed with idelalisib • To estimate health resource utilization associated with administration of idelalisib

1.2. Study Design

Design Configuration and Subject Population	Study GS-US-312-0117 is a separate, multicenter, 2-arm, double-blind, parallel-group extension study that is a companion trial to Study GS-US-312-0116; in this trial, compliant subjects from GS-US-312-0116 who are tolerating primary study therapy but experience definitive CLL progression are eligible to receive active blinded idelalisib therapy at the standard dose or a higher dose, with allocation based on the original primary study randomization.

	Since GS-US-312-0116 was stopped early due to overwhelming efficacy following an interim analysis, subjects who were on Study GS-US-312-0116 at that time transitioned to GS-US-312-0117. Additionally, GS-US-312-0117 became an open-label study offering idelalisib 150 mg BID to GS-US-312-0116 subjects who were randomized to placebo, and subjects randomized to idelalisib continued idelalisib at 150 mg BID.  Target Population: Subjects in the primary Phase 3 study (GS-US-312-0116) who are compliant, are tolerating primary study therapy, and 1) have definitive progression of CLL while receiving primary study drug therapy (idelalisib/placebo) or 2) are actively participating in Study GS-US-312-0116 at the time the study is stopped, including if stopped early due to overwhelming efficacy following an interim analysis.
Treatment Groups	<u>Blinded Portion</u> • Arm A: Idelalisib + rituximab (Study GS-US-312-0116) — high-dose idelalisib (300 mg BID) (Study GS-US-312-0117) • Arm B: Placebo + rituximab (Study GS-US-312-0116) — standard-dose idelalisib (150 mg BID) (Study GS-US-312-0117) <u>Open-Label Extension Portion (following unblinding)</u> • Arm A: subjects already on 300 mg BID will continue, and newly enrolled subjects will receive 150 mg BID • Arm B: subjects already on 150 mg BID will continue, and newly enrolled subjects will receive 150 mg BID

Key Eligibility Criteria	Key Inclusion Criteria 1) Participation in Study GS-US-312-0116. 2) Occurrence of confirmed, definitive CLL progression while receiving study drug therapy (idelalisib/placebo) in Study GS-US-312-0116. ***Note: Definitive disease progression is CLL progression based on standard criteria and occurring for any reason (ie, increasing lymphadenopathy, organomegaly, or bone marrow involvement; decreasing platelet count, hemoglobin, or neutrophil count; or worsening of disease-related symptoms) other than lymphocytosis***. ***Subjects must have confirmation by the sponsor working in collaboration with an independent review committee (IRC) that the disease has progressed on the primary clinical trial (Study GS-US-312-0116) before receiving secondary idelalisib therapy on this extension trial (Study GS-US-312-0117).*** 3) Presence of measurable lymphadenopathy (defined as the presence of ≥ 1 nodal lesion that measures ≥ 2.0 cm in the longest diameter [LD] and ≥ 1.0 cm in the longest perpendicular diameter [LPD] as assessed by computed tomography [CT] or magnetic resonance imaging [MRI]). 4) Permanent cessation of Study GS-US-312-0116 treatment (rituximab and/or idelalisib/placebo) and no intervening or continuing therapy (including radiotherapy, chemotherapy, immunotherapy, or investigational therapy) for the treatment of CLL. ***Note: Subjects may receive corticosteroids to manage CLL manifestations.*** 5) The time from permanent cessation of Study GS-US-312-0116 treatment (rituximab and/or idelalisib/placebo) and the initiation of Study GS-US-312-0117 therapy is ≤12 weeks. ***Note: Study procedures performed as part of Study GS-US-312-0116 need not be repeated and can be used as screening procedures for Study GS-US-312-0117 if performed within 4 weeks prior to initiation of study drug therapy on Study GS-US-312-0117.*** 6) Karnofsky performance score of ≥ 40. 7) Required baseline laboratory data (within 4 weeks prior to initiation of study treatment) as shown in the table below. ***Note: Confirmation should be considered for out-of-range values to determine if the abnormality is real or artifactual. Values should be obtained within the screening period and should generally be the most recent measurement obtained. Subjects with any degree of neutropenia, thrombocytopenia, or anemia due to CLL or prior therapy may enroll.***

	Key Exclusion Criteria 1) Known histological transformation from CLL to an aggressive lymphoma (ie, Richter transformation). 2) Evidence of ongoing systemic bacterial, fungal, or viral infection at the time of the start of study treatment (Visit 2). ***Note: Subjects with localized fungal infections of skin or nails are eligible. Subjects may be receiving prophylactic antiviral or antibacterial therapies at the discretion of the investigator; anti-pneumocystis prophylaxis is encouraged.*** 3) Pregnancy or breastfeeding. 4) Intentional breaking of the blind in Study GS-US-312-0116 by the investigator or the study subject. 5) Concurrent participation in another therapeutic clinical trial. 6) Prior or ongoing clinically significant illness, medical condition, surgical history, physical finding, electrocardiogram (ECG) finding, or laboratory abnormality that, in the investigator's opinion, could adversely affect the safety of the subject or impair the assessment of study results. In the event Study GS-US-312-0116 is stopped early, subjects who are actively participating in Study GS-US-312-0116 will become eligible for this study, provided the following inclusion are met: 1) Participation in Study GS-US-312-0116 within 12 weeks of enrollment onto 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 offers 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 is aware of the neoplastic nature of the disease and has been 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.
Study Periods/Phases	Clinic/laboratory visits will occur every 2 weeks for the first 12 weeks, every 4 weeks between Weeks 12 and 24, and every 6 weeks between Weeks 24 and 48. Subjects continuing on study drug past Week 48 will have clinic visits every 12 weeks. Subjects will be assessed for safety at each visit. Subjects will be assessed for CLL disease status by physical and laboratory examinations at each visit and by CT or MRI at Weeks 8, 16, 24, 36, and 48 and every 12 weeks thereafter. Following unblinding of the study: • Subjects who were randomized to idelalisib on Study GS-US-312-0116 and who received ≥ 24 weeks idelalisib will have Visit 16+, conducted 12 weeks from the date of their last radiology assessment (CT/MRI) and study visits will continue every 12 weeks thereafter. Visits 3 through 15 will not be required. • Subjects who have received < 24 weeks idelalisib will have all Study GS-US-312-0117 assessments completed per the Schedule of Procedures until they have received idelalisib for 24 weeks cumulative across both studies. After completion of 24 weeks of cumulative idelalisib treatment, Visit 16+ will be conducted 12 weeks from the date of their last radiology assessment (CT/MRI), after which time study visits will occur every 12 weeks.

Schedule of Assessments

The schedule of assessments is located in Appendix 2 of this statistical analysis plan (SAP).

Treatment Assignment	• Assignment to Arm A or Arm B with allocation based on the original primary study randomization • Implementation through an interactive web response system (IWRS)
Site and/or Stratum Enrollment Limits	Approximately 90 centers in the United States and in Europe.
Study Duration	Study drug will be 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.

1.3. Sample Size and Power

Planned Sample Size	Total of up to ~180 subjects (up to ~90 subjects per treatment arm)
Power Statement	The sample size for this extension study is not based upon a formal statistical hypothesis. The upper bound of the sample size in this study is determined by the sample size of the preceding primary clinical trial (Study GS-US-312-0116). 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 are expected to be enrolled into Study GS-US-312-0117.
Actual Enrollment and Impact on Power	• Actual enrollment: 161 subjects enrolled into Study GS-US-312-0117. • Impact on power: Not applicable

2. TYPE OF PLANNED ANALYSIS

The data monitoring committee (DMC) will have access to serious adverse events requiring expedited reporting and will be provided with accumulating safety data on a regular basis. Interim safety reviews will be conducted by the DMC in conjunction with safety reviews of the primary clinical trial (Study GS-US-312-0116), if applicable, at intervals of ~6 months; the specific frequency of these reviews will depend upon the rate at which the trials are enrolled, the nature of any emerging safety signals, and monitoring recommendations from the DMC. At each review, all available safety data will be summarized and evaluated.

The efficacy analysis of the blinded portion of this clinical trial (Study GS-US-312-0117) is planned to take place at the time of the final analysis of the blinded portion of the primary study (GS-US-312-0116). Once outstanding data queries have been resolved, the database will be finalized for the blinded portion, and the blind will be broken.

Following unblinding, interim and final analyses are planned to be performed in support of regulatory review of data from the primary study. An analysis of efficacy and safety may be included to satisfy regulatory requirements and to perform long-term efficacy, safety, and OS follow-up. The timing of the final analysis is expected to occur within 48 months of accrual of the final subject to Study GS-US-312-0117.

3. GENERAL CONSIDERATIONS FOR DATA ANALYSES

3.1. Analysis Sets

3.1.1. Intent-to-Treat Analysis Set

The intent-to-treat (ITT) analysis set includes all subjects who are randomized in Study GS-US-312-0116 regardless of whether subjects receive any study drug(s), or receive a different regimen from the regimen they were randomized to. Treatment assignment will be designated according to randomization. This analysis set will be used for OS analyses.

3.1.2. Full Analysis Set

The full analysis set (FAS) includes all subjects in the ITT analysis set who receive ≥ 1 dose of IDELA, with treatment assignments designated according to randomization. Because all the subjects received correct treatment as randomized, this analysis set will be used for both the efficacy and safety analyses.

3.1.3. Pharmacokinetic/Pharmacodynamic Analysis Sets

The pharmacokinetic/pharmacodynamic (PK/PD) analysis sets include data from subjects in the FAS who have the necessary baseline and on-study measurements to provide interpretable results for the specific parameters of interest.

These analysis sets will be used in the analyses of IDELA plasma concentrations.

3.2. Strata and Covariates

Not applicable.

3.3. Examination of Subject Subsets

Selected efficacy endpoints will be summarized in the following subgroups:

- Prognostic factors
  - 17p deletion and/or p53 mutation: either or neither
  - 17p deletion: Yes or No

AEs and lab abnormalities will be examined in the following subgroups:

- Gender (Male or Female)
- Age group (< 65 or ≥ 65)
- Race (White or Non-White)

3.4. Missing Data and Outliers

Missing Data

A missing data point for a given study visit may be due to any of the following reasons:

- A visit occurred in the window but data were not collected or were unusable
- A visit did not occur in the window
- A subject permanently discontinued from the study before reaching the window

In general, values for missing data will not be imputed unless methods for handling missing data are specified.

Missing data in Functional Assessment of Cancer Therapy: Leukemia (FACT-Leu) will be handled according to the administration and scoring guidelines.

Outliers

No data will be excluded from the analyses, including any outliers.

