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*
Name of Test Drug:	Idelalisib (IDELA; GS-1101)
Study Number:	GS-US-312-0117
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LIST OF ABBREVIATIONS

AE	adverse event
ALC	absolute lymphocyte count
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ANC	absolute neutrophil count
AST	aspartate aminotransferase
ATC	Anatomical-Therapeutic-Chemical classification
BID	twice per day
BMI	body mass index
BOR	best overall response
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
CTCAE	Common Terminology Criteria for Adverse Events
DMC	data monitoring committee
DOR	duration of response
DSPH	Drug Safety and Public Health
eCRF	electronic case report form
ECG	electrocardiogram
EDC	electronic data capture
EOT	end of treatment
EQ-5D	EuroQoL Five-Dimension utility measure
EWB	emotional well-being
FACT-Leu	Functional Assessment of Cancer Therapy: Leukemia
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
LD	longest diameter
LLT	low level term

LIST OF ABBREVIATIONS (CONTINUED)

LNR	lymph node response
LPD	longest perpendicular diameter
LVD	longest vertical dimension
LymS	lymphoma subscale
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
PI3K	phosphatidylinositol 3-kinase
PI3Kδ	phosphatidylinositol 3-kinase p110δ isoform
PFS	progression-free survival
PPD	product of the perpendicular diameters
PR	partial response
PT	preferred term
PWB	physical well-being
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
TOI	trial outcome index
TTR	time to response
WHODRUG	World Health Organization Drug Dictionary

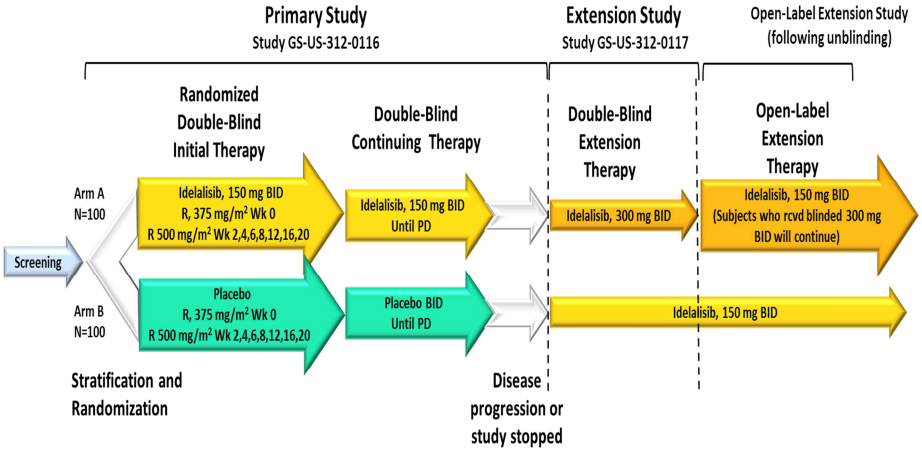
1. INTRODUCTION

This document details the planned analysis for the blinded 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 for previously treated chronic lymphocytic leukemia (CLL) patients. 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. In the event GS-US-312-0116 is stopped early due to overwhelming efficacy following an interim analysis or at the final analysis, subjects who are on Study GS-US-312-0116 at that time may transition to GS-US-312-0117. Additionally, GS-US-312-0117 will become an open-label study offering idelalisib 150mg BID to GS-US-312-0116 subjects who were randomized to placebo, and subjects randomized to idelalisib will continue idelalisib at 150mg 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)

	Open-Label Extension Portion (following unblinding) • 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) 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. 5) 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.

Schedule of Assessments

The schedule of assessments is located in Appendix 2 of this 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	Study will be conducted at 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 ~160 subjects (up to ~80 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, ~160 subjects are expected to be enrolled into Study GS-US-312-0117.
Actual Enrollment and Impact on Power	Not applicable at this point in the study.

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). Thus, interim safety reviews will be performed by the DMC 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 blinded analysis 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.

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 receive ≥1 dose of idelalisib. This analysis set will be used for both the efficacy and safety analyses.

3.1.2. Pharmacokinetic/Pharmacodynamic Analysis Sets

The pharmacokinetic/pharmacodynamic (PK/PD) analysis sets include data from subjects in the ITT analysis set 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 idelalisib plasma concentrations.

3.2. Strata and Covariates

Not applicable

3.3. Examination of Subject Subsets

Not applicable

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 will be presented for subjects in the ITT analysis set 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 ITT 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.

