STATISTICAL ANALYSIS PLAN

Study Title:	A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Efficacy and Safety of Idelalisib (GS-1101) in Combination with Bendamustine and Rituximab for Previously Treated Chronic Lymphocytic Leukemia
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CONFIDENTIAL AND PROPRIETARY INFORMATION

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LIST OF ABBREVIATIONS

AE	adverse event
AEI	adverse event of interest
ALC	absolute lymphocyte count
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ANC	absolute neutrophil count
ATC	Anatomical-Therapeutic-Chemical classification system for drugs
BID	twice per day
CI	confidence interval
CIRS	Cumulative Illness Rating Scale
CLL	chronic lymphocytic leukemia
CR	complete response
CRi	complete response with incomplete marrow recovery
CSR	clinical study report
CT	computerized tomography
CTCAE	common terminology criteria for adverse events
DMC	data monitoring committee
eCRF	electronic case report form
ECG	electrocardiogram
EOT	end of treatment
EQ-5D	EuroQoL five-dimension utility measure
FACT-Leu	Functional Assessment of Cancer Therapy: Leukemia questionnaire
HLGT	high level group term
HLT	high level term
HR	hazard ratio
HRQL	health-related quality of life
Ig	immunoglobulin (including subtypes A, E, G, and M)
IgHV	immunoglobulin heavy chain variable region
IRC	independent review committee
ITT	intent to treat
IWCLL	International Workshop on CLL
IWRS	interactive web response system
JAK	Janus kinase
LD	longest diameter
LLN	lower limit of normal
LLT	low level term
LNR	lymph node response
LPD	longest perpendicular diameter

MedDRA	Medical dictionary for regulatory activities
MST	Medical Search Term
MRI	magnetic resonance imaging
ND	no disease
NE	non evaluable
ORR	overall response rate
OS	overall survival
PD	progressive disease
PI3K	phosphatidylinositol 3-kinase
PI3Kδ	phosphatidylinositol 3-kinase p110δ isoform
PFS	progression-free survival
PR	partial response
PT	preferred term
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
SUSAR	suspected, unexpected, serious adverse reaction
SFWB	social/family well-being
SYk	spleen tyrosine kinase
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
WHODRUG	World Health Organization Drug Dictionary

1. INTRODUCTION

This document details the final analyses for Study GS-US-312-0115, a Phase 3, randomized, double-blind, placebo-controlled study evaluating the efficacy and safety of idelalisib (GS-1101) in combination with bendamustine and rituximab for previously treated chronic lymphocytic leukemia (CLL). Related documents are the study protocol and electronic case report form (eCRF).

1.1. Study Objectives

Primary Study Objectives	• To evaluate the effect of the addition of idelalisib (formerly GS-1101) to bendamustine/rituximab on progression-free survival (PFS) in subjects with previously treated CLL
Secondary Study Objectives	• To evaluate the effect of the addition of idelalisib to bendamustine/rituximab on the onset, magnitude, and duration of tumor control • To assess the effect of the addition of idelalisib to bendamustine/rituximab on measures of subject well-being, including overall survival (OS), health-related quality of life (HRQL), and performance status • To assess the effects of the addition of idelalisib to bendamustine/rituximab on disease associated biomarkers and to evaluate potential mechanisms of resistance to idelalisib • To characterize the effect of bendamustine/rituximab on idelalisib exposure through evaluations of idelalisib plasma concentrations over time • To describe the safety profile observed with the addition of idelalisib to bendamustine/rituximab • To estimate health resource utilization associated with the addition of idelalisib to bendamustine/rituximab

1.2. Study Design

Design Configuration and Subject Population	Study GS-US-312-0115 is a Phase 3, multicenter, 2-arm, randomized, double-blind, placebo-controlled, parallel-group clinical trial. Target Population: Adult subjects with previously treated recurrent CLL who have measurable lymphadenopathy; require therapy for CLL; have received prior therapy containing a purine analog or bendamustine and an anti-CD20 monoclonal antibody; are not refractory to bendamustine; have experienced CLL progression <36 months since the completion of the last prior therapy; and are currently sufficiently fit to receive cytotoxic therapy.
Treatment Groups	• Arm A: idelalisib + bendamustine/rituximab (IDL+B/R) • Arm B: placebo + bendamustine/rituximab (PBO+B/R)
Key Eligibility Criteria	Please refer to Protocol Section 4.2 for subject inclusion and exclusion criteria.
Treatment Duration	Study drug (idelalisib/placebo) 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. Subjects who are tolerating study drug (idelalisib/placebo) will be encouraged to continue study drug even if bendamustine or rituximab must be discontinued due to bendamustine- or rituximab-related toxicities. Rituximab will be administered until the earliest of a maximum of 6 infusions, subject withdrawal from study, definitive progression of CLL, intolerable rituximab-related toxicity, pregnancy, substantial noncompliance with study procedures, or study discontinuation. Bendamustine will be administered until the earliest of a maximum of 12 infusions, subject withdrawal from study, definitive progression of CLL, intolerable bendamustine-related toxicity, pregnancy, substantial noncompliance with study procedures, or study discontinuation. Following a decision to unblind the study based on the interim analysis results and the data monitoring committee (DMC)'s recommendation, treatment assignments will be unblinded. Subjects randomized to Arm A (idelalisib +bendamustine/rituximab) may continue study treatment with idelalisib, whereas subjects randomized to Arm B (placebo + bendamustine/rituximab) should discontinue placebo tablets and continue with study procedures per protocol.