3.5. Data Handling Conventions and Transformations

- By-subject listings will be created for important variables in each eCRF module, and sorted by subject number, visit, and time (if applicable).
- Summary tables for continuous variables will contain the following statistics: N (number in analysis set), n (number with data), mean, standard deviation (StD), median, Q1, Q3, minimum, and maximum. The same number of decimal places as in the raw data will be presented when reporting minimum and maximum, 1 more decimal place than in the raw data will be presented when reporting mean, median and 2 more decimal places than in the raw data will be presented when reporting StD.
- Summary tables for categorical variables for baseline and safety data will include: N, n, percentage. The tables for efficacy endpoints will include standard error, and 95% confidence intervals (CI) on the percentage, where appropriate. Unless otherwise indicated, 95% CIs for binary variables will be calculated using the binomial distribution. The denominator for the percentages will be the number of subjects in the specified analysis set at the same treatment or total as appropriate, unless otherwise specified. Missing data will be included as a row in tables where it is appropriate. All percentages will be presented as 1-decimal point, unless otherwise specified. Percent equal to 100 will be presented as 100% and percent will not be presented for zero frequencies.
- Data from all sites will be pooled for all analyses.

- Analyses will be based upon the observed data unless methods for handling missing data are specified.

- For Kaplan-Meier estimates, the 95% CIs will be calculated using the Greenwood's formula with (complementary) log-log transformation.

3.5.1. Data Handling for Treatment Groups

Subjects who developed disease progression, confirmed by independent review committee (IRC), in Study GS-US-312-0116 could consider participation in Study GS-US-312-0117. Upon enrollment, subjects who were randomized into Arm A received IDELA 300 mg BID and those who were randomized into Arm B received IDELA 150 mg BID.

Study GS-US-312-0116 was stopped early due to overwhelming efficacy based on results from the first interim analysis and the primary study was unblinded. Under the protocol amendment, all remaining subjects were given the opportunity to enroll in Study GS-US-312-0117 and received IDELA 150 mg BID. The dose increase to IDELA 300 mg BID after confirmed PD on Arm A was no longer offered.

For disposition data summaries, subjects will be assigned into 1 of the following 4 treatment groups:

- IDELA 150 mg BID in GS-US-312-0116 and GS-US-312-0117:

  — Includes all subjects who are randomized to Arm A in Study GS-US-312-0116 except for those who take IDELA 300 mg BID in Study GS-US-312-0117

  — Referred to 'IDELA+R/IDELA' throughout this SAP and the tables, figures, and listings (TFLs)

  — Baseline for efficacy endpoints will be the date of randomization in Study GS-US-312-0116.

  — Baseline for safety endpoints will be the first dosing of IDELA in Study GS-US-312-0116.

  — In the analysis, the Study GS-US-312-0117 portion will include all the data collected on or after the enrollment date of Study GS-US-312-0117.

- IDELA 150 mg BID in GS-US-312-0116 + IDELA 300 mg BID in GS-US-312-0117:

  — Includes subjects who experience IRC confirmed progressive disease (PD) in Arm A of Study GS-US-312-0116 and subsequently enroll into Study GS-US-312-0117 to receive IDELA 300 mg BID during the double-blind portion of the study

  — Referred to 'IDELA+R (PD)/IDELA' throughout this SAP and the TFLs

— Baseline for efficacy and safety endpoints will be the first dosing of IDELA 300 mg BID, unless otherwise specified.

— In the analysis, the Study GS-US-312-0117 portion will include all the data collected on or after the enrollment date of Study GS-US-312-0117.

- Placebo in GS-US-312-0116 + IDELA 150 mg BID (open-label):

  — Includes subjects who are randomized to Arm B in Study GS-US-312-0116 and transition to receive IDELA 150 mg BID during the open-label portion of the study

  — Referred to 'Placebo+R/IDELA' throughout this SAP and the TFLs

  — Baseline for efficacy and safety endpoints will be the first dosing of IDELA, unless otherwise specified.

  — In the analysis, the Study GS-US-312-0117 portion will include all the data collected on or after the first dosing date of IDELA. The Study GS-US-312-0117 portion may include data collected in Study GS-US-312-0116, if a subject switches to open-label IDELA in Study GS-US-312-0116 while waiting for the protocol amendment.

- Placebo in GS-US-312-0116 + IDELA 150 mg BID in GS-US-312-0117:

  — Includes subjects who experience IRC confirmed PD in Arm B of Study GS-US-312-0116 and subsequently enroll into Study GS-US-312-0117 to receive IDELA 150 mg BID during the double-blind portion of the study

  — Referred to 'Placebo+R (PD)/IDELA' throughout this SAP and the TFLs

  — Baseline for efficacy and safety endpoints will be the first dosing of IDELA, unless otherwise specified.

  — In the analysis, the Study GS-US-312-0117 portion will include all the data collected on or after the enrollment date of Study GS-US-312-0117.

Efficacy and safety data collected during the primary and extension studies will be presented in the following 3 treatment groups:

- IDELA+R (PD, non-PD)/IDELA

  — Includes all subjects who are randomized to Arm A in Study GS-US-312-0116 (ie, all subjects in IDELA+R/IDELA and IDELA+R (PD)/IDELA)

  — For those in IDELA+R (PD)/IDELA, only data collected in Study GS-US-312-0116 (ie, while taking IDELA 150 mg BID) will be included. For those in IDELA+R/IDELA, all the data collected across Study GS-US-312-0116 and GS-US-312-0117 will be included. By this summary, the efficacy and safety profile of IDELA 150 mg BID can be explored for subjects randomized to Arm A in Study GS-US-312-0116.

- Baseline for efficacy endpoints will be the date of randomization in Study GS-US-312-0116.
- Baseline for safety endpoints will be the first dosing of IDELA 150 mg BID in Study GS-US-312-0116.

- Placebo+R/IDELA
- Placebo+R (PD)/IDELA

Due to the small sample size (N = 4) for the IDELA + R (PD)/IDELA group, data collected from this group in Study GS-US-312-0117 (ie, while taking IDELA 300 mg BID) will only be presented in listings.

Baseline for each data summary is described in Table 3-1.

Table 3-1. Baseline for Data Summaries by Treatment Group

Treatment Group	Baseline for Disposition Summary		Baseline for Efficacy Summary		Baseline for Safety Summary
	312-0116	312-0117	All endpoints except for OS	OS	All endpoints
IDELA+R/IDELA	Date of randomization in Study GS-US-312-0116	Enrollment date of Study GS-US-312-0117	Date of randomization in Study GS-US-312-0116	Date of randomization in Study GS-US-312-0116	First dosing date of IDELA in Study GS-US-312-0116
IDELA+R (PD)/IDELA	Date of randomization in Study GS-US-312-0116	Enrollment date of Study GS-US-312-0117	First dosing date of IDELA 300 mg BID in Study GS-US-312-0117		First dosing date of IDELA 300 mg BID in Study GS-US-312-0117
Placebo+R/IDELA	Not applicable	First dosing date of IDELA (Switching date to open-label IDELA)	First dosing date of IDELA (Switching date to open-label IDELA)		First dosing date of IDELA (Switching date to open-label IDELA)
Placebo+R (PD)/IDELA	Not applicable	Enrollment date of Study GS-US-312-0117	First dosing date of IDELA 150 mg BID in Study GS-US-312-0117		First dosing date of IDELA 150 mg BID in Study GS-US-312-0117
IDELA+R(PD, non-PD)/ IDELA	Not applicable	Not applicable	Date of randomization in Study GS-US-312-0116		First dosing date of IDELA in Study GS-US-312-0116

Data from subjects who are randomized to Arm B in Study GS-US-312-0116 and never received IDELA in Study GS-US-312-0117 will be excluded from the analyses, unless otherwise specified.

3.5.2. Data Handling for Efficacy and Safety Endpoints

- If there is a significant degree of non-normality for a continuous endpoint, analyses may be performed on log-transformed data or using nonparametric methods, as appropriate.

- Analyses will be descriptive in nature and formal comparisons of outcomes between treatment groups are not planned.

3.5.3. Data Handling for Laboratory data

Laboratory data that are continuous in nature but are less than the lower limit of quantitation or above the upper limit of quantitation will be imputed as follows:

- A value that is 1 unit less than the limit of quantitation will be used for calculation of descriptive statistics if the data is reported in the form of "< x" (x is considered the limit of quantitation). For example, if the values are reported as < 50 and < 5.0, then values of 49 and 4.9 will be used for calculation of summary statistics, respectively. However, for direct bilirubin, a value of "< 0.1" will be treated as 0.05 for calculation of summary statistics.

- A value that is 1 unit above the limit of quantitation will be used for calculation of descriptive statistics if the data is reported in the form of "> x" (x is considered the limit of quantitation). For example, if the values are reported as > 50 and > 5.0, then values of 51 and 5.1 will be used for calculation of summary statistics, respectively.

- The limit of quantitation will be used for calculation of descriptive statistics if the data is reported in the form of "≤ x" or "≥ x" (x is considered as the limit of quantitation).

3.6. Visit Windows

3.6.1. Analysis Windows

When applicable, the nominal visit as recorded on the eCRF will be used. For parameters assessed at the end of treatment (EOT) visit, the assessment results will be assigned to the next scheduled visit where the respective data were scheduled to be collected for summary. Unscheduled scans will be used for determination of the time-to-event and tumor response efficacy endpoints.

For data collected after unblinding of the study, nominal visit may no longer be applicable. In such case, summary by visit will be based on the following visit windows as described in Table 3-2.

Table 3-2. Analysis Visit Window

Start (day)	Stop (day)	Scheduled Visit day	Week
1	1	1	0
2	21	15	2
22	35	29	4
36	49	43	6
:	:	:	:
7*(X-1)+1	7*(X+1)	X*7+1	X

3.6.2. Selection of Data in the Event of Multiple Records in a Window

Depending on the statistical analysis method, single values may be required for each analysis window. For example, change from baseline by visit usually requires a single value per visit, whereas a time-to-event analysis would not require 1 value per analysis window but rather 1 value for the study. Unless otherwise noted throughout the rest of this document, when a single value is needed, the following rule(s) will be used:

- If more than 1 assessment occurs during the same nominal visit, select the record closest to the nominal day for that visit.
- If there are 2 assessments that are equidistant from the nominal day, the data of the assessment after the scheduled study day will be used.
- The last measurement will be used if multiple measurements are all taken on the same day.

4. SUBJECT DISPOSITION

4.1. Subject Enrollment

A listing of all subjects in the FAS will be generated to describe site, subject number, first and last IDELA dosing dates, treatment group, the reason for discontinuing study treatment, and the reason for discontinuing study. The site summary will be based on the original site ID from Study GS-US-312-0116.