- Tables and figures will be displayed by visit (as appropriate) for each treatment group and total (as appropriate).

- 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.

- Unscheduled visits will only be included in listings and the best or worst post-baseline summary. Unscheduled visits will not be included in the by-visit summary tables, unless otherwise 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 Efficacy 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 generally focus on evaluation of outcomes within each treatment arm; formal analyses comparing outcomes in Arm A to those in Arm B are not planned.

3.5.2. 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

For parameters that will be summarized by visit, 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. There will be no additional analysis windowing done based on the assessment date. Unscheduled visit prior to the first dosing will be included for the calculation of baseline values. Unscheduled scans will be used for determination of the time-to-event and tumor response efficacy endpoints.

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 treated subjects will be generated to describe site, subject number, first treatment date, actual treatment arm, exposure of idelalisib, the reason for discontinuing study treatment, and the reason for discontinuing study. A by-subject listing for subjects who were screened but not treated will be listed separately.

4.2. Disposition of Subjects

A summary of subject disposition will be provided by treatment group. This summary will present number of subjects:

- treated with study drug
- ongoing treatment with study drug
- discontinued the study drug (with summary of reason for not completing)
- ongoing on study
- completed the study (summary of reason for study completion)
- discontinued the study (with summary of reasons for not completing)
- discontinued the long-term follow-up (with summary of reasons for not completing)

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

4.3. Extent of Exposure

4.3.1. Duration of Exposure to Study Drugs

Duration of exposure to idelalisib will be defined as (min(last idelalisib dosing date [ie, captured on study drug completion CRF page], data cutoff date) – first idelalisib dosing date in Study GS-US-312-0117 + 1), regardless of temporary interruptions in study drug administration, and will be expressed in months. Duration of exposure to idelalisib will be summarized for the ITT analysis set using descriptive statistics and as the number and percentage of subjects exposed for at least 1 day, 2, 4, 6, and 12 months, and every 6 months thereafter.

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

4.3.2. Adherence with idelalisib

Adherence (%) with idelalisib will be calculated as:

Adherence (%) = {sum of pills dispensed minus pills returned} divided by {sum over all dosing period of (total daily pills x dosing duration)}, taking into account investigator-prescribed interruptions.

Descriptive statistics for adherence along with the number and percentage of subjects belonging to adherence categories (eg, < 75% or ≥ 75%) will be provided by treatment group for the ITT analysis set. No inferential statistics will be provided.

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) based on the ITT analysis set. A listing will be provided for all 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 ITT analysis set. 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 first dose in Study GS-US-312-0117.

Age (years) = (date of first dose – 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 for the above demographic data.

5.2. Medical History

Total cumulative illness rating scale (CIRS) scores assessed in IWRS and CIRS score by organ systems will be summarized using descriptive statistics and presented by treatment group based on the ITT analysis set. In addition, the number (%) of subjects with CIRS > 6 and ≤ 6 will be summarized.

A by-subject listing of 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 {12154}, as specifically modified for this study to reflect current recommendations which consider the mechanism of action of idelalisib and similar drugs {22541}. The findings of the IRC will be considered primary for analyses of tumor control endpoints.

Unless otherwise specified, time-to-event analyses will be performed with reference to the date of first treatment on this study (GS-US-312-0117). Similarly, evaluations of on-therapy changes will reference the baseline values obtained prior to treatment in this extension study.

6.1. Efficacy Endpoints

6.1.1. Definition of Efficacy Endpoints

- Progression-free survival (PFS) – defined as the interval from the start of study drug 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 ≥50% decrease from baseline in the sum of the products of the greatest perpendicular diameters (SPD) of index lesions per IRC assessments

- CR rate – defined as the proportion of subjects who achieve a CR

- Time to response (TTR) – defined as the interval from the start of study drug 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 lesions

- Splenomegaly response rate – defined as the proportion of subjects with a 50% decrease (minimum 2 cm) from baseline in the enlargement of the spleen in its longest vertical dimension (LVD) or to ≤ 12 cm by imaging.

- Hepatomegaly response rate – defined as the proportion of subjects with a 50% decrease (minimum 2 cm) from baseline in the enlargement of the liver in its LVD or to ≤ 18 cm by imaging.