Schedule of Assessments	• The schedule of assessments is located in Appendix 1 of this SAP.
Randomization and Stratification	• 1:1 allocation to Arm A versus Arm B with implementation through an interactive web response system (IWRS) • Fixed-block centralized randomization with allocation of subjects within the 8 strata as defined by the intersection of 3 binary stratification factors: 17p deletion and/or p53 mutation in CLL cells: either vs neither (or indeterminate) Immunoglobulin heavy chain variable region (IgHV) mutation: unmutated (or IgHV3-21) vs mutated (or indeterminate) Disease status: refractory (CLL progression <6 months from completion of prior therapy) vs relapsed (CLL progression ≥6 months from completion of prior therapy)
Site and/or Stratum Enrollment Limits	Approximately 180 centers in North America, South America, Australia Pacific, and Europe
Study Duration	The study will continue until approximately the 260th PFS event occurs. It is expected that the study accrual period is approximately 18 months and the 260th event will occur after a minimum of 24 months of follow-up.

1.3. Sample Size and Power

Planned Sample Size	The planned sample size is 390 subjects (~195 subjects per treatment arm).
Power Statement	Based on data from prior studies, it is reasonable to assume that administration of bendamustine/rituximab to subjects with previously treated CLL in Arm B of this trial will result in a median PFS of ~15 months. An improvement in median PFS from 15 months to 22.5 months due to the addition of idelalisib to bendamustine/rituximab in Arm A of the study would correspond to a benefit ratio of 1.5 (hazard ratio 0.67). It is assumed that PFS times are exponentially distributed in each of the 2 arms. With a hazard ratio equal to 1 under the null hypothesis of no difference between the 2 treatment arms and a hazard ratio of 0.67 under the alternative hypothesis of superiority of the idelalisib-containing combination, 260 events (definitive CLL progressions or deaths) are required to achieve a power of 0.90 based on a stratified log-rank test with a 2-sided significance level of 0.05. Further assuming a planned accrual period of 18 months (with approximately half of the subjects enrolled during the initial 60% of the accrual period, and the remaining half of the subjects enrolled during the last 40% of the accrual period), a minimum follow-up period of 24 months, and an expectation that 15% of subjects will be lost to follow-up (7% during the accrual period and 8% during the follow-up period), ~195 subjects per treatment arm (~390 total) are to be enrolled in order to achieve the expected number of events by the end of the planned minimum 24-month follow-up period. It is expected that there will be approximately 135 deaths at the time of the final analysis. This would provide >95% power to detect a HR of 0.45 for overall survival based on a log-rank test at a 2-sided alpha level of 0.032.
Actual Enrollment and Impact on Power	The study is fully enrolled as originally planned and there is no impact on the power of the planned analyses.

2. TYPE OF PLANNED ANALYSIS

2.1. Interim Analysis

The interim analysis was conducted with the data cut-off date 07 October 2015. IDL+B/R demonstrated superior efficacy over PBO+B/R in the primary endpoint PFS and all key secondary endpoints. Gilead unblinded the study following the DMC's recommendation.

2.2. Final Analysis

The final anlaysis will be conducted when all subjects discontinue from the study. A synoptic clinical study report (CSR) will be developed and there will be no multiplicity control for the primary and secondary efficacy analysis.

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 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 in the analyses of subject characteristics, efficacy endpoints including PFS, overall response rate (ORR), OS, lymph node response (LNR) rate, and complete response (CR) rate, and health outcome variables.

3.2. Safety Analysis Set

A Safety Analysis Set will include data from subjects who receive ≥1 dose of study treatment, with treatment assignments designated according to the actual treatment received.

This analysis set will be used in the analyses of safety variables as well as study treatment administration.

3.2.1. Pharmacokinetic/ Pharmacodynamic Analysis Sets

The Pharmacokinetic/Pharmacodynamic Analysis Set is not applicaple for the final analysis.

3.3. Strata and Covariates

Subjects will be stratified to receive study treatment via IWRS based on the following stratification factors:

- 17p deletion and/or p53 mutation in CLL cells: either vs neither (or indeterminate)
- IgHV mutation: unmutated (or IgHV3-21) vs mutated (or indeterminate)
- Disease status: refractory (CLL progression < 6 months from completion of prior therapy) vs relapsed (CLL progression ≥ 6 months from completion of prior therapy)

For subjects with discrepancies between the stratification factor values at randomization (ie, according to IWRS) and the actual values as documented in the eCRF, the actual strata information will be used in the analyses.

Analyses will be adjusted for the randomization strata. In the situation that there is insufficient information in a stratum (ie, if there are < 6 subjects or there is no informative event in a stratum), that stratum will be pooled with the smallest adjacent stratum for stratified analyses; the smallest stratum is defined as that stratum having the fewest number of subjects or the fewest number of events in case the former is a tie and the adjacent stratum is defined as a stratum having 2 factors of the 3 at the same level.