A by-subject listing for subjects who were screened but not treated in Study GS-US-312-0117 will be listed separately.

4.2. Disposition of Subjects

A summary of subject disposition will be provided for the FAS.

Study treatment disposition will present the number of subjects who:

- were treated in Study GS-US-312-0116
- completed/discontinued treatment in Study GS-US-312-0116 and were not treated in Study GS-US-312-0117
  - — met primary study endpoint according to the investigator
  - — discontinued study drug with summary of reason for discontinuation
- were treated in Study GS-US-312-0117
- has treatment ongoing in Study GS-US-312-0117
- completed/discontinued treatment in Study GS-US-312-0117
  - — met primary study endpoint according to the investigator
  - — discontinued study drug with summary of reason for discontinuation

Study disposition will present the number of subjects who:

- were randomized in Study GS-US-312-0116
- completed/discontinued Study GS-US-312-0116 and were not enrolled into Study GS-US-312-0117
  - — met primary study endpoint according to the investigator
  - — discontinued study with summary of reason for discontinuation

- enrolled into Study GS-US-312-0117
- are ongoing in Study GS-US-312-0117
- completed/discontinued Study GS-US-312-0117
  - met primary study endpoint according to the investigator
  - discontinued study with summary of reason for discontinuation

Long-term follow-up disposition will present the number of subjects who:

- entered long-term follow-up
- completed long-term follow-up
- are ongoing with long-term follow-up
- discontinued the long-term follow-up with summary of reasons for discontinuation

The denominator for the percentages of subjects in each category will be the number of subjects in the FAS. No inferential statistics will be generated.

4.3. Extent of Exposure

4.3.1. Duration of Exposure to Study Drugs

Duration of exposure to IDELA will be defined as minimum of (last IDELA dosing date, data cutoff date) – first IDELA dosing date +1, regardless of temporary interruptions in study drug administration, and will be expressed in months. For subjects who are randomized to Arm A, exposure duration will reference to the first dosing date of IDELA in Study GS-US-312-0116.

Duration of exposure to IDELA will be summarized for the FAS using descriptive statistics and as the number and percentage of subjects exposed for at least 2, 4, and 6 months, and every 6 months thereafter.

Number and percentage of subjects who had IDELA dose modification (dose reduction and dose re-escalation) will also be summarized. IDELA dosing records, drug accountability (dispense and return), and dose modification records will be listed in detail.

4.4. Protocol Deviations

Protocol deviations will be categorized before database finalization by Gilead. The important (major) protocol deviations will be summarized by type of deviation in the clinical study report (CSR) for subjects who enroll into Study GS-US-312-0117. A listing will be provided for important protocol deviations.

5. BASELINE DATA

5.1. Demographics and Baseline Characteristics

Demographics including gender, race, ethnicity, age (years), weight (kg), height (cm), and body mass index (BMI, kg/m^2) will be summarized for the FAS. Gender, race, ethnicity, and Karnofsky performance status will be summarized by using summary statistics for categorical variables. Age (years), weight (kg), and height (cm) will be summarized using summary statistics for continuous variables. Age will be calculated as the number of years between date of birth and date of randomization in Study GS-US-312-0116.

Age (years) = (date of randomization in Study GS-US-312-0116 – date of birth + 1) / 365.25 (round down to an integer)

BMI (kg/m^2) = weight / $(height)^2$ (round to 1 decimal point)

Number and percentage of subjects < 65 and ≥ 65 years will also be summarized. A data listing will be presented.

5.2. Medical History

A listing of total cumulative illness rating scale (CIRS) scores and medical history will be provided.

6. EFFICACY ANALYSES

An IRC was established for this study and includes primary board-certified radiologists and a board-certified adjudicating radiologist from a pool of radiologists, and an independent board-certified hematologist or oncologist to perform an independent review of response and disease progression for each subject. The review will comprise an assessment of radiographic images and prospectively defined clinical data acquired during the study according to the Gilead Protocol GS-US-312-0117 Imaging Charter. The determination of CLL response and progression will be based on standardized criteria promulgated by the International Workshop on CLL (IWCLL) {12154}, as specifically modified for this study to reflect current recommendations which consider the mechanism of action of IDELA and similar drugs {22541}. The findings of the IRC will be considered primary for analyses of tumor control endpoints.

6.1. Efficacy Endpoints

6.1.1. Definition of Efficacy Endpoints

- Progression-free survival (PFS) – defined as the interval from the baseline reference date for efficacy endpoints, as defined in Section 3.5.1, 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 {12154}, {22541} other than lymphocytosis alone.

- Overall response rate (ORR) – defined as the proportion of subjects who achieve a complete response (CR) or partial response (PR)

- Lymph node response (LNR) rate – defined as the proportion of subjects who achieve a $\geq$ 50% decrease from baseline in the sum of the products of the greatest perpendicular diameters (SPD) of index lesions per IRC assessments

- Complete response (CR) rate – defined as the proportion of subjects who achieve a CR

- Time to response (TTR) – defined as the interval from the baseline reference date for efficacy endpoints 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 an on-study 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 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 achieve an on-study ALC $< 4 \times 10^9$/L or demonstrate a $\geq$ 50% decrease in ALC from baseline; ALC values within 4 weeks post-baseline will be 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 achieve an on-study platelet count $\geq 100 \times 10^9$/L or demonstrate a $\geq$ 50% increase in platelet count from baseline without need for exogenous growth factors. Platelet values within 4 weeks post-baseline or after 8 days post transfusion will be 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 achieve an on-study hemoglobin ≥110 g/L (11.0 g/dL) or demonstrate a $\geq$ 50% increase in hemoglobin from baseline without red blood cell transfusions or need for exogenous growth factors. Hemoglobin values within 4 weeks post-baseline or after 4 weeks of receiving packed cell/whole blood transfusion or after 6 weeks receiving exogenous growth factors (e.g., Darbepoetin alfa) will be excluded for 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 without need for exogenous growth factors. ANC values within 4 weeks of post-baseline or after 2 weeks of receiving exogenous growth factors (e.g., Filgrastim, G-CSF, Lenograstim) or after 4 weeks of receiving Neulasta will be excluded for the neutrophil response evaluation.
- Overall Survival (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 from baseline in HRQL using FACT-Leu scores
- Changes from baseline in Karnofsky performance status
- Change from baseline in overall health and summary of single-item dimension scores as assessed using the EuroQoL Five-Dimension (EQ-5D) utility measure

6.1.2. Analysis Methods for Efficacy Endpoints

6.1.2.1. Progression-Free Survival

PFS will be described in the FAS using Kaplan-Meier methods by treatment groups. Median PFS with Q1 and Q3, the Kaplan-Meier estimates of PFS rate with corresponding 95% CIs will be presented at 24, 48 weeks and so forth depending on the follow-up duration. The Kaplan-Meier curve will also be plotted.

The date of definitive CLL progression will be the timepoint at which progression is first identified by relevant objective radiographic or clinical data by the IRC.

Data will be censored on the date of the last tumor assessment (including assessments with a not evaluable [NE] outcome) for subjects who do not have disease progression, or who do not die on study. Data will also be censored on the date of the last tumor assessment (including NE) prior to the initiation of new anti-tumor therapy, or prior to ≥ 2 consecutive missing tumor assessments before disease progression or death. Subjects without adequate baseline tumor response evaluation will be censored on the baseline reference date for efficacy endpoints.

For subjects with disease progression by the IRC, the reasons for PD will be summarized by treatment groups.

The following disease progression criteria will be included:

- Progression based on index lesion
  - Increase from the nadir by ≥ 50% in the SPD of index lesions
  - A new node that measures > 1.5 cm in the LD and >1.0 cm in the LPD
  - Increase from the nadir by ≥ 50% in the LD of an individual node
- Progression based on non-index lesion
  - Unequivocal increase in the size of non-index disease
- Progression based on hepatomegaly
  - New or recurrent hepatomegaly
  - Hepatic progression
- Progression based on splenomegaly
  - New or recurrent splenomegaly
  - Splenic progression
- Progression based on hematological parameters confirmed by bone marrow
  - The current platelet count is < 100×10^9/L and there has been a decrease by >50% from the highest on-study platelet count
  - The current hemoglobin is < 110 g/L (11.0 g/dL) and there has been a decrease by > 20 g/L (2 g/dL) from the highest on-study hemoglobin
- Transformation to a more aggressive histology

6.1.2.2. Overall Response Rate

Responses will be categorized as CR, PR, stable disease (SD), or PD. In addition, a response category of not evaluable (NE) is provided for situations in which there is inadequate information to otherwise categorize response status. A response category of no disease (ND) is included for situations in which there is no evidence of tumor either at baseline or on study.

The ORR using the IRC assessments will be presented with 95% CI by treatment groups. In the calculation of response rates, subjects who do not have sufficient baseline or on-study tumor assessment to characterize response will be included in the denominator.

6.1.2.3. Lymph Node Response Rate

LNR rate will be presented with 95% CI by treatment groups. Only subjects that have both baseline and ≥ 1 evaluable post-baseline SPD will be included for this analysis.

6.1.2.4. Complete Response Rate

The same analyses as specified for ORR in Section 6.1.2.2 will be performed for the CR rate.

6.1.2.5. Time to Response and Duration of Response

TTR and DOR will be evaluated using IRC assessments based on subjects who achieve a CR or PR. Descriptive statistics will be provided for TTR. DOR will be summarized using Kaplan-Meier methods (medians, Q1, Q3, and corresponding 95% CIs) and the Kaplan-Meier curves will also be provided by treatment groups.

For the DOR analysis, data will be censored with the same manner as described in Section 6.1.2.1 for subjects who do not have disease progression, or who do not die on study, or start new anti-tumor therapy, or have ≥ 2 consecutive missing tumor assessments before disease progression or death.

6.1.2.6. Best Percent Change in Lymph Node Area

The best percent change in SPD from baseline during the study will be summarized using descriptive statistics. The summary is based on subjects with sufficient baseline and on-study tumor measurements for the SPD calculation per IRC. The best percent change from baseline in SPD is defined as the largest decrease in tumor size during the study. The baseline SPD will be the last value collected prior to the baseline reference date for efficacy endpoints. Note that for subjects who only have increases in tumor size from baseline, the smallest increase will be considered as the best change from baseline in SPD. Waterfall plots of best on-study percent change in SPD will be provided for each treatment group using IRC data.

6.1.2.7. Other Categorical Endpoints

Splenomegaly response rate, hepatomegaly response rate, ALC response rate, platelet response rate, hemoglobin response rate, and neutrophil response rate will be presented with 95% CIs. In the calculation of response rates, only subjects who have relevant abnormality, sufficient baseline and post-baseline assessments to characterize response will be included in the analysis.