- Absolute lymphocyte count (ALC) response rate – defined as the proportion of subjects with baseline lymphocytosis (ALC ≥ 4 x 10^9/L) who achieve an on-study ALC <4 x 10^9/L or demonstrate a ≥ 50% decrease in ALC from baseline

- Platelet response rate – defined as the proportion of subjects with baseline thrombocytopenia (platelet count <100 x 10^9/L) who achieve an on-study platelet count ≥100 x 10^9/L or demonstrate a ≥ 50% increase in platelet count from baseline without need for exogenous growth factors. Platelet values collected within 4 weeks after the first dosing date 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 ≥ 50% increase in hemoglobin from baseline without red blood cell transfusions or need for exogenous growth factors. Hemoglobin values collected within 4 weeks after the first dosing date will be excluded from the hemoglobin response rate evaluation.

- Neutrophil response rate – defined as the proportion of subjects with baseline neutropenia (absolute neutrophil count [ANC] ≤1.5 x 10^9/L) who achieve an ANC >1.5 x 10^9/L or demonstrate a≥ 50% increase in ANC from baseline without need for exogenous growth factors. ANC values collected within 4 weeks after the first dosing date, 2 weeks after receiving G-CSF or other growth factors, and 4 weeks after receiving Neulasta will be excluded from the neutrophil response rate evaluation.

- OS – defined as the interval from the date of first study drug in Study GS-US-312-0117 to death from any cause during the study

- Change from baseline in HRQL domain and symptom scores based on FACT-Leu

- Changes from baseline in Karnofsky performance status

- Change from baseline in overall health and 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 ITT analysis set using Kaplan-Meier methods by treatment group. 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. 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 die after study discontinuation, or

- who start new anti-tumor therapy prior to documented disease progression, or

- who have ≥ 2 consecutive missing tumor assessments before disease progression or death.

Subjects without adequate baseline tumor response evaluation will be censored on the first dosing date.

6.1.2.2. Overall response rate

Responses will be categorized as CR, PR, stable disease (SD), or progressive disease (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 treatment.

The proportion of subjects who achieve a CR or PR will be presented with 95% CI by treatment group. 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.

The ORR analysis will be evaluated using the IRC assessments based on the ITT analysis set.

6.1.2.3. Lymph node response rate

LNR rate will be presented with 95% CI by treatment group. 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 6.1.2.1 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 ITT 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 group.

For the DOR analysis, data will be censored on the date of the last tumor assessment (including assessments with a NE outcome) for subjects:

- who do not have disease progression or die after study discontinuation, or
- who start new anti-tumor therapy prior to documented disease progression, or
- who 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 ITT 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 prior to the start of study treatment. 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.

6.1.2.8. Overall Survival

OS will be described in the ITT analysis set using Kaplan-Meier methods by treatment group. 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.

6.1.2.9. Health-Related Quality of Life

The Functional Assessment of Cancer Therapy: Leukemia (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 (Lymphoma Subscale, LymS, 15 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:

- Physical well-being: all individual items
- Social/family well-being: none
- Emotional well-being: 5 individual items (except for the second item, "I am satisfied with how I am coping with my illness")
- Functional well-being: none
- Additional concerns: all individual items

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] x [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: 0-116) = PWB + FWB + LymS
- FACT_Leu Total Score (score range: 0-168) = PWB + SWB + EWB + FWB + LymS

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.

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 and a decline of at least 3 points will define symptom worsening. The cumulative distribution function (CDF) of best (or worst) change from baseline will be provided. For the MID improvement comparison, subjects with baseline score >57 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 PRO assessment time.

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

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 and worst changes from baseline during the study will also be summarized. The best change from baseline is defined as the highest change score at post baseline. The worst change from baseline is defined as the lowest change score at post baseline.

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. Data collected from the EQ-5D will not be reconciled with adverse event or laboratory data or with FACT-Leu findings.

6.1.3. Between-Study Comparisons

To evaluate the benefits of single-agent idelalisib relative to single-agent rituximab in the same subjects, between-study analyses of Study GS-US-312-0116 and GS-US-312-0117 will be performed among subjects who participate in Arm B of both studies.

Baseline characteristics (eg, age, CIRS, etc.) and selected efficacy endpoints (eg, PFS, ORR, OS, TTR, etc.) will be summarized for Study GS-US-312-0117 relative to those in Study GS-US-312-0116.