3.4. Examination of Subject Subsets

Not applicable for the final analysis

3.5. Multiple Comparisons

Not applicable for the final analysis

3.6. 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.

Outliers

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

3.7. 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.
- Summary tables for categorical variables for baseline and safety data will include: N, n, and percentage. The tables for efficacy endpoints will include standard error, and 95% confidence intervals (CIs) 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 stratum 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. Percentages equal to 100 will be presented as 100% and percentages 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).
- The actual stratification factor values at randomization from eCRF (not the ones from IWRS) will be used in all analyses.
- 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. If there is a significant degree of non-normality, analyses may be performed on log-transformed data or nonparametric tests may be applied, as appropriate.
- 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.

3.7.1. 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.

The baseline for the efficacy endpoints is date of randomization.

3.7.2. 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).

A baseline laboratory value will be defined as the last measurement obtained on or prior to the date/time of the first dose of study drug

3.8. Visit Windows

3.8.1. 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 visits prior to randomization 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.

3.8.2. 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

The summary of enrollment and randomization were performed in the interim analyses, and will not be performed in the final analysis.

4.2. Disposition of Subjects

Study treatment disposition and study disposition summaries will be provided by treatment group.

Study treatment disposition will present the number of subjects who:

- were randomized
- were randomized but were not treated
- were treated with study drug
- discontinued study drug with summary of reason for discontinuation

Primary study disposition will present the number of subjects who:

- were randomized
- were randomized but were not treated
- were treated with study drug
- discontinued primary study with summary of reason for discontinuation

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

- completed/discontinued primary study
- entered long-term follow-up
- completed 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 for the treatment and study dispostion will be the number of subjects in the ITT analysis set. The denominator for the percentages of subjects in each category for the long-term follow-up disposition dispostion will be the number of subjects who entered lonter term follow-up.

A by-subject listing with reasons for study drug or primary study discontinuation and a separate one with long-term follow-up contact will be provided by subject identification (ID) number in ascending order to support the above summary table.

4.3. Extent of Exposure

4.3.1. Duration of Exposure to Study Drug

Duration of exposure to idelalisib/placebo will be defined as (last idelalisib/placebo dosing date-first idelalisib/placebo dosing date + 1) regardless of temporary interruptions in study drug administration, and will be expressed in months. Duration of exposure to idelalisib/placebo will be summarized for the Safety 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.

If the last study drug dosing date is missing, the latest date among the study drug end date, clinical visit date, laboratory sample collection date, and vital signs assessment date that occurred during the on-treatment period will be used. On-treatment period is defined as the time between the first dosing date to the study drug end date.

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

Duration of exposure to rituximab will be defined as (last rituximab dose date - first rituximab dose date + 1) and will be summarized for the Safety Analysis Set using descriptive statistics. The same summary will be provided for the duration of exposure to bendamustine. Furthermore, the number of rituximab and bendamustine cycles will be summarized using descriptive statistics and the number and percentage of subjects who received at least 1, 2 …, 6 cycles will be presented.

4.3.2. Adherence with Idelalisib/placebo

Adherence (%) with idelalisib/placebo 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 interruption, reductions, and escalations.

The period matched drug dispense/ return records and drug exposure records are included in the calculation. The records with missing return dates are excluded and the duration of treatment at a dispense/return period of a study drug is calculated as the minimum of a) the last returned date at this period, and b) the next pill dispense date, minus dispense date of the study drug.

Descriptive statistics for adherence along with the number and percentage of subjects belonging to adherence categories (eg, $< 75\%$ or $\geq 75\%$) will be provided.

A by-subject listing of study drug administration in clinic will be provided by subject ID number in ascending order and visit in chronological order. Continuous dosing recrods of idelalisb/placebo will also 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 CSR based on the ITT Analysis Set. A listing will be provided for all important protocol deviations.

5. BASELINE DATA

The analyses of the baseline data including demographics, baseline characteristics, medical history, and disease history were performed in the interim analyses, and will not be performed in the final analysis.

6. EFFICACY ANALYSES

An IRC was established for this study and includes primary board-certified radiologists, a board certified adjudicating radiologist, and an independent board-certified hematologist or oncologist to perform an independent review of response and disease progression for each subject. The review comprises of an assessment of radiographic images and prospectively defined clinical data acquired during the study according to the Gilead Protocol GS-US-312-0115 Imaging Charter. The determination of CLL response and progression will be based on standardized criteria promulgated by the International Workshop on CLL {Cheson 2012}, as specifically modified for this study to reflect current recommendations which consider the mechanism of action of idelalisib and similar drugs {Cheson 2012}. The findings of the IRC will be considered primary for analyses of PFS and other tumor control endpoints.

6.1. Definition of the Primary Efficacy Endpoint

The primary endpoint for this study is PFS, defined as the interval from randomization 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 ({Hallek 2008}, {Cheson 2012}) other than lymphocytosis alone.