The ALC, platelet, hemoglobin, and neutrophil responses will be listed with flags to indicate the use of any supportive care for corresponding hematologic lab parameters.

6.1.2.8. Overall Survival

OS will be described in the ITT analysis set using Kaplan-Meier methods by treatment group according to the original randomization in Study GS-US-312-0116. Median OS with Q1, Q3, and the Kaplan-Meier estimates of OS rate by every 6 months with corresponding 95% CIs will be presented. The Kaplan-Meier curve will also be plotted.

Data from surviving subjects will be censored at the last time that the subject was known to be alive on study or long term follow up.

Sensitivity analyses will be conducted by censoring OS on the first date of IDELA dosing for subjects in Arm B. OS will also be analyzed using the rank-preserving structural failure time (RPSFT) model {33006} to adjust for cross over effects.

6.1.2.9. Health-Related Quality of Life

The FACT-Leu questionnaire includes subscales for physical well-being (PWB, 7 items), social/family well-being (SWB, 7 items), emotional well-being (EWB, 6 items), functional well-being (FWB, 7 items), and additional concerns (Leukemia-Specific Subscale [LeuS], 17 items). The FACT-Leu scoring guide identifies those negatively stated items that must be reversed before being added to obtain subscale totals. Negatively stated items are reversed by subtracting the response from “4”. After reversing proper items, all subscale items are summed to a total, which is the subscale score. For all FACT-Leu scales and symptom indices, the higher score is associated with the better quality of life. The scores in the following items need to be reversed according to the standard scoring guidelines:

- Physical well-being: all individual items
- Social/family well-being: none
- Emotional well-being: 5 individual items (except for GE2: “I am satisfied with how I am coping with my illness”)
- Functional well-being: none
- Additional concerns: all individual items (except for C6: “I have a good appetite” and An7: “I am able to do my usual activities”)

The subscale scores will be a summation of each individual item score. If ≤ 50% of item scores are missing, the subscale score will be calculated by multiplying the sum of the item scores by the number of items in the subscale, then divided by the number of non-missing item scores. This imputes the missing scores by the mean of the non-missing scores within a subscale.

Prorated subscale score = [sum of item scores] × [N of items in subscale] / [N of items answered]

The following composite scores will be derived from the above subscale total scores:

- Trial Outcome Index (TOI, score range: 0-124) = PWB + FWB + LeuS
- FACT-G Total Score (score range: 0-108) = PWB + SWB + EWB + FWB
- FACT-Leu Total Score (score range: 0-176) = PWB + SWB + EWB + FWB + LeuS

The total scores will be set to missing if 20% or more of the included items are missing or any of the component subscales are missing. TOI scores are set to missing if any of the component subscales are missing.

As a baseline, the last value obtained prior to the baseline reference date for efficacy endpoints, as defined in Section 3.5.1, will be used. The mean and change from baseline in mean scores to each subsequent assessment will be summarized for the subscale and composite scores. The best change from baseline during the study, defined as the highest positive value among all post-baseline visits minus the baseline value, will also be summarized.

Each subject's FACT-Leu subscales (ie, PWB, EWB, SWB, and FWB) scores at each assessment will be compared to their baseline scores. The minimally important difference (MID) for these subscales is 3 points {26297}. An increase of at least 3 points will be required as a definition of symptom improvement. The cumulative distribution function (CDF) of best change from baseline will be provided. For the MID improvement comparison, subjects with baseline score > 55 will be excluded (ie, subjects with no room for improvement). Time to symptom response will be assessed by defining the first occurrence of symptom improvement as an event. Subjects who do not experience a symptom improvement compared to baseline will be censored at their last available FACT-Leu assessment time.

A data listing for each individual item, the subscale scores, and the composite scores will be presented for each subject at each time point.

6.1.2.10. Karnofsky Performance Status

The Karnofsky performance status scores and the change from baseline scores to each subsequent assessment will be summarized. The best change from baseline, defined as the highest change from baseline during the study, will also be summarized.

6.1.2.11. EQ-5D

The EQ-5D questionnaire data will be scored, processed, and standardized according to the user manual. As for the FACT-Leu, data will be analyzed using appropriate methods specified in the user manual to account for incomplete completion of questionnaires. A single utility index of EQ-5D will be derived by applying US preference-weighted index {28010}. Data collected from the EQ-5D will not be reconciled with adverse event or laboratory data or with FACT-Leu findings.

Each EQ-5D dimension will be summarized using frequency and proportion. Change from baseline in EQ-5D visual analogue scale (VAS) and EQ-5D index will be summarized.

6.1.3. Between-Study Comparisons

PPD

6.2. Changes From Protocol-Specified Efficacy Analyses

The per-protocol analysis set and the safety analysis set are no longer applicable. The FAS will be used for both efficacy and safety analyses.

7. SAFETY ANALYSES

7.1. Adverse Events and Deaths

The focus of adverse event (AE) summarization will be on treatment-emergent AEs (TEAEs). All AEs and deaths happened on study will be summarized by treatment group and will be listed in detail based on the FAS.

7.1.1. Adverse Event Dictionary

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) by system organ class (SOC), high level group term (HLGT), high level term (HLT), preferred term (PT), and lower level term (LLT).

7.1.2. Adverse Event Severity

The severity of AEs will be graded by the investigator according to the common terminology criteria for adverse events (CTCAE), Version 4.03, whenever possible. If a CTCAE criterion does not exist, the grade corresponding to the appropriate adjective will be used by the investigator to describe the maximum intensity of the AE. The severity grade will be categorized as:

- Grade 1 (mild)
- Grade 2 (moderate)
- Grade 3 (severe)
- Grade 4 (life threatening), or
- Grade 5 (fatal)

A missing severity grade will be considered as missing.

7.1.3. Relationship of Adverse Events to Study Drug

The relationship of an AE to IDELA should be assessed using clinical judgment by the investigator, describing the event as either unrelated or related. Events for which the investigator did not record relationship to IDELA will be considered related to IDELA. Data listings will show relationship as missing.

7.1.4. Serious Adverse Events

Serious adverse events (SAEs) are those identified as serious in the clinical database. The clinical database will be reconciled with the SAE database from the Drug Safety and Public Health (DSPH) Department before database finalization.

7.1.5. Treatment-Emergent Adverse Events

7.1.5.1. Definition of Treatment-Emergent

TEAEs are events in a given study period that meet one of the following criteria:

- Events with onset dates on or after the start of IDELA and up to 30 days after the permanent discontinuation of IDELA.
- AEs resulting in IDELA discontinuation after the start of treatment.

7.1.5.2. Incomplete Dates

All AEs with partial onset or stop dates will be identified and the partial dates will be imputed as follows:

- For AE onset date: If day and month are missing but year is available, then the imputed day and month will be 01Jan or the first dosing date of IDELA if they have the same year, whichever is later. If day is missing but the month and year are available, then the imputed day will be the first day of the month or the first dosing date of IDELA if they have the same month and year, whichever is later.
- For AE stop date: If day and month are missing but year is available, then the imputed day and month will be 31Dec or 30 days after the last dose of study treatment if they have the same year, whichever is earlier. If day is missing but the month and year are available, then the imputed day will be the last day of the month or 30 days after the last dose of study treatment if they have the same month and year, whichever is earlier.

7.1.6. Summaries of Adverse Events and Deaths

A brief summary of TEAEs by treatment group will show the number and percentage of subjects who (1) had any AE, (2) had any Grade ≥ 3 AE, (3) had any IDELA-related AE, (4) had any Grade ≥ 3 IDELA-related AE, (5) had any SAE, (6) had any IDELA-related SAE, (7) discontinued from study drug due to an AE, (8) dose interruption due to an AE, (9) dose reduction due to an AE, (10) dose modification (interruption and/or reduction) due to an AE, (11) death due to AEs.

Summaries (number and percentage of subjects) of TEAEs (by SOC, HLT and PT) will be provided by treatment group using the FAS as follows:

- AEs
- AEs by CTCAE Grade
- Grade ≥ 3 AE

- IDELA-related AEs
- SAEs
- IDELA-related SAEs
- AEs leading to IDELA modification (reduction and/or interruption)
- AEs leading to IDELA reduction
- AEs leading to IDELA interruption
- AEs leading to permanent discontinuation from IDELA
- AEs leading to death
- TEAE incidence rate adjusted for total exposure

Multiple events will be counted once only per subject in each summary. For data presentation, SOC, HLT and PT will be sorted by decreasing frequency based on IDELA + R/IDELA treatment group. For summaries by severity grade, the most severe event will be selected. In addition to the presentation by SOC and HLT, selected summary will also be presented by preferred term only, ordered by decreasing frequency.

In addition to the by-treatment summaries, data listings will be provided for the following:

- All TEAEs
- SAEs
- AEs leading to discontinuation of IDELA
- Deaths

Relative day from the baseline reference date for safety endpoints, as defined in Section 3.5.1., will be provided for each AE in the listings. The relative day will be calculated as (AE onset date - baseline reference date for safety endpoints + 1).

7.1.7. Treatment-Emergent Adverse Events of Interest

The treatment-emergent AEs of interest (AEI) include:

- **Rash** based on Gilead medical search list including multiple MedDRA preferred terms dermatitis exfoliative, drug eruption, rash, rash erythematous, rash generalised, rash macular, rash maculo-papular, rash papular, rash prutitic, rash morbilliform, and exfoliative rash
- **Diarrhea/Colitis** including diarrhea or colitis

- **Pneumonitis**

- **Anaphylaxis** including anaphylactic reaction, anaphylactic shock, anaphylactic transfusion reaction, anaphylactoid reaction, anaphylactoid shock, circulatory collapse, first use syndrome, kounis syndrome, shock, type I hypersensitivity

- **Bowel perforation** including rectal perforation, duodenal perforation, duodenal ulcer perforation, duodenal ulcer perforation obstructive, diverticular perforation, gastrointestinal perforation, gastrointestinal ulcer perforation, appendicitis perforated, ileal perforation, ileal ulcer perforation, intestinal perforation, intestinal ulcer perforation, jejunal perforation, jejunal ulcer perforation, large intestinal ulcer perforation, large intestine perforation, small intestinal perforation, small intestinal ulcer perforation

Summaries of TEAEs of interest will be provided for the following:

- AEIs by CTCAE Grade

- AEIs leading to modification (interruption and/or reduction)

- AEIs leading to interruption

- AEIs leading to reduction

- AEIs leading to IDELA discontinuation

- AEIs by time interval (12 weeks intervals)

Incidence and prevalence of AEIs by time interval will be summarized by 12 weeks intervals up to 84 weeks (eg, 0 to < 12 weeks, 12 to < 24 weeks, … ,72 to < 84 weeks) and ≥ 84 weeks. Incidence of AEIs in the interval is defined as the proportion of subjects with onset of AEI in that interval out of those at risk at the beginning of the interval. Prevalence of AEI is defined as the proportion of subjects experiencing AEI in that interval out of those at risk at the beginning of the interval. The subjects at risk include those on IDELA or within 30 days post last dose date for subjects who didn't die at the beginning of the interval.