6.2. Changes From Protocol-Specified Efficacy Analyses

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

The following analyses will be removed as they are deemed to be less informative:

Changes from baseline in HRQL parameters or in performance status in the 2 treatment groups will be described by treatment group considering both: 1) all subjects that have baseline and at least one post-baseline assessment for HRQL or performance status with the worst score assigned to those subjects who have progressed or died at the timepoint, and 2) all subjects that have baseline and at least one post-baseline assessment for HRQL or performance status who have not progressed or died at the timepoint.

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 arms and will be listed in detail based on the ITT analysis set.

7.1.1. Adverse Event Dictionary

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

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 adverse event to idelalisib 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 study drug will be considered related to study drug. 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 treatment and up to 30 days after the permanent discontinuation of the study treatment.

- The continuing AEs diagnosed prior to the start of treatment and worsening in severity grade, or non-serious AEs at baseline which become serious, or AEs resulting in treatment 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 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 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 arms 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 or modification due to an AE, (9) death due to AEs (10) on-study deaths and (11) all deaths including long-term follow up.

Summaries (number and percentage of subjects) of TEAEs (by SOC, HLT and PT) will be provided by treatment arms using the ITT analysis set as follows:

- AEs
- AEs by CTCAE Grade
- Grade ≥3 AE
- IDELA-related AEs
- SAEs
- IDELA-related SAEs
- AEs leading to IDELA reduction
- AEs leading to permanent discontinuation from IDELA
- AEs leading to death

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 treatment Arm A (high-dose Idelalisib). For summaries by severity grade, the most severe event will be selected. In addition to the presentation by SOC and HLT, each 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 AEs (with a variable indicating whether the event is treatment-emergent)
- SAEs (with a variable indicating whether the event is treatment-emergent)
- AEs leading to discontinuation of study drug
- Deaths

Relative day from first dose date will be provided for each AE in the listings. If the AE onset date is after the first dose date, the relative day will be calculated as (AE onset date - first dose date + 1), however, if the AE onset date is prior to the first dose date, the relative day will be calculated as (first dose date – AE onset date).

7.2. Laboratory Evaluations

All laboratory data will be listed. 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 ITT analysis set.

7.2.1. Summaries of Numeric Laboratory Results

Descriptive statistics (sample size, mean, standard deviation, 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 all lab parameters will be plotted over time by treatment arms.

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 at baseline and each scheduled post-dose assessment by treatment arms.

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 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.

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 in the period from the first dose of study drug 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 arms. 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 ITT analysis set. A listing of treatment-emergent Grade ≥ 3 laboratory abnormalities will be provided.

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 ITT analysis set. Number and percentage of subjects will be summarized by treatment arms 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 due to Grade 3 or 4 ALT/AST elevation
- 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 start of study treatment 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 – date of first dose of study drug +1). 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 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. In addition, the same analysis will be performed for subjects who are re-challenged due to Grade 3 or 4 treatment-emergent ALT/AST elevations.

7.3. Concomitant Medications

Concomitant medications will be coded by means of the World Health Organization Drug Dictionary (WHODRUG) dictionary, Q1 2011 into Anatomical-Therapeutic-Chemical classification (ATC) codes.

Concomitant medications are defined as any medications meeting the following criteria:

- Starting on or after the first dose of study drug up to 30 days post the last dose
- Starting before and continuing after the first dose of study drug up to 30 days post the last dose

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

Prior medications are defined as any medications stopped before the first dose of study drug. Summaries of the number and percentage of subjects who used prior and concomitant medications will be presented in tabular form by preferred drug name based on the ITT analysis set. The summary tables will be sorted by descending frequency based on treatment Arm A (high-dose idelalisib). Subjects will only be counted once for multiple drug use (by preferred drug name) per subject.

Concomitant medications started on/-after the start of study medication or ongoing medications will be flagged on the prior and concomitant medication data listing.

The summaries and listings will be based on the ITT analysis set.

7.4. Body Weight and Vital Signs

Body weight at each visit, and change from baseline in body weight will be summarized for the ITT analysis set using descriptive statistics by treatment group for each post baseline analysis window. In the case of multiple values in an analysis window, data will be selected for analysis as described in Section 3.6.2 Selection of Data in the Event of Multiple Records in a Window. No inferential statistics will be generated.