6.2. Statistical Hypothesis for the Primary Efficacy Endpoint

H_0: Hazard ratio (HR) equals to 1 between Arm A (idelalisib + bendamustine/rituximab) and Arm B (Placebo + bendamustine/rituximab)

H_1: HR is less than 1 (Arm A is superior to Arm B in terms of PFS)

6.3. Analysis of the Primary Efficacy Endpoint

For the primary efficacy analysis, the PFS between the 2 treatment arms will be compared based on the ITT Analysis Set using a stratified log-rank test, adjusted for the stratification factors used for randomization. The analysis strategy for the situation where there is insufficient information in a stratum is detailed in Section 3.3. Medians, Q1, Q3, the proportion of subjects who are progression-free at 6 months and 12 months from randomization (based on Kaplan-Meier estimates), HRs, and corresponding 95% CIs (as calculated using a Cox proportional hazards regression model) will be presented. The Kaplan-Meier curve will also be plotted.The date of definitive CLL progression will be the time point at which progression is 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 prior to the end of study.

Data will be censored on the date of the last tumor assessment (including assessments of NE) prior to the initiation of new anti-tumor therapy for subjects who start new anti-tumor therapy prior to documented disease progression.

Data will be censored on the date of the last tumor assessment (including assessments of NE) prior to ≥ 2 consecutive missing tumor assessments for subjects who have ≥ 2 consecutive missing tumor assessments before disease progression or death.

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

The worst-case sensitivity analysis and Cox regression modeling were performed in the interim analyses, and will not be performed in the final analysis.

6.4. Secondary Efficacy Endpoints

6.4.1. Definition of Secondary Efficacy Endpoints

Secondary efficacy endpoints include:

- ORR defined as the proportion of subjects who achieve a CR, CR with incomplete marrow recovery (CRi), or partial response (PR) and maintain their response for at least 12 weeks (with a 1-week window)

- LNR rate defined as the proportion of subjects who achieve a ≥50% decrease from baseline in the sum of the products of the perpendicular diameters (SPD) of index lesions per IRC assessments. The denominator is the number of subjects in the ITT analysis set sho have both baseline and at least one evaluable post-baseline SPD

- OS defined as the interval from randomization to death from any cause

- CR rate defined as the proportion of subjects who achieve a CR and maintain their response for at least 12 weeks (with a 1-week window)

Subjects in the ITT Analysis Set who do not have sufficient baseline or on-study tumor status information to be adequately assessed for response status will be included in the denominators in the calculation of ORR and CR rate.

6.4.2. Analysis Methods for Secondary Efficacy Endpoints

6.4.2.1. Overall response rate

Responses will be categorized as CR, CRi, PR, stable disease (SD), or PD. For subjects who initially responded but did not have an evaluable follow up visit or did not maintain a response for at least 12 weeks (with a 1-week window) will be categorized as having a SD. In addition, a response category of 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.

ORR is defined as the proportion of subjects who achieve a CR, CRi, or PR during the study and maintain the response for at least 12 weeks (with a 1-week window). ORR between the treatment arms will be compared using CMH Chi-square tests after adjusting for stratification factors. Odds ratios and the corresponding 95% CIs will be presented.

The primary ORR analysis will be evaluated using the IRC assessments based on the ITT Analysis Set.

The ORR analyses using investigator assessments were performed in the interim analyses, and will not be performed in the final analysis.

6.4.2.2. Lymph node response rate

Differences in LNR between the 2 treatment arms will be compared using CMH Chi-square tests after adjusting for stratification factors. Only subjects that have both baseline and ≥ 1 evaluable post-baseline SPD will be included for this analysis.

6.4.2.3. Overall Survival

The OS analysis will be performed using the ITT Analysis Set which includes all available survival information during the study and long-term follow-up. Data from surviving subjects will be censored at the last time that the subject was known to be alive on study or in the long term follow up. Differences between treatment arms in OS will be assessed using a stratified log-rank test, adjusted for the stratification factors. Medians, Q1, Q3, HRs, and corresponding 95% CIs will be presented by treatment arm with Kaplan-Meier plots.

6.4.2.4. Complete Response Rate

The same analyses as specified for ORR in Section 6.4.2.1 will be performed for the CR rate.

6.5. Exploratory Efficacy Endpoints

The analyses for the exploratory efficacy endpoints were performed in the interim analyses, and will not be performed in the final analysis.

6.6. Changes From Protocol-Specified Efficacy Analyses

There are no deviations from the protocol-specified efficacy analyses.

7. SAFETY ANALYSES

7.1. Adverse Events and Deaths

The focus of adverse event summarization will be on treatment-emergent AEs (TEAEs). All TEAEs and deaths occurring on study will be summarized by treatment arm based on the Safety Analysis Set. All AEs will be listed in detail based on the ITT Analysis Set.

7.1.1. Adverse Event Dictionary

AEs will be coded using the current 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 the component of study drug (idelalisib/placebo), rituximab and bendamustine should be assessed by the investigator using clinical judgment, describing the event as either unrelated or related. Events for which the investigator did not record relationship will be considered related to study drug, rituximab and bendamustine. Data listings will show relationship as missing.