- Time to first onset and resolution of AEIs

Time to onset of AEIs (in weeks) is defined as time from the baseline reference date for safety endpoints to the date of first incident of AEI. In the absence of an event, the onset date will be censored at the earliest from the following dates: last IDELA dosing date (ie, captured on study drug completion CRF page) + 30 days, analysis data cut-off date and death date. Time to resolution of AEIs is calculated as (AEI stop date − start date of first occurrence of AEI + 1) / 7.

7.1.8. Exposure-adjusted TEAE Rate

The exposure-adjusted TEAE rate is defined as the number of subjects with a specific event divided by the total exposure-time among the subjects in the treatment group and at risk of an initial occurrence of the event. Specifically,

$$\textit{Exposure-Adjusted TEAE Rate} = \frac{n}{T} = \frac{n}{\sum t_i}$$

Where n is the number of subjects with events, t_i is the i^{th} subject exposure time in years and T is the total exposure time in years of all subjects. If a subject has multiple events, the t_i is the time of the first event. For a subject with no event, the t_i will be censored at the time of data cut-off date if the subject is still taking IDELA; and the t_i will be censored at the time of last does date plus 30 days or data cutoff date whichever is earlier if the subject discontinues IDELA.

The exposure-adjusted TEAE rate will be summarized for AEI by treatment group based on the FAS.

7.2. Laboratory Evaluations

Summaries of laboratory data (including hematology, serum chemistry, urinalysis, and selected immunoglobulin parameters) will be provided. Summaries of laboratory data will be based on observed data and will be reported using SI units. The focus of laboratory data summarization will be on treatment-emergent laboratory abnormalities using the FAS.

7.2.1. Summaries of Numeric Laboratory Results

Descriptive statistics (sample size, mean, StD, median, Q1, Q3, minimum and maximum) will be provided for each laboratory test specified in the study protocol as follows:

- Baseline values
- Values at each post-baseline visit
- Change from baseline at each post-baseline visit

In the case of multiple values in an analysis window, data will be selected for analysis as described in Section 3.6.2. In addition, mean change from baseline (± standard error) and median (± Q1/Q3) for selected lab parameters will be plotted over time by treatment groups.

7.2.2. Summaries of Categorical Laboratory Results

Laboratory data that are categorical will be summarized using number and percentage of subjects in the study with the given response by treatment groups and visit based on analysis window.

7.2.3. Graded Laboratory Values

Applicable hematological and serum biochemistry laboratory data will be programmatically graded according to CTCAE, Version 4.03 severity grade [grade laboratory results as Grade 0, mild (Grade 1), moderate (Grade 2), severe (Grade 3), or life threatening (Grade 4)]. Grade 0 includes all values that do not meet criteria for an abnormality of at least Grade 1. Some laboratory tests have criteria for both increased and decreased levels; analyses for each direction (ie, increased, decreased) will be presented separately. For all laboratory tests except for lipids (cholesterol and triglyceride), lab normal ranges will override the common terminology criteria (CTC) grade criteria (ie, all labs within normal ranges will be programmatically assigned a CTCAE grade of 0) when lab normal ranges overlaps with CTC grade criteria. Local labs will be graded with central lab normal ranges with Gilead in-house macro. Local labs of ANC, lymphocytes, Platelet, hemoglobin, aspartate aminotransferase, alanine aminotransferase, total bilirubin, and alkaline phosphatase are included in the table summaries when central labs are not available. All other local labs are listed.

7.2.3.1. Treatment-Emergent Laboratory Abnormalities

A treatment-emergent laboratory abnormality is defined as an abnormality that, compared to baseline, worsens by ≥ 1 grade during the post-baseline period up to 30 days after the last dose of study treatment. If baseline data are missing, then any graded abnormality (ie, an abnormality that is Grade ≥ 1 in severity) will be considered treatment-emergent.

7.2.3.2. Summaries of Laboratory Abnormalities

Summary (number and percentage of subjects) of baseline and worst post-baseline treatment-emergent laboratory abnormalities will be provided by treatment groups. Subjects will be categorized according to most severe abnormality grade.

For all summaries of laboratory abnormalities, the denominator is the number of subjects in the FAS. A listing of treatment-emergent laboratory abnormalities will be provided.

7.2.3.3. Exposure-adjusted Treatment-Emergent Laboratory Abnormalities Rate

The exposure-adjusted treatment-emergent lab abnormalities will be analyzed similarly to the exposure-adjusted TEAE rates (outlined in Section 7.1.8).

7.2.4. Shift in CTCAE Grade Relative to Baseline

Shift tables will be presented by showing change in CTCAE severity grade from baseline to the worst grade post baseline.

7.2.5. Transaminase Elevations

Analyses of transaminase elevations will be based on laboratory values using the FAS. Number and percentage of subjects will be summarized by treatment groups for subjects:

- with Grade 3 or 4 alanine aminotransferase (ALT)/aspartate aminotransferase (AST) elevation
- with Grade 3 or 4 ALT/AST elevation resolved to both ALT/AST of Grade 1 or less
- re-challenged after dose interruption
- with recurrence of Grade 3 or 4 ALT/AST elevation among re-challenged
- with recurrent Grade 3 or 4 ALT/AST elevation resolved to both ALT/AST of Grade 1 or less

Kaplan-Meier curves and estimates will be provided for time to onset of first Grade 3 or 4 treatment-emergent ALT/AST elevations. Time to onset of first event is defined as time from the baseline reference date for safety endpoints to the start date of first Grade 3 or 4 treatment-emergent ALT/AST elevation, ie, time in weeks is calculated as (start date of first occurrence – baseline reference date for safety endpoints + 1) / 7. In the absence of an event, the censoring date applied will be the earliest from the following dates: last dose date (if treatment discontinued) + 30 days, analysis data cut-off date and death date.

For subjects with at least 1 episode of Grade 3 or 4 ALT/AST elevation, time to resolution of the first episode of treatment-emergent Grade 3 or 4 ALT/AST elevation to Grade 1 or less will be summarized using Kaplan-Meier estimates. The same censoring rule described above for time to onset will be used.

7.2.6. Liver-Related Laboratory Tests

The number and percentage of subjects will be summarized for the following liver-related laboratory tests and categories:

- AST: (a) 3 to < 5 × upper limit normal (ULN), (b) 5 to < 10 × ULN, (c) 10 to < 20 × ULN, (d) ≥ 20 × ULN
- ALT: (a) 3 to < 5 × ULN, (b) 5 to < 10 × ULN, (c) 10 to < 20 × ULN, (d) ≥ 20 × ULN
- AST or ALT: (a) 3 to < 5 × ULN, (b) 5 to < 10 × ULN, (c) 10 to < 20 × ULN, (d) ≥ 20 × ULN
- Total bilirubin: (a) > ULN, (b) > 1.5 × ULN, (c) > 2 × ULN
- AST or ALT > 3 × ULN and total bilirubin > 1.5 × ULN

- AST or ALT > 3 × ULN and total bilirubin > 2 × ULN
- Alkaline Phosphatase > 1.5 × ULN

For individual laboratory tests, subjects will be counted once based on the most severe post-baseline values.

Among the subjects with elevated AST or ALT (> 3 × ULN), the following 2 approaches will be used for counting subjects with total bilirubin elevation/normal alkaline phosphatase (≤ 1.5 × ULN):

- Subjects will be counted once when total bilirubin elevation/normal alkaline phosphatase occurred at any post-baseline visit.
- Subjects will be counted once when total bilirubin elevation/normal alkaline phosphatase occurred concurrently at the same post-baseline visit with AST or ALT elevation.

In addition, a listing of subjects meeting each category will be provided.

7.3. Prior Therapy

Number of prior regimens and time since the completion of last regimen collected in study GS-US-312-0116 will be summarized by treatment groups using descriptive statistics (n, mean, StD, median, Q1, Q3, minimum and maximum) based on the FAS. A partial completion date will be imputed using the following algorithm for the last regimen:

- If day and month are missing but year is available, then the imputed day and month will be 01Jan or the starting date of the last regimen, whichever is later;
- If day is missing but the month and year are available, then the imputed day will be the first day of the month, or the starting date of the last regimen, whichever is later;
- If year is missing, no imputation will be done and the completion date will be treated as missing.

Number (%) of subjects who received 1, 2, 3, ... prior regimens and the type of prior regimens that the subjects received will be summarized. The last prior regimen subjects received prior to study entry of GS-US-312-0116 will be summarized.

7.4. Concomitant Medications

Concomitant medications will be coded by means of the World Health Organization Drug Dictionary (WHODRUG) dictionary, Q2 2014 into Anatomical-Therapeutic-Chemical classification (ATC) codes.

Concomitant medications are defined as any medications meeting the following criteria

- Starting on or after the baseline reference date for safety endpoints, up to 30 days post the last dose

- Starting before and continuing after the baseline reference date for safety endpoints, up to 30 days post the last dose

The incomplete dates handling method for AE will be used for concomitant medication summaries (Section 7.1.5.2).

Summaries of the number and percentage of subjects who use concomitant medications will be presented in tabular form by preferred drug name based on the FAS. The summary tables will be sorted by descending frequency based on IDELA + R/IDELA treatment group. Subjects will only be counted once for multiple drug use (by preferred drug name).

The summaries and listings of concomitant medications will be based on the FAS.

7.5. Other Safety Measures

Physical examination results will be summarized by body system and analysis visit. All results will be listed.

A data listing will be provided for subjects experiencing pregnancy during the study.

7.6. Changes From Protocol-Specified Safety Analyses

Summary of study drug compliance will be removed as the accurate calculation of drug accountability is not feasible for subjects who cross over to open-label IDELA in Study GS-US-312-0116.

8. PHARMACOKINETIC ANALYSES

Bioanalytical analyses will be performed independently so that the study team and investigators will not have knowledge of data from individual subjects. IDELA plasma concentrations immediately pre-dose and at 1.5 hours after administration of the dose of study drug at each relevant clinic visit will be summarized by visit using descriptive statistics.

9. PHARMACODYNAMIC ANALYSES

A separate biomarker analysis plan will be prepared to detail pharmacodynamics and biomarker analyses.