7.5. Oxygen Saturation Levels

Oxygen percent saturation and its change from baseline will be summarized for the ITT analysis set using descriptive statistics by treatment group and by visit. The number and percentage of subjects who achieve the lowest value below 92% and ≥5% decrease from baseline in oxygen percent saturation will be summarized by treatment group. Subjects will be characterized only once for each of these categorizations, based on their lowest value observed.

7.6. Other Safety Measures

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

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

7.7. Changes From Protocol-Specified Safety Analyses

Not applicable

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. Idelalisib 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 treatment and visit using descriptive statistics.

9. PHARMACDYNAMIC ANALYSES

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

10. REFERENCES

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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.

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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

Table Number	Title	Analysis Set
	Subject Disposition	ITT
	Analysis Sets	ITT
	Important Protocol Deviations	ITT
	Subject Demographics and Baseline Characteristics	ITT
	Subject Demographics and Baseline Characteristics (Between-Study Analysis)	ITT
	CIRS Scores	ITT
	CIRS Scores (Between-Study Analysis)	ITT
	Study Drug (IDELA/Placebo) Exposure	ITT
	Progression-free Survival - IRC Assessment	ITT
	Progression-free Survival - IRC Assessment (Between-Study Analysis)	ITT
	Overall Response Rate (ORR) - IRC assessment	ITT
	Overall Response Rate (ORR) - IRC assessment (Between-Study Analysis)	ITT
	Lymph Node Response (LNR) Rate - IRC assessment	ITT
	Lymph Node Response (LNR) Rate - IRC assessment (Between-Study Analysis)	ITT
	Complete Response (CR) Rate - IRC assessment	ITT
	Overall Survival (OS)	ITT
	Time to Response (TTR) - IRC Assessment	ITT
	Time to Response (TTR) - IRC Assessment (Between-Study Analysis)	ITT
	Duration of Response (DOR) - IRC Assessment	ITT
	Duration of Response (DOR) - IRC Assessment (Between-Study Analysis)	ITT
	Best Percent Change in SPD - IRC assessment	ITT
	Best Percent Change in SPD - IRC assessment (Between-Study Analysis)	ITT
	Splenomegaly Response Rate - IRC assessment	ITT
	Splenomegaly Response Rate - IRC assessment (Between-Study Analysis)	ITT
	Hepatomegaly Response Rate - IRC Assessments	ITT
	Hepatomegaly Response Rate - IRC Assessments (Between-Study Analysis)	ITT
	ALC Response Rate	ITT
	ALC Response Rate (Between-Study Analysis)	ITT
	Platelet Response Rate	ITT

Table Number	Title	Analysis Set
	Platelet Response Rate (Between-Study Analysis)	ITT
	Hemoglobin Response Rate	ITT
	Hemoglobin Response Rate (Between-Study Analysis)	ITT
	Neutrophil Response Rate	ITT
	Neutrophil Response Rate (Between-Study Analysis)	ITT
	CLL Assessment by CT/MRI - Investigator assessment	ITT
	Health Related Quality of Life (HRQL) – Summary of Change in FACT-Leu Subscale Scores	ITT
	Health Related Quality of Life (HRQL) - Summary of Symptom Improvement/Worsening in FACT-Leu Subscale Scores	ITT
	Change in Karnofsky Performance Status	ITT
	Change in EuroQoL Five Dimension Utility Measure	ITT
	Overall Summary of Adverse Events	ITT
	TEAEs by MedDRA SOC, HLT and PT	ITT
	TEAEs by MedDRA SOC, HLT, PT and CTCAE Grade	ITT
	TEAEs Related to IDELA/Placebo by MedDRA SOC, HLT and PT	ITT
	TEAEs Related to Rituximab by MedDRA SOC, HLT and PT	ITT
	Grade ≥ 3 TEAEs by MedDRA SOC, HLT and PT	ITT
	Grade ≥ 3 TEAEs Related to IDELA by MedDRA SOC, HLT and PT	ITT
	Serious TEAEs by MedDRA SOC, HLT and PT	ITT
	Serious TEAEs Related to IDELA by MedDRA SOC, HLT and PT	ITT
	TEAEs Leading to Reduction of IDELA by MedDRA SOC, HLT, PT and CTCAE grade	ITT
	TEAEs Leading to IDELA Discontinuation by MedDRA SOC, HLT and PT	ITT
	TEAEs Leading to Death by MedDRA SOC, HLT and PT term	ITT
	TEAEs by MedDRA PT and CTCAE Grade	ITT
	All Grade and Grade ≥ 3 TEAEs by MedDRA PT	ITT
	All Grade and Grade ≥ 3 TEAEs Related to IDELA by MedDRA PT	ITT
	Serious TEAEs by MedDRA PT	ITT
	TEAEs Leading to Reduction of IDELA by MedDRA PT and CTCAE grade	ITT
	TEAEs Leading to IDELA Discontinuation by MedDRA PT	ITT
	TEAEs Leading to Death by MedDRA PT	ITT