7.1.4. Serious Adverse Events

Serious adverse events (SAEs) will be identified and captured as SAEs if the AEs met the definitions of SAEs that were specified in the study protocol. SAEs captured and stored in the clinical database will be reconciled with the SAE database from the Gilead Pharmacovigilance and Epidemiology Department before data 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.
- 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. If AE onset date is later than 30 days after the last dose of study treatment, then the imputed day will be the last day of the month if day is missing but the month and year are available.

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 TEAE, (2) had any Grade ≥3 TEAE, (3) had any idelalisib/placebo-related TEAE, (4) had any rituximab-related TEAE, (5) had any bendamustine-related TEAE, (6) had any Grade ≥3 idelalisib/placebo-related TEAE, (7) had any Grade ≥3 rituximab-related TEAE, (8) had any Grade ≥3 bendamustine-related TEAE, (9) had any Serious TEAE, (10) had any idelalisib/placebo-related Serious TEAE, (11) had any rituximab-related Serious TEAE, (12) had any bendamustine-related SAE, (13) had any TEAE leading to idelalisib/placebo reduction, (14) had any TEAE leading to idelalisib/placebo interruption, (15) had any AE leading to idelalisib/placebo discontinuation, (16) had any TEAE leading to death.

A summary (number and percentage of subjects) of TEAEs by SOC, HLT and PT will be provided by treatment arms. Summaries of TEAEs by SOC and PT will be provided by treatment arms as follows:

- TEAEs by CTCAE Grade
- Grade ≥3 TEAE
- Idelalisib/placebo, rituximab and bendamustine-related TEAEs
- TE SAEs
- Idelalisib/placebo, rituximab and bendamustine related SAEs
- TEAEs leading to idelalisib/placebo interruption
- TEAEs leading to idelalisib/placebo reduction
- TEAEs leading to idelalisib/placebo discontinuation
- TEAEs leading to death

Multiple events will be counted once only per subject in each summary. For data presentation, SOC and PT will be sorted by decreasing frequency. For summaries by severity grade, the most severe event will be selected.

In addition to the above summary tables, all TEAEs, TEAEs of Grade 3 or higher, and TE SAEs will be summarized by PT only in descending order of total frequency. Data listings will be provided for the following:

- All AEs, indicating whether the event is treatment emergent
- All SAEs
- All AEs leading to interruption, reduction and discontinuation of idelalisib/placebo
- All AEs leading to death

Relative day from the first dose date will be provided for each AE in the listings. The relative day will be calculated as (AE onset date - first dose date + 1).

7.1.6.1. Summary of Deaths

A summary (number and percentage of subjects) of deaths will be provided by treatment group. Summary will include the following categories:

- All deaths
- On-study deaths
- Deaths occurred in long-term follow-up

Death between the randomization and within 30 days from end of study is considered as on-study death. A listing of death with date and cause will also be provided.

7.1.7. 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 last dosing date plus 30 days.

The exposure-adjusted TEAE rate will be summarized by treatment arm based on the Safety Analysis Set. The rate difference between two arms with 95% CI calculated using normal approximation is also provided.

7.1.8. Treatment-Emergent Adverse Events (TEAEs) of Interest

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

- Grade ≥ 3 diarrhea/colitis
- Grade ≥ 3 rash in Medical Search Term (MST) (Appendix 2)
- Any grade pneumonitis
- Any grade bowel perforation
- Any grade progressive multifocal leukoencephalopathy (PML)
- Grade ≥ 3 febrile neutropenia
- Grade ≥ 3 infection
- Any grade *pneumocystis jiroveci* pneumonia (PJP)
- Any grade cytomegalovirus (CMV) infection
- Any grade organising pneumonia (OP)

Table 7-1 below describes grouped terms used for each AEI.

Table 7-1. Grouped Terms for Adverse Events of Interest

AEI	Grouped Terms
Diarrhea/Colitis	PT: Diarrhoea or Colitis
Rash	MST defined in Appendix 2
Pneumonitis	PT: Pneumonitis
Febrile neutropenia	PT: Febrile neutropenia
Infection	SOC: Infections and infestations or PT: Febrile neutropenia
PJP	HLT: Pneumocystis infections
PML	PT: Progressive multifocal leukoencephalopathy
Organising pneumonia	PT: Organising pneumonia
CMV	HLT: Cytomegaloviral infections or PT: Cytomegalovirus test positive or Reported terms (i.e., verbatim's) with the strings "CMV" or "cytomegalo"
Bowel perforation	SMQ for Gastrointestinal perforation

The AEIs will be summarized similarly to TEAE by treatment arms. The following summaries will be provided for subjects:

- Number of subjects with AEI
- Number (%) of Subjects with IDL discontinuation due to AEI
- Number (%) of Subjects with IDL interruption caused due to AEI
- Number (%) of Subjects who re-challenged after IDL dose interruption
- Number (%) of Subjects who re-challenged successfully after interruption with resumption of IDL at the starting dose
- Number (%) of Subjects who re-challenged successfully after interruption with resumption of IDL at a reduced dose
- Number (%) of Subjects with recurrence of AE of Interest among re-challenged

Time to the first onset of AEIs and time to resolution of the first AEI will be summarized using summary statistics. Time to onset of the first event is defined as time from start of study treatment to the date of first incident AEI, ie, time in weeks is calculated as (start date of first occurrence of AEI date of first dose of study drug + 1)/7. In the absence of an event, the censoring date will be the earliest from the following dates: last dose date + 30 days (if treatment discontinued) and death date. Time to resolution of the first AEI is calculated as (AEI stop date - start date of first occurrence of AEI + 1)/7.