10. REFERENCES

12154 Hallek M, Cheson BD, Catovsky D, Caligaris-Cappio F, Dighiero G, Dohner H, et al. Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia (IWCLL) updating the National Cancer Institute-Working Group (NCI-WG) 1996 guidelines. Blood 2008;111 (12):5446-56.

22541 Cheson BD, Byrd JC, Rai KR, Kay NE, O'Brien SM, Flinn IW, et al. Novel targeted agents and the need to refine clinical end points in chronic lymphocytic leukemia. J Clin Oncol 2012;30 (23):2820-2.

26297 Yost KJ, Eton DT. Combining distribution- and anchor-based approaches to determine minimally important differences: the FACIT experience. Evaluation & the health professions 2005;28 (2):172-91.

28010 Shaw JW, Johnson JA, Coons SJ. US valuation of the EQ-5D health states: development and testing of the D1 valuation model. Medical care 2005;43 (3):203-20.

33006 Robins JM, Tsiatis AA. Correcting for Non-Compliance in Randomized Trials Using Rank Preserving Structural Failure Time Models. Communication in Statistics-Theory and Methods 1991;20 (8):2609–31.

11. SOFTWARE

SAS® Software Version 9.2. SAS Institute Inc., Cary, NC, USA.

12. SAP REVISION

Revision Date (dd month, yyyy)	Section	Summary of Revision	Reason for Revision

13. APPENDICES

Appendix 1. Table of Contents for Statistical Tables, Figures, and Listings
Appendix 2. Schedule of Study Procedures

Appendix 1. Table of Contents for Statistical Tables, Figures, and Listings

Table Number	Title	Analysis Set
1.1	Subject Study Disposition	FAS
1.2	Subject Study Treatment Disposition	FAS
1.3	Subject Long-Term Follow-Up (LTFU) Disposition	FAS
1.4	Analysis Sets	
1.5	Important Protocol Deviations	FAS
1.6	Subject Distribution by Stratification Factors	FAS
1.7	Subject Demographics and Baseline Characteristics	FAS
1.8	CLL Disease History	FAS
1.9	Prior Therapy	FAS
1.10.1	Study Drug (IDELA) Exposure	FAS
1.10.2	Summary of Dose Modification of IDELA	FAS
2.1.1	Progression-free Survival by IRC Assessment	FAS
2.1.2	Progression-free Survival by IRC Assessment - del17p/TP53 Mutation (Either)	FAS
2.1.3	Progression-free Survival by IRC Assessment - del17p/TP53 Mutation (Neither)	FAS
2.1.4	Progression-free Survival by IRC Assessment - 17p deletion	FAS
2.1.5	Progression-free Survival by IRC Assessment - No 17p deletion	FAS
2.1.6	Disease Progression Criteria	FAS
2.1.7	Progression-free Survival by IRC Assessment (Between-Study Analysis)	Placebo+R (PD)/IDELA
2.2.1	Overall Response Rate (ORR) by IRC Assessment	FAS
2.2.2	Overall Response Rate (ORR) by IRC Assessment - del17p/TP53 Mutation (Either)	FAS
2.2.3	Overall Response Rate (ORR) by IRC Assessment - del17p/TP53 Mutation (Neither)	FAS
2.2.4	Overall Response Rate (ORR) by IRC Assessment - 17p deletion	FAS
2.2.5	Overall Response Rate (ORR) by IRC Assessment - No 17p deletion	FAS
2.2.6	Overall Response Rate (ORR) by IRC Assessment (Between-Study Analysis)	Placebo+R (PD)/IDELA
2.3.1	Lymph Node Response (LNR) Rate by IRC Assessment	FAS
2.3.2	Lymph Node Response (LNR) Rate by IRC Assessment - del17p/TP53 Mutation (Either)	FAS
2.3.3	Lymph Node Response (LNR) Rate by IRC Assessment - del17p/TP53 Mutation (Neither)	FAS

Table Number	Title	Analysis Set
2.3.4	Lymph Node Response (LNR) Rate by IRC Assessment - 17p deletion	FAS
2.3.5	Lymph Node Response (LNR) Rate by IRC Assessment – No 17p deletion	FAS
2.4.1	Overall Survival (OS)	ITT Analysis Set
2.4.2	Overall Survival (OS) - del17p/TP53 Mutation (Either)	ITT Analysis Set
2.4.3	Overall Survival (OS) - del17p/TP53 Mutation (Neither)	ITT Analysis Set
2.4.4	Overall Survival (OS) - 17p deletion	ITT Analysis Set
2.4.5	Overall Survival (OS) - No 17p deletion	ITT Analysis Set
2.4.6	Overall Survival (OS) Sensitivity Analysis	ITT Analysis Set
2.4.7	Overall Survival (OS) Adjusted for Treatment Crossover	ITT Analysis Set
2.5.1	Time to Response (TTR) by IRC Assessment	FAS
2.5.2	Time to Response (TTR) by IRC Assessment - del17p/TP53 Mutation (Either)	FAS
2.5.3	Time to Response (TTR) by IRC Assessment - del17p/TP53 Mutation (Neither)	FAS
2.5.4	Time to Response (TTR) by IRC Assessment - 17p deletion	FAS
2.5.5	Time to Response (TTR) by IRC Assessment - No 17p deletion	FAS
2.6.1	Duration of Response (DOR) by IRC Assessment	FAS
2.6.2	Duration of Response (DOR) by IRC Assessment - del17p/TP53 Mutation (Either)	FAS
2.6.3	Duration of Response (DOR) by IRC Assessment - del17p/TP53 Mutation (Neither)	FAS
2.6.4	Duration of Response (DOR) by IRC Assessment - 17p deletion	FAS
2.6.5	Duration of Response (DOR) by IRC Assessment - No 17p deletion	FAS
2.7	Best Percent Change in SPD - IRC assessment	FAS
2.8	Splenomegaly Response Rate - IRC Assessment	FAS
2.9	Hepatomegaly Response Rate - IRC Assessment	FAS
2.10	ALC Response Rate	FAS
2.11	Platelet Response Rate	FAS
2.12	Hemoglobin Response Rate	FAS
2.13	Neutrophil Response Rate	FAS
2.14	Functional Assessment of Cancer Therapy: Leukemia (FACT-Leu) - Actual and Change from Baseline	FAS
2.15	Karnofsky Performance Status - Observed and Change from Baseline	FAS

Table Number	Title	Analysis Set
2.16.1	Summary of EuroQoL Five Dimension Descriptive System (EQ-5D) by Dimension	FAS
2.16.2	Summary of EuroQol Visual Analogue Score (VAS) - Actual Values and Change from Baseline	FAS
3.1.1	Overall Summary of Adverse Events	FAS
3.1.1.1	Overall Summary of Adverse Events - Male	FAS
3.1.1.2	Overall Summary of Adverse Events - Female	FAS
3.1.1.3	Overall Summary of Adverse Events - Age < 65 (years)	FAS
3.1.1.4	Overall Summary of Adverse Events - Age ≥ 65 (years)	FAS
3.1.1.5	Overall Summary of Adverse Events - Race White	FAS
3.1.1.6	Overall Summary of Adverse Events - Race Non-White	FAS
3.1.2	Treatment-Emergent Adverse Events by MedDRA SOC, HLT and PT	FAS
3.1.2.1	Treatment-Emergent Adverse Events by MedDRA SOC, HLT and PT - Male	FAS
3.1.2.2	Treatment-Emergent Adverse Events by MedDRA SOC, HLT and PT - Female	FAS
3.1.2.3	Treatment-Emergent Adverse Events by MedDRA SOC, HLT and PT - Age < 65 (years)	FAS
3.1.2.4	Treatment-Emergent Adverse Events by MedDRA SOC, HLT and PT - Age ≥ 65 (years)	FAS
3.1.2.5	Treatment-Emergent Adverse Events by MedDRA SOC, HLT and PT - Race White	FAS
3.1.2.6	Treatment-Emergent Adverse Events by MedDRA SOC, HLT and PT - Race Non-White	FAS
3.1.3	Treatment-Emergent Adverse Events by MedDRA SOC, HLT, PT and CTCAE Grade	FAS
3.1.4	Treatment-Emergent Adverse Events Related to IDELA by MedDRA SOC, HLT, PT and CTCAE Grade	FAS
3.1.5	Grade ≥ 3 Treatment-Emergent Adverse Events by MedDRA SOC, HLT and PT	FAS
3.1.6	Grade ≥ 3 Treatment-Emergent Adverse Events Related to IDELA by MedDRA SOC, HLT and PT	FAS
3.1.7	Serious Treatment-Emergent Adverse Events by MedDRA SOC, HLT and PT	FAS
3.1.7.1	Serious Treatment-Emergent Adverse Events by MedDRA SOC, HLT and PT - Male	FAS
3.1.7.2	Serious Treatment-Emergent Adverse Events by MedDRA SOC, HLT and PT - Female	FAS

Table Number	Title	Analysis Set
3.1.7.3	Serious Treatment-Emergent Adverse Events by MedDRA SOC, HLT and PT - Age < 65 (years)	FAS
3.1.7.4	Serious Treatment-Emergent Adverse Events by MedDRA SOC, HLT and PT - Age ≥ 65 (years)	FAS
3.1.7.5	Serious Treatment-Emergent Adverse Events by MedDRA SOC, HLT and PT - Race White	FAS
3.1.7.6	Serious Treatment-Emergent Adverse Events by MedDRA SOC, HLT and PT - Race Non-White	FAS
3.1.8	Serious Treatment-Emergent Adverse Events Related to IDELA by MedDRA SOC, HLT and PT	FAS
3.1.9	Treatment-Emergent Adverse Events Leading to Modification of IDELA by MedDRA SOC, HLT, PT and CTCAE Grade	FAS
3.1.10	Treatment-Emergent Adverse Events Leading to IDELA Reduction by MedDRA SOC, HLT, PT and CTCAE Grade	FAS
3.1.11	Treatment-Emergent Adverse Events Leading to IDELA Interruption by MedDRA SOC, HLT, PT and CTCAE Grade	FAS
3.1.12	Treatment-Emergent Adverse Events Leading to IDELA Discontinuation by MedDRA SOC, HLT and PT	FAS
3.1.13	Treatment-Emergent Adverse Events Leading to Death by MedDRA SOC, HLT and PT	FAS
3.1.14	Treatment-Emergent Adverse Events by MedDRA PT and CTCAE Grade	FAS
3.1.14.1	Treatment-Emergent Adverse Events by MedDRA PT and CTCAE Grade - Male	FAS
3.1.14.2	Treatment-Emergent Adverse Events by MedDRA PT and CTCAE Grade - Female	FAS
3.1.14.3	Treatment-Emergent Adverse Events by MedDRA PT and CTCAE Grade - Age < 65 (years)	FAS
3.1.14.4	Treatment-Emergent Adverse Events by MedDRA PT and CTCAE Grade - Age ≥ 65 (years)	FAS
3.1.14.5	Treatment-Emergent Adverse Events by MedDRA PT and CTCAE Grade - Race White	FAS
3.1.14.6	Treatment-Emergent Adverse Events by MedDRA PT and CTCAE Grade - Race Non-White	FAS
3.1.15	All Grades and Grade ≥ 3 Treatment-Emergent Adverse Events by MedDRA PT	FAS
3.1.16	All Grades and Grade ≥ 3 Treatment-Emergent Adverse Events Related to IDELA by MedDRA PT	FAS
3.1.17	Serious Treatment-Emergent Adverse Events by MedDRA PT	FAS