Table Number	Title	Analysis Set
	Death On Study	ITT
	Deaths On Study and Long-term Follow up	ITT
	Prior Medications	ITT
	Concomitant Medications	ITT
	Hematology: Summary of Actual Values and Change from Baseline	ITT
	Hematology: Treatment-Emergent Laboratory Abnormalities	ITT
	Hematology: Shift from Baseline to worst CTCAE Severity Grade	ITT
	Serum Chemistry: Summary of Actual Values and Change from Baseline	ITT
	Serum Chemistry: Treatment-Emergent Laboratory Abnormalities	ITT
	Serum Chemistry: Shift from Baseline to worst CTCAE Severity Grade	ITT
	Summary of Transaminase Elevations	ITT
	Time to Onset and Time to Resolution of Transaminase Elevations	ITT
	Urinalysis: Summary of Actual Values at Baseline	ITT
	Immunoglobulin: Summary of Actual Values and Change from Baseline	ITT
	Oxygen Saturation: Summary of Actual Values and Change from Baseline	ITT
	Decrease of Oxygen Saturation Level	ITT
	Physical Examination	ITT

Listing Number	Title	Analysis Set
	Screen Failures	
	Subject Disposition	ITT
	Analysis Set	ITT
	Major Protocol Deviations	ITT
	Subject Demographics and Baseline Characteristics	ITT
	CIRS Score	ITT
	IDELA Accountability	ITT
	Study Drug Administration	ITT
	IDELA Interruption and Modification	ITT
	Tumor Assessment: Measurable Lesions - IRC Assessment	ITT
	Tumor Assessment: Non-Measurable Lesions - IRC Assessment	ITT
	Tumor Response Assessment - IRC Assessment	ITT
	CLL Assessment by Physical Examination – Investigator Assessment	ITT
	CLL Assessment by CT/MRI scan – Investigator Assessment	ITT
	Tumor Response Assessment - Investigator Assessment	ITT
	Progression Free Survival	ITT
	Overall Survival	ITT
	Duration of Response	ITT
	Time to First Response	ITT
	Overall Tumor Response Assessment	ITT
	Bone Marrow Aspirate and Biopsy	ITT
	Health Related Quality of Life (HRQL) - FACT-Leu Scores	ITT
	Karnofsky Performance Status	ITT
	EuroQoL Five-Dimension	ITT
	Laboratory Tests: Hematology	ITT
	Laboratory Tests: Chemistry	ITT
	Laboratory Tests: Urinalysis	ITT
	Laboratory Tests: Immunoglobulin	ITT
	Treatment-Emergent Laboratory Abnormalities	ITT
	Transaminase Elevations	ITT
	Treatment Emergent Adverse Events	ITT
	Non-Treatment Emergent Adverse Events	ITT

Listing Number	Title	Analysis Set
	Serious Treatment Emergent Adverse Events	ITT
	TEAEs Leading to Interruption or Modification of IDELA	ITT
	TEAEs Leading to IDELA Discontinuation	ITT
	Adverse Events Leading to Death	ITT
	All Deaths	ITT
	Vital Sign and Oxygen Saturation	ITT
	Prior and Concomitant Medications	ITT
	Concomitant Therapy	ITT
	Transfusion Log	ITT
	Hospitalization	ITT
	Pregnancy	ITT
	Long term Follow up Contact	ITT
	Comment	ITT