The exposure-adjusted TEAE rate as well as the 95% confidence interval will be summarized for the AEs of interest by treatment group based on the Safety Analysis Set.

In addition, Sumarry of TEAEs of interestleading to idelalisib/placebo discontinuation and listing of TEAEs of interest will be provided.

7.2. Laboratory Evaluations

Summaries of laboratory data (including hematology and serum chemistry) will be provided. 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 Safety Analysis Set.

7.2.1. Summaries of Numeric Laboratory Results

The summaries of numeric laboratory results were performed in the interim analyses, and will not be performed in the final analysis.

7.2.2. 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. Local labs will be graded based on central lab normal ranges with in-house macro. In the event that both central and local lab results are collected in the clinical database, the worst toxicity grade will be used for the summary of lab toxicities. All central and local labs will be listed.

7.2.2.1. 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.

7.2.2.2. 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 postbaseline abnormality grade.

For all summaries of laboratory abnormalities, the denominator is the number of subjects in the

Safety Analysis Set. A listing of treatment-emergent laboratory abnormalities will be provided.

7.2.2.3. Exposure-adjusted Treatment-Emergent Laboratory Abnormalities Rate

The exposure-adjusted treatment-emergent laboratory abnormalities rates were calculated in the interim analyses, and will not be performed in the final analysis.

7.2.3. 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.

7.2.4. Transaminase elevations

Analyses of transaminase elevations will be based on laboratory values using the Safety Analysis Set. Number and percentage of subjects will be summarized by treatment arms for subjects:

- with Grade 3 or 4 ALT/AST elevation

  with Grade 3 or 4 ALT elevation

  with Grade 3 or 4 AST elevation

  with Grade 3 and 4 ALT/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

Cumulative incidence function estimates using the competing risk model will be provided for time to onset of the first Grade 3 or 4 treatment-emergent ALT/AST elevations. Grade 3 or 4 ALT/AST elevation is considered as event, death without Grade 3 or 4 ALT/AST elevation is considered as competing event and discontinuation of study drug without event will be censored. Time to onset of the first event is defined as time from start of study treatment to the start date of the 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)/7. In the absence of an event or death, the censoring date applied will be the last dose date + 30 days.

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. In the absence of resolution, the censoring date applied will be the earlier one of the last dose date + 30 days and death date.

7.2.5. 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 x upper limit of normal (ULN), (b) 5 to <10 x ULN, (c) 10 to <20 x ULN, (d) ≥ 20 x ULN
- ALT: (a) 3 to <5 x ULN, (b) 5 to <10 x ULN, (c) 10 to <20 x ULN, (d) ≥ 20 x ULN
- AST or ALT: (a) 3 to <5 x ULN, (b) 5 to <10 x ULN, (c) 10 to <20 x ULN, (d) ≥ 20 x ULN
- Total bilirubin: (a) > ULN, (b) > 1.5 x ULN, (c) > 2 x ULN
- Alkaline Phosphatase >1.5 x ULN
- AST or ALT > 3 x ULN and total bilirubin > 1.5 x ULN
- AST or ALT > 3 x ULN and total bilirubin > 2 x 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 x ULN), the following 2 approaches will be used for counting subjects with total bilirubin elevation/normal alkaline phosphatase (≤1.5 x 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 (Including Radiation)

The analyses for the prior therapies were performed in the interim analyses, and will not be performed in the final analysis.

7.4. Concomitant Medications

Concomitant medications will be coded by means of the current World Health Organization Drug (WHODRUG) dictionary 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).

Summaries of the number and percentage of subjects who used concomitant medications will be presented in tabular form by preferred drug name based on the Safety Analysis Set. The summary tables will be sorted by descending frequency of preferred terms. Subjects will only be counted once for multiple drug use (by preferred drug name).

All prior and concomitant medications (other than per-protocol study drugs) will be provided in a by-subject listing sorted by subject ID number and administration date in chronological order.

7.5. Body Weight and Vital Signs

The analyses for the body weights and vital signs were performed in the interim analyses, and will not be performed in the final analysis.

7.6. Electrocardiogram Results

The summary for the electrocardiogram results was performed in the interim analyses, and will not be performed in the final analysis. A by-subject listing for ECG assessment results will be provided by subject ID number and visit in chronological order.

7.7. Other Safety Measures

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

7.8. Changes From Protocol-Specified Safety Analyses

Not applicable.

8. PHARMACOKINETIC ANALYSES

There are no PK samples collected since the interim analysis.

9. PHARMACODYNAMIC ANALYSES

Not applicable.

10. REFERENCES

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.