Table Number	Title	Analysis Set
3.1.18	Treatment-Emergent Adverse Events Leading to Modification of IDELA by MedDRA PT and CTCAE grade	FAS
3.1.19	Treatment-Emergent Adverse Events Leading to Reduction of IDELA by MedDRA PT and CTCAE grade	FAS
3.1.20	Treatment-Emergent Adverse Events Leading to Interruption of IDELA by MedDRA PT and CTCAE grade	FAS
3.1.21	Treatment-Emergent Adverse Events Leading to IDELA Discontinuation by MedDRA PT	FAS
3.1.22	Treatment-Emergent Adverse Events Leading to Death by MedDRA PT	FAS
3.1.23	Exposure-Adjusted Incidence Rate of Treatment-Emergent Adverse Events	FAS
3.1.24.1	Treatment-Emergent Adverse Events of Interest by MedDRA PT and CTCAE Grade	FAS
3.1.24.2	Treatment-Emergent Adverse Events of Interest Leading to Modification of IDELA/Placebo by MedDRA PT and CTCAE Grade	FAS
3.1.24.3	Treatment-Emergent Adverse Events of Interest Leading to Reduction of IDELA/Placebo by MedDRA PT and CTCAE Grade	FAS
3.1.24.4	Treatment-Emergent Adverse Events of Interest Leading to Interruption of IDELA/Placebo by MedDRA PT and CTCAE Grade	FAS
3.1.24.5	Treatment-Emergent Adverse Events of Interest Leading to IDELA/Placebo Discontinuation by MedDRA PT	FAS
3.1.24.6	Incidence of Treatment-Emergent Adverse Events of Interest by 12-weeks Intevals	FAS
3.1.24.7	Prevalence of Treatment-Emergent Adverse Events of Interest by 12-weeks Intevals	FAS
3.1.24.8	Time to First Onset and Resolution of Treatment-Emergent Adverse Events of Interest	FAS
3.1.24.9	Exposure-Adjusted Incidence Rate of Treatment-Emergent Adverse Events of Interest	FAS
3.1.25	Summary of Malignant Transformation and Second Malignancies	FAS
3.1.26	Summary of Deaths	FAS
3.2.1	Hematology: Summary of Actual Values and Change from Baseline	FAS
3.2.2	Hematology: Summary of Treatment-Emergent Laboratory Abnormalities	FAS
3.2.3	Hematology: Shift from Baseline to worst CTCAE Severity Grade	FAS
3.2.4	Hematology: Exposure-adjusted Incidence Rate of Treatment-Emergent Lab Abnormalities	FAS

Table Number	Title	Analysis Set
3.3.1	Serum Chemistry: Summary of Actual Values and Change from Baseline	FAS
3.3.2	Serum Chemistry: Summary of Treatment-Emergent Laboratory Abnormalities	FAS
3.3.3	Serum Chemistry: Shift from Baseline to worst CTCAE Severity Grade	FAS
3.3.4	Serum Chemistry: Exposure-adjusted Incidence Rate of Treatment-Emergent Lab Abnormalities	FAS
3.4	Summary of Liver-related Laboratory Abnormalities	FAS
3.5	Urinalysis: Summary of Actual Values at Baseline	FAS
3.6.1	Summary of Transaminase Elevations	FAS
3.6.2	Time to First Onset and Resolution of Treatment-Emergent Transaminase Elevation	FAS
3.6.3	Immunoglobulin: Summary of Actual Values and Change from Baseline	FAS
3.7	Concomitant Medications	FAS
4.1	Idelalisib Plasma Pharmacokinetic Concentration (ng/mL)	PK Analysis Set
4.2	Idelalisib Metabolite GS-563117 Plasma Pharmacokinetic Concentration (ng/mL)	PK Analysis Set

Listing Number	Title	Analysis Set
1.1	Screen Failures	
1.2.1	Subject Study Disposition	FAS
1.2.2	Subject Study Treatment Disposition	FAS
1.3	Subjects Excluded From Any Analysis Set	FAS
1.4	Important Protocol Deviations	FAS
1.5	Medical History	FAS
1.6.1	IDELA Interruption and Modification	FAS
1.6.2	IDELA Accountability	FAS
1.6.3	IDELA Administration	FAS
1.6.4	IDELA Assignment by IWRS	FAS
2.1.1	Tumor Assessment: Index Lesions - IRC Assessment	FAS
2.1.2	Tumor Assessment: Non-index Lesions - IRC Assessment	FAS
2.1.3	Spleen and Liver Assessment - IRC Assessment	FAS
2.1.4	Tumor Response Assessment - IRC Assessment	FAS
2.1.5	Tumor Assessment: Index Lesions - IRC Assessment (Between-Study Analysis)	Placebo+R (PD)/IDELA
2.1.6	Tumor Assessment: Non-index Lesions - IRC Assessment (Between-Study Analysis)	Placebo+R (PD)/IDELA
2.1.7	Spleen and Liver Assessment - IRC Assessment (Between-Study Analysis)	Placebo+R (PD)/IDELA
2.1.8	Tumor Response Assessment - IRC Assessment (Between-Study Analysis)	Placebo+R (PD)/IDELA
2.2.1	CLL Assessment by Physical Examination - Investigator Assessment	FAS
2.2.2	CLL Assessment by CT/MRI Scan - Investigator Assessment	FAS
2.2.3	Overall CLL Assessment - Investigator Assessment	FAS
2.3.1	Progression-free Survival	FAS
2.3.2	Progression-free Survival (Between-Study Analysis)	Placebo+R (PD)/IDELA
2.4	Overall Survival (Study 116 and 117)	ITT Analysis Set
2.5.1	Time to First Response and Duration of Response	FAS
2.5.2	Time to First Response and Duration of Response (Between-Study Analysis)	Placebo+R (PD)/IDELA
2.6.1	ALC Response	FAS
2.6.2	Platelet Response and Supportive Cares	FAS
2.6.3	Hemoglobin Response and Supportive Cares	FAS
2.6.4	Neutrophil Response and Supportive Cares	FAS

Listing Number	Title	Analysis Set
2.7.1	Other Efficacy Response Assessment	FAS
2.7.2	Other Efficacy Response Assessment (Between-Study Analysis)	Placebo+R (PD)/IDELA
2.8	Bone Marrow Aspirate and Biopsy	FAS
2.9	Organ Biopsy	FAS
2.10.1	Functional Assessment of Cancer Therapy: Leukemia (FACT-Leu) Scores	FAS
2.10.2	Functional Assessment of Cancer Therapy: Leukemia (FACT-Leu) Scores (Between-Study Analysis)	Placebo+R (PD)/IDELA
2.11.1	Karnofsky Performance Status	FAS
2.11.2	Karnofsky Performance Status (Between-Study Analysis)	Placebo+R (PD)/IDELA
2.12.1	EuroQoL Five-Dimension	FAS
2.12.2	EuroQoL Five-Dimension (Between-Study Analysis)	Placebo+R (PD)/IDELA
3.1.1	Laboratory Tests: Hematology	FAS
3.1.2	Laboratory Tests: Chemistry	FAS
3.1.3	Laboratory Tests: Urinalysis	FAS
3.1.4	Laboratory Tests: Immunoglobulin	FAS
3.1.5	Laboratory Tests: Circulating Cells	FAS
3.2	Transaminase Elevations	FAS
3.3	Listing of liver-related Laboratory Abnormalities	FAS
3.4.1	All Adverse Events	FAS
3.4.2	Serious Treatment Emergent Adverse Events	FAS
3.4.3	TEAEs Leading to Interruption or Modification of IDELA	FAS
3.4.4	TEAEs Leading to IDELA Discontinuation	FAS
3.4.5	Adverse Events Leading to Death	FAS
3.4.6	Second Malignancies	FAS
3.4.7	CLL Transformation	FAS
3.4.8	All Deaths	FAS
3.4.9	Non-Treatment Emergent Adverse Events	FAS
3.5	Subject Characteristics and Oxygen Saturation	FAS
3.6	Prior and Concomitant Medications	FAS
3.7	Concomitant Therapy Status	FAS
3.8	Transfusion Log	FAS
3.9	Surgical and Medical Procedures	FAS

Listing Number	Title	Analysis Set
3.10	Hospitalization	FAS
3.11	Pregnancy	FAS
3.12.1	Long-term Follow-up	FAS
3.12.2	Post Study Anti-Cancer Therapy in Long-term Follow-up	FAS
3.13	Comment	FAS

Figure Number	Title	Analysis Set
1.1	Kaplan-Meier Curve of Progression-free Survival by IRC Assessment	FAS
1.1.1	Kaplan-Meier Curve of Progression-free Survival by IRC Assessment - del17p/TP53 Mutation (Either)	FAS
1.1.2	Kaplan-Meier Curve of Progression-free Survival by IRC Assessment - del17p/TP53 Mutation (Neither)	FAS
1.1.3	Kaplan-Meier Curve of Progression-free Survival by IRC Assessment - 17p deletion	FAS
1.1.4	Kaplan-Meier Curve of Progression-free Survival by IRC Assessment - No 17p deletion	FAS
1.2	Kaplan-Meier Curve of Overall Survival	ITT Analysis Set
1.2.1	Kaplan-Meier Curve of Overall Survival - del17p/TP53 Mutation (Either)	ITT Analysis Set
1.2.2	Kaplan-Meier Curve of Overall Survival - del17p/TP53 Mutation (Neither)	ITT Analysis Set
1.2.3	Kaplan-Meier Curve of Overall Survival - 17p Deletion	ITT Analysis Set
1.2.4	Kaplan-Meier Curve of Overall Survival - No 17p Deletion	ITT Analysis Set
1.3	Kaplan-Meier Curve of Duration of Response by IRC Assessment	FAS
1.3.1	Kaplan-Meier Curve of Duration of Response by IRC Assessment - del17p/TP53 Mutation (Either)	FAS
1.3.2	Kaplan-Meier Curve of Duration of Response by IRC Assessment - del17p/TP53 Mutation (Neither)	FAS
1.3.3	Kaplan-Meier Curve of Duration of Response by IRC Assessment - 17p Deletion	FAS
1.3.4	Kaplan-Meier Curve of Duration of Response by IRC Assessment - No 17p Deletion	FAS
1.4	Kaplan-Meier Curve of Time to Response by IRC Assessment	FAS
1.4.1	Kaplan-Meier Curve of Time to Response by IRC Assessment - del17p/TP53 Mutation (Either)	FAS
1.4.2	Kaplan-Meier Curve of Time to Response by IRC Assessment - del17p/TP53 Mutation (Neither)	FAS
1.4.3	Kaplan-Meier Curve of Time to Response by IRC Assessment - 17p Deletion	FAS
1.4.4	Kaplan-Meier Curve of Time to Response by IRC Assessment – No 17p Deletion	FAS
1.5	Waterfall Plot of Best Percent Change from Baseline in SPD by IRC Assessment	FAS
1.5.1	Waterfall Plot of Best Percent Change from Baseline in SPD by IRC Assessment - del17p/TP53 Mutation (Either)	FAS