Figure Number	Title	Analysis Set
	Kaplan-Meier Curve of Progression Free Survival – IRC Assessment	ITT
	Forest Plot of Overall Response Rate (ORR) and 95% Confidence Interval (CI) – IRC Assessment	ITT
	Forest Plot of Lymph Node Response Rate and 95% Confidence Interval (CI) – IRC Assessment	ITT
	Forest Plot of Complete Response (CR) Rate and 95% Confidence Interval (CI) – IRC Assessment	ITT
	Kaplan-Meier Curve of Overall Survival	ITT
	Kaplan-Meier Curve of Duration of Response – IRC Assessment	ITT
	Kaplan-Meier Curve of Time to Response – IRC Assessment	ITT
	Waterfall Plot of Best Percent Change from Baseline in SPD	ITT
	Cummulative Distribution Fuction of Best Change from Baseline: FACT-Leu Physical Well-being	ITT
	Cummulative Distribution Fuction of Worst Change from Baseline: FACT-Leu Physical Well-being	ITT
	Cummulative Distribution Fuction of Best Change from Baseline: FACT-Leu Social/Family Well-being	ITT
	Cummulative Distribution Fuction of Worst Change from Baseline: FACT-Leu Social/Family Well-being	ITT
	Cummulative Distribution Fuction of Best Change from Baseline: FACT-Leu Emotional Well-being	ITT
	Cummulative Distribution Fuction of Worst Change from Baseline: FACT-Leu Emotional Well-being	ITT
	Cummulative Distribution Fuction of Best Change from Baseline: FACT-Leu Functional Well-being	ITT
	Cumulative Distribution Function of Worst Change from Baseline: FACT-Leu Functional Well-being	ITT
	Cumulative Distribution Function of Best Change from Baseline: FACT-Leu Additional Concerns	ITT
	Cummulative Distribution Function of Worst Change from Baseline: FACT-Leu Additional Concerns	ITT
	Volcano Plot of Treatment-Emergent Adverse Events	ITT
	Volcano Plot of Treatment-Emergent Laboratory Abnormalities	ITT
	Kaplan-Meier Curve of Time to Onset of First Grade 3 or 4 ALT/AST Elevation	ITT
	Kaplan-Meier Curve of Time to Onset of First Grade 3 or 4 ALT/AST Elevation – Rechallenged Subjects Only	ITT

Figure Number	Title	Analysis Set
	Kaplan-Meier Curve of Time to Resolution of First Grade 3 or 4 ALT/AST Elevation	ITT
	Kaplan-Meier Curve of Time to Resolution of First Grade 3 or 4 ALT/AST Elevation – Rechallenged Subjects Only	ITT
	Median and Q1/Q3 Over Time: Albumin (g/L)	ITT
	Median and Q1/Q3 Over Time: Alkaline Phosphatase (U/L)	ITT
	Median and Q1/Q3 Over Time: ALT (U/L)	ITT
	Median and Q1/Q3 Over Time: AST (U/L)	ITT
	Median and Q1/Q3 Over Time: Chloride (mmol/L)	ITT
	Median and Q1/Q3 Over Time: Creatinine (umol/L)	ITT
	Median and Q1/Q3 Over Time: GGT (U/L)	ITT
	Median and Q1/Q3 Over Time: Glucose (mmol/L)	ITT
	Median and Q1/Q3 Over Time: Phosphorus (mmol/L)	ITT
	Median and Q1/Q3 Over Time: Creatinine (umol/L)	ITT
	Median and Q1/Q3 Over Time: Potassium (mmol/L)	ITT
	Median and Q1/Q3 Over Time: Sodium (mmol/L)	ITT
	Median and Q1/Q3 Over Time: Total Bilirubin (umol/L)	ITT
	Median and Q1/Q3 Over Time: Total Protein (g/L)	ITT
	Median and Q1/Q3 Over Time: Triglycerides (mmol/L)	ITT
	Median and Q1/Q3 Over Time: Basophils (K/uL)	ITT
	Median and Q1/Q3 Over Time: Eosinophils (K/uL)	ITT
	Median and Q1/Q3 Over Time: Hematocrit (%)	ITT
	Median and Q1/Q3 Over Time: Hemoglobin (g/L)	ITT
	Median and Q1/Q3 Over Time: Lymphocytes (10^9/L)	ITT
	Median and Q1/Q3 Over Time: Monocytes (10^9/L)	ITT
	Median and Q1/Q3 Over Time: Neutrophils (10^9/L)	ITT
	Median and Q1/Q3 Over Time: Platelets (10^9/L)	ITT
	Median and Q1/Q3 Over Time: RBC (10^12/L)	ITT
	Median and Q1/Q3 Over Time: WBC (10^9/L)	ITT
	Mean and SE Over Time: Albumin (g/L)	ITT
	Mean and SE Over Time: Alkaline Phosphatase (U/L)	ITT
	Mean and SE Over Time: ALT (U/L)	ITT
	Mean and SE Over Time: AST (U/L)	ITT