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.

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
15 August 2019		The analyses that will not repeated in the final CSR are deleted.	Update for the final Synoptic CSR analysis

13. APPENDICES

Appendix 1. Schedule of Assessments

Period	Screen	Treatment																								Follow-up	
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25+		30 day	Long-term
Week	-4	0		2	4		6	8		10	12		14	16		18	20		22	24	30	36	42	48				
Study Day	Within -28 days	1	2	15	29	30	43	57	58	71	85	86	99	113	114	127	141	142	155	169	211	253	295	337	Q12 wks	End of Study	Within +30 days	To +5 yrs
Visit Window			+1	±2	±2[a]	+1	±1	±2[a]	+1	±2	±3[a]	+1	±2	±2[a]	+1	±2	±2[a]	+1	±2	±3	±3	±3	±3	±3	±7			
Informed consent	X																											
Medical history	X																											
CIRS assessment	X																											
Serum virology	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[d]																									X		
CLL serology	X																									X		
Coagulation	X																											
Urinalysis	X																											
12 lead ECG	X																											
Genotyping and expression analysis		X																								X		
IWRS	X	X			X			X			X			X			X			X	X	X	X	X	X	X		
HRQL/healthy utility FACT Leu/ EQ 5D		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	
Concomitant medications		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		

Period	Screen	Treatment																								Follow-up	
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25+		30 day	Long-term
Week	-4	0		2	4		6	8		10	12		14	16		18	20		22	24	30	36	42	48				
Study Day	Within -28 days	1	2	15	29	30	43	57	58	71	85	86	99	113	114	127	141	142	155	169	211	253	295	337	Q12 wks	End of Study	Within +30 days	To +5 yrs
Visit Window			+1	±2	±2[a]	+1	±1	±2[a]	+1	±2	±3[a]	+1	±2	±2[a]	+1	±2	±2[a]	+1	±2	±3	±3	±3	±3	±3	±7			
Oxygen saturation (by pulse oximetry)	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		
Hematology/serum chemistry	X	X[b]		X[c]	X		X[c]	X		X[c]	X		X[c]	X		X[c]	X		X[c]	X	X	X	X	X	X	X		
Circulating cells/ biomarkers/ serum Igs		X			X			X			X			X			X			X	X	X	X	X	X	X		
CMV viral load[j]																									X[j]			
HBV DNA by PCR[f]		X[f]			X[f]			X[f]			X[f]			X[f]			X[f]			X[f]		X[f]		X[f]	X[f]	X[f]	X[f]	X[f]
Idelalisib/ placebo administration in clinic		X			X			X			X			X			X			X								
Premedication		X	X		X	X		X	X		X	X		X	X		X	X											
Rituximab administration		X			X			X			X			X			X												
Bendamustine administration		X	X		X	X		X	X		X	X		X	X		X	X											
PJP prophylaxis[k]																									X[k]	X[k]			
CD4+ T cell Count[k] (related to PJP prophylaxis)																										X[k]			
Assess rituximab infusion severity and duration		X			X																								

Period	Screen	Treatment																									Follow-up	
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25+		30 day	Long-term
Week	-4	0		2	4		6	8		10	12		14	16		18	20		22	24	30	36	42	48				
Study Day	Within -28 days	1	2	15	29	30	43	57	58	71	85	86	99	113	114	127	141	142	155	169	211	253	295	337	Q12 wks	End of Study	Within +30 days	To +5 yrs
Visit Window			+1	±2	±2[a]	+1	±1	±2[a]	+1	±2	±3[a]	+1	±2	±2[a]	+1	±2	±2[a]	+1	±2	±3	±3	±3	±3	±3	±7			
Idelalisib pharmacokinetics		X			X			X			X			X			X			X								
Idelalisib/ placebo dispensing/ accounting		X									X									X		X		X	X	X		
Radiology assessment (CT/MRI)	X[d]										X[g]									X[g]		X[g]		X[g]	X[g]	X[a, h]		
Bone marrow biopsy/ aspirate	X[e]										X[e]									X[e]		X[e]		X[e]	X[e]			
Post treatment CLL therapy																												X
Long term follow up																												X

a. Windows for the specified clinic visits may be extended to account for delayed recovery from drug related adverse events (eg, myelotoxicity)
b. Hematology will be assessed locally at Visit 2, in addition to the central lab assessment, so that results will be available if the central lab results are compromised
c. More frequent (eg, weekly) hematology/serum chemistry assessments may be appropriate in subjects experiencing Grade ≥3 myelosuppression or ALT/AST elevations Throughout the study, local lab results may be requested in the event central laboratory results are not available for assessment of disease response, progression, safety monitoring, or the evaluation of a significant event
d. Radiology assessment (CT/MRI) if performed within <6 weeks of randomization and assessed to be adequate by the IRC and CLL peripheral blood evaluation if performed within <12 weeks of randomization and assessed to be adequate by the central lab do not need to be repeated
e. A bone marrow biopsy/aspirate demonstrating CLL involvement following the last therapy must be available if Grade >2 neutropenia, thrombocytopenia, or anemia is present at screening, or at investigator discretion to determine extent of CLL involvement and bone marrow cellularity. Post screening, to be performed to confirm response category in subjects with potential CR or to confirm a hematologically based disease progression
f. Only subjects who are HBc antibody positive and HBV DNA negative at screening. Subjects will be tested monthly for the duration of rituximab therapy and every 3 months thereafter for 1 year from the last dose of rituximab
g. CT or MRI imaging of neck, chest, abdomen, and pelvis within 1 week prior to the study visit; assessment should be done even if study drug has been interrupted
h. An end of study CT/MRI tumor assessment should be performed unless the subject already has radiographic confirmation of definitive disease progression progression or a CT/MRI has been performed within 4 weeks prior to the end of study visit.
i. Circulating cells/serum Igs/Immune monitoring should be performed at the the End of Study visit.