Figure Number	Title	Analysis Set
1.5.2	Waterfall Plot of Best Percent Change from Baseline in SPD by IRC Assessment - del17p/TP53 Mutation (Neither)	FAS
1.5.3	Waterfall Plot of Best Percent Change from Baseline in SPD by IRC Assessment - 17p deletion	FAS
1.5.4	Waterfall Plot of Best Percent Change from Baseline in SPD by IRC Assessment - No 17p deletion	FAS
2.1.1	Cumulative Distribution Function of Best Change from Baseline: FACT-Leu Physical Well-being	FAS
2.1.2	Cumulative Distribution Function of Best Change from Baseline: FACT-Leu Social/Family Well-being	FAS
2.1.3	Cumulative Distribution Function of Best Change from Baseline: FACT-Leu Emotional Well-being	FAS
2.1.4	Cumulative Distribution Function of Best Change from Baseline: FACT-Leu Functional Well-being	FAS
2.1.5	Cumulative Distribution Function of Best Change from Baseline: FACT-Leu Additional Concerns	FAS
2.2.1	Change from Baseline: FACT-Leu Physical Well-being	FAS
2.2.2	Change from Baseline: FACT-Leu Social/Family Well-being	FAS
2.2.3	Change from Baseline: FACT-Leu Emotional Well-being	FAS
2.2.4	Change from Baseline: FACT-Leu Functional Well-being	FAS
2.2.5	Change from Baseline: FACT-Leu Additional Concerns	FAS
2.2.6	Change from Baseline: FACT-Leu Total Outcome Index	FAS
2.2.7	Change from Baseline: FACT-Leu Total Score	FAS
2.3.1	Change from Baseline: EQ VAS	FAS
2.3.2	Change from Baseline: EQ-5D Utility Index (US)	FAS
3.1.1	Median Over Time: Hemoglobin (g/L)	FAS
3.1.2	Median Over Time: Hemoglobin (g/L) - Subjects with Abnormality at Baseline and at Least One Post-baseline Measurements	FAS
3.1.3	Median Over Time: Platelets (x10^9/L)	FAS
3.1.4	Median Over Time: Platelets (x10^9/L) - Subjects with Abnormality at Baseline and at Least One Post-baseline Measurements	FAS
3.1.5	Median Over Time: Neutrophils (x10^9/L)	FAS
3.1.6	Median Over Time: Neutrophils (x10^9/L) - Subjects with Abnormality at Baseline and at Least One Post-baseline Measurements	FAS
3.1.7	Median Over Time: ALT (U/L)	FAS
3.1.8	Median Over Time: AST (U/L)	FAS

Figure Number	Title	Analysis Set
3.1.9	Median Over Time: Lymphocytes (x10^9/L)	FAS
3.1.10	Median Over Time: Total Bilirubin (umol/L)	FAS
3.1.11	Median Over Time: Triglycerides (mmol/L)	FAS
3.1.12	Median Over Time: Serum Glucose (mmol/L)	FAS
3.2.1	Change From Baseline: Hemoglobin (g/L)	FAS
3.2.2	Change From Baseline: Hemoglobin (g/L) - Subjects with Abnormality at Baseline and at Least One Post-baseline Measurements	FAS
3.2.3	Change From Baseline: Platelets (x10^9/L)	FAS
3.2.4	Change From Baseline: Platelets (x10^9/L) - Subjects with Abnormality at Baseline and at Least One Post-baseline Measurements	FAS
3.2.5	Change From Baseline: Neutrophils (x10^9/L)	FAS
3.2.6	Change From Baseline: Neutrophils (x10^9/L) - Subjects with Abnormality at Baseline and at Least One Post-baseline Measurements	FAS
3.2.7	Change From Baseline: ALT (U/L)	FAS
3.2.8	Change From Baseline: AST (U/L)	FAS
3.2.9	Change From Baseline: Lymphocytes (x10^9/L)	FAS
3.2.10	Change From Baseline: Total Bilirubin (umol/L)	FAS
3.2.11	Change From Baseline: Triglycerides (mmol/L)	FAS
3.2.12	Change From Baseline: Serum Glucose (mmol/L)	FAS
4.1.1	Kaplan-Meier Curve of Time to Onset of First Episode of Grade 3 and Above Transaminase Elevation	FAS
4.1.2	Kaplan-Meier Curve of Time to Resolution of First Episode of Grade 3 and Above Transaminase Elevation	FAS

Appendix 2. Schedule of Study Procedures

Period	Screen	Treatment															Follow-up	
Visit	**1**	**2**	**3[a]**	**4**	**5[a]**	**6**	**7[a]**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16+**			
Week	**-4**	**0**	**2**	**4**	**6**	**8**	**10**	**12**	**16**	**20**	**24**	**30**	**36**	**42**	**48**			**30 days**	**Long-term**
Study Day	**Within -28 Days**	**1**	**15**	**29**	**43**	**57**	**71**	**85**	**113**	**141**	**169**	**211**	**253**	**295**	**337**	**Q12 Weeks**	**End of Study**	**Within +30 days**	**To +5 years**
Visit Window			**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±7**			
Informed consent	X																		
CIRS assessment	X																		
β-HCG (women of childbearing potential)	X	X		X		X		X	X	X	X	X	X	X	X	X	X		
CLL peripheral blood evaluation	X																X		
CLL serology	X																X		
IWRS	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X		
Genotyping and expression analysis	X																X		
HRQL/ healthy utility – FACT-Leu/EQ-5D		X	X	X	X	X		X	X	X	X	X	X	X	X	X	X		
Adverse events		X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	
Concomitant medications	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	

Period	Screen	Treatment																Follow-up	
Visit	**1**	**2**	**3[a]**	**4**	**5[a]**	**6**	**7[a]**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16+**			
Week	**-4**	**0**	**2**	**4**	**6**	**8**	**10**	**12**	**16**	**20**	**24**	**30**	**36**	**42**	**48**			**30 days**	**Long-term**
Study Day	**Within -28 Days**	**1**	**15**	**29**	**43**	**57**	**71**	**85**	**113**	**141**	**169**	**211**	**253**	**295**	**337**	**Q12 Weeks**	**End of Study**	**Within +30 days**	**To +5 years**
Visit Window			**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±7**			
Performance status	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X		
Physical exam (includes nodes, liver, spleen)	X	X		X		X		X	X	X	X	X	X	X	X	X	X		
Oxygen saturation (by pulse oximetry)	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X		
Hematology	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Serum chemistry	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Circulating cells	X		X	X		X		X	X	X	X	X	X	X	X	X	X		
Biomarkers	X		X	X		X		X	X	X	X	X	X	X	X	X	X		
Serum Igs	X		X	X		X		X	X	X	X	X	X	X	X	X	X		
Study drug administration in clinic		X[b]	X	X		X		X	X	X	X								
Idelalisib pharmacokinetics[b]		X	X	X		X		X	X	X	X								
Study drug dispensing/ accounting[b]		X		X		X		X	X	X	X		X		X	X	X		

Period	Screen	Treatment															Follow-up	
Visit	**1**	**2**	**3[a]**	**4**	**5[a]**	**6**	**7[a]**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16+**			
Week	**-4**	**0**	**2**	**4**	**6**	**8**	**10**	**12**	**16**	**20**	**24**	**30**	**36**	**42**	**48**			**30 days**	**Long-term**
Study Day	**Within -28 Days**	**1**	**15**	**29**	**43**	**57**	**71**	**85**	**113**	**141**	**169**	**211**	**253**	**295**	**337**	**Q12 Weeks**	**End of Study**	**Within +30 days**	**To +5 years**
Visit Window			**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±7**			
Radiology assessment (CT/MRI)[d]	X					X			X		X		X		X	X	X		
Bone marrow biopsy/aspirate[c]	X					X			X		X		X		X	X	X		
Post-treatment CLL therapy																			X
Long-term follow-up																			X

a Following unblinding of the study, visits 3, 5, and 7 will not be applicable for subjects who were randomized to idelalisib on Study GS-US-312-0116

b Subjects who were randomized to placebo on Study GS-US-312-0116 and enroll following unblinding, may have idelalisib treatment (and associated PK testing) delayed at the Investigator's discretion until the time of disease progression or until the investigator determines the subject may benefit by the initiation of idelalisib treatment

c At screening, to be performed at investigator discretion to determine extent of CLL involvement and bone marrow cellularity. Post-screening, to be performed to confirm CR or PD; if the subject does not otherwise meet criteria for CR or if the nature of PD does not require bone marrow confirmations, it is not necessary to obtain a follow-up bone marrow biopsy/aspirate

d Following unblinding of the study, the imaging schedule will follow standard of care for subjects who were randomized to idelalisib on Study GS-US-312-0116 and subjects who were randomized to placebo on Study GS-US-312-0116 and enroll on Study GS-US-312-0117 will follow local standard of care for follow-up imaging until initiation of idelalisib, at which time the per-protocol schedule will be followed

Abbreviations: β-HCG = beta human chorionic gonadotropin, CIRS = chronic illness rating scale, CLL = chronic lymphocytic leukemia, CR = complete response, CT = computed tomography, EQ-5D = EuroQoL Five-Dimension, FACT-Leu = Functional Assessment of Cancer Therapy- Leukemia, HRQL = health-related quality of life, Ig = immunoglobulin, IWRS = interactive web response system, MRI = magnetic resonance imaging.