Figure Number	Title	Analysis Set
	Mean and SE Over Time: Chloride (mmol/L)	ITT
	Mean and SE Over Time: Creatinine (umol/L)	ITT
	Mean and SE Over Time: GGT (U/L)	ITT
	Mean and SE Over Time: Glucose (mmol/L)	ITT
	Mean and SE Over Time: Phosphorus (mmol/L)	ITT
	Mean and SE Over Time: Creatinine (umol/L)	ITT
	Mean and SE Over Time: Potassium (mmol/L)	ITT
	Mean and SE Over Time: Sodium (mmol/L)	ITT
	Mean and SE Over Time: Total Bilirubin (umol/L)	ITT
	Mean and SE Over Time: Total Protein (g/L)	ITT
	Mean and SE Over Time: Triglycerides (mmol/L)	ITT
	Mean and SE Over Time: Basophils (K/uL)	ITT
	Mean and SE Over Time: Eosinophils (K/uL)	ITT
	Mean and SE Over Time: Hematocrit (%)	ITT
	Mean and SE Over Time: Hemoglobin (g/L)	ITT
	Mean and SE Over Time: Lymphocytes (10^9/L)	ITT
	Mean and SE Over Time: Monocytes (10^9/L)	ITT
	Mean and SE Over Time: Neutrophils (10^9/L)	ITT
	Mean and SE Over Time: Platelets (10^9/L)	ITT
	Mean and SE Over Time: RBC (10^12/L)	ITT
	Mean and SE Over Time: WBC (10^9/L)	ITT
	Mean Change From Baseline: Albumin (g/L)	ITT
	Mean Change From Baseline: Alkaline Phosphatase (U/L)	ITT
	Mean Change From Baseline: ALT (U/L)	ITT
	Mean Change From Baseline: AST (U/L)	ITT
	Mean Change From Baseline: Chloride (mmol/L)	ITT
	Mean Change From Baseline: Creatinine (umol/L)	ITT
	Mean Change From Baseline: GGT (U/L)	ITT
	Mean Change From Baseline: Glucose (mmol/L)	ITT
	Mean Change From Baseline: Phosphorus (mmol/L)	ITT
	Mean Change From Baseline: Creatinine (umol/L)	ITT
	Mean Change From Baseline: Potassium (mmol/L)	ITT

Figure Number	Title	Analysis Set
	Mean Change From Baseline: Sodium (mmol/L)	ITT
	Mean Change From Baseline: Total Bilirubin (umol/L)	ITT
	Mean Change From Baseline: Total Protein (g/L)	ITT
	Mean Change From Baseline: Triglycerides (mmol/L)	ITT
	Mean Change From Baseline: Basophils (K/uL)	ITT
	Mean Change From Baseline: Eosinophils (K/uL)	ITT
	Mean Change From Baseline: Hematocrit (%)	ITT
	Mean Change From Baseline: Hemoglobin (g/L)	ITT
	Mean Change From Baseline: Lymphocytes (10^9/L)	ITT
	Mean Change From Baseline: Monocytes (10^9/L)	ITT
	Mean Change From Baseline: Neutrophils (10^9/L)	ITT
	Mean Change From Baseline: Platelets (10^9/L)	ITT
	Mean Change From Baseline: RBC (10^12/L)	ITT
	Mean Change From Baseline: WBC (10^9/L)	ITT

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+**	**End of Study**	**30 days**	**Long-term**
Week	**-4**	**0**	**2**	**4**	**6**	**8**	**10**	**12**	**16**	**20**	**24**	**30**	**36**	**42**	**48**	**Q12 Weeks**			
Study Day	**Within -28 Days**	**1**	**15**	**29**	**43**	**57**	**71**	**85**	**113**	**141**	**169**	**211**	**253**	**295**	**337**			**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	
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		

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+**	**End of Study**	**30 days**	**Long-term**
Week	**-4**	**0**	**2**	**4**	**6**	**8**	**10**	**12**	**16**	**20**	**24**	**30**	**36**	**42**	**48**	**Q12 Weeks**			
Study Day	**Within -28 Days**	**1**	**15**	**29**	**43**	**57**	**71**	**85**	**113**	**141**	**169**	**211**	**253**	**295**	**337**			**Within +30 days**	**To +5 years**
Visit Window			**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±7**			
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		
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.