j. CMV viral load should be performed approximately every 4 weeks throughout idelalisib treatment. If unequivocal clinical or laboratory evidence of CMV infection is present, refer to Section 5.4.5 (“Infectious Events”) for required actions.
k. PJP prophylaxis: subjects must receive trimethoprim sulfamethoxazole or other established prophylaxis for PJP throughout the course of idelalisib treatment and for 2 to 6 months following the last dose of idelalisib as specified in Section 5.4.5 (“Infectious Events”).
l. As of Amendment 10, Version 11, CT/MRI assessments will no longer be performed at the every 12 week scheduled visits, and will only be performed at the time of clinically suspected disease progression or at study discontinuation.

Abbreviations: β HCG beta human chorionic gonadotropin, CIRS chronic illness rating scale, CLL chronic lymphocytic leukemia, CR complete response, CT computed tomography, CMV cytomegalovirus, ECG electrocardiogram, 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, PJP *Pneumocystis jirovecii* pneumonia.

Appendix 2. Gilead List of Medical Search Terms for Rash based on MedDRA Version 22.0

MedDRA Term Name	MedDRA Code	MedDRA Level
Acute generalised exanthematous pustulosis	10048799	PT
Angina bullosa haemorrhagica	10064223	PT
Autoimmune dermatitis	10075689	PT
Blister	10005191	PT
Blister rupture	10073385	PT
Butterfly rash	10067982	PT
Cervical bulla	10050019	PT
Dermatitis exfoliative	10012455	PT
Dermatitis exfoliative generalised	10012456	PT
Dermatosis	10048768	PT
Drug eruption	10013687	PT
Drug reaction with eosinophilia and systemic symptoms	10073508	PT
Eosinophilic pustular folliculitis	10052834	PT
Epidermolysis	10053177	PT
Epidermolysis bullosa	10014989	PT
Eruptive pseudoangiomatosis	10068095	PT
Erythema multiforme	10015218	PT
Erythema nodosum	10015226	PT
Erythrosis	10056474	PT
Exfoliative rash	10064579	PT
Fixed eruption	10016741	PT
Flagellate dermatitis	10075467	PT
Interstitial granulomatous dermatitis	10067972	PT
Lichenoid keratosis	10064000	PT
Macule	10025421	PT
Mucocutaneous rash	10056671	PT
Mucocutaneous ulceration	10028084	PT
Mucosa vesicle	10028103	PT
Necrolytic migratory erythema	10060821	PT
Neurodermatitis	10029263	PT
Oculomucocutaneous syndrome	10030081	PT
Oral mucosal blistering	10030995	PT
Oropharyngeal blistering	10067950	PT
Palmar plantar erythrodysaesthesia syndrome	10033553	PT
Palpable purpura	10056872	PT
Papule	10033733	PT
Paraneoplastic rash	10074687	PT
Pemphigoid	10034277	PT

MedDRA Term Name	MedDRA Code	MedDRA Level
Pemphigus	10034280	PT
Penile blister	10052898	PT
Prurigo	10037083	PT
Rash	10037844	PT
Rash erythematous	10037855	PT
Rash follicular	10037857	PT
Rash generalised	10037858	PT
Rash macular	10037867	PT
Rash maculo papular	10037868	PT
Rash maculovesicular	10050004	PT
Rash morbilliform	10037870	PT
Rash papular	10037876	PT
Rash papulosquamous	10037879	PT
Rash pruritic	10037884	PT
Rash pustular	10037888	PT
Rash rubelliform	10057984	PT
Rash scarlatiniform	10037890	PT
Rash vesicular	10037898	PT
Seborrhoeic dermatitis	10039793	PT
Skin disorder	10040831	PT
Skin plaque	10067723	PT
Skin reaction	10040914	PT
Skin toxicity	10059516	PT
Stevens Johnson syndrome	10042033	PT
Symmetrical drug related intertriginous and flexural exanthema	10078325	PT
Toxic epidermal necrolysis	10044223	PT
Toxic erythema of chemotherapy	10074982	PT
Toxic skin eruption	10057970	PT
Umbilical erythema	10055029	PT
Urticarial vasculitis	10048820	PT
Vaginal exfoliation	10064483	PT
Vasculitic rash	10047111	PT
Viral rash	10047476	PT
Vulvovaginal rash	10071588	PT