STATISTICAL ANALYSIS PLAN

Study Title:	A Phase 2, Open-Label Study Evaluating the Efficacy, Safety, Tolerability, and Pharmacodynamics of GS-9973 in Subjects with Relapsed or Refractory Hematologic Malignancies
Name of Test Drug:	Entospletinib (ENTO)
Study Number:	GS-US-339-0102
Protocol Version (Date):	Amendment 8 (31 March 2017)
Analysis Type:	Final CSR
Analysis Plan Version:	Version 1.0
Analysis Plan Date:	16 September 2019
Analysis Plan Author:	PPD

CONFIDENTIAL AND PROPRIETARY INFORMATION

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LIST OF ABBREVIATIONS

AE	adverse event
ATC	Anatomical-Therapeutic-Chemical (drug coding system)
BCR	B-cell receptor
BID	twice a day
BLQ	below the limit of quantitation
BMI	body mass index
BOR	best overall response
CI	confidence interval
CLL	chronic lymphocytic leukemia
CR	complete response
eCRF	electronic case report form
CRF	case report form
CSR	clinical study report
CT	computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variation
DLBCL	diffuse large B-cell lymphoma
DOR	duration of response
ECG	electrocardiogram
ENTO	Entospletinib
FL	follicular lymphoma
HLGT	high-level group term
HLT	high-level term
iNHL	indolent non-Hodgkin lymphoma
IRC	independent review committee
LOQ	lower limit of quantification
LLT	low level term
LPL	lymphoplasmacytoid lymphoma
MedDRA	Medical Dictionary for Regulatory Activities
MCL	mantle cell lymphoma
MM	mono-mesylate
MRI	magnetic resonance imaging
MZL	marginal zone lymphoma
ND	no disease
NE	not evaluable
NHL	non-Hodgkin lymphoma
ORR	objective response rate
PD	progressive disease
PFS	progression-free survival

PK	pharmacokinetic
PPI	proton pump inhibitors
PR	partial response
PT	preferred term
QTc	QT interval corrected
QTc-B	QT interval corrected for heart rate using Bazett's formula
QTc-F	QT interval corrected for heart rate using Fridericia's formula
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
SDD	spray dried dispersion
SE	standard error
SLL	small lymphocytic lymphoma
StD	standard deviation
SOC	system organ class
SPD	sum of the product of the diameters (of nodal or tumor masses)
SPEP	serum protein electrophoresis
TEAE	treatment-emergent adverse event
TLF	tables, figures, and listings
TTR	time to response
WHO	World Health Organization
WM	Waldenström macroglobulinemia

1. INTRODUCTION

This statistical analysis plan (SAP) describes the statistical analysis methods and data presentations to be used in tables, figures, and listings (TFLs) in the clinical study report (CSR) for Study GS-US-339-0102. This SAP is based on the study protocol Amendment 8 dated 31 March 2017 and the electronic case report form (eCRF). The SAP will be finalized before database finalization. Any changes made after the finalization of the SAP will be documented in the CSR.

Based on the Sponsor's strategic plan for entospletinib development, the CSR will be in synoptic version.

1.1. Study Objectives

The primary objective of this study is as follows:

- To evaluate the efficacy of entospletinib (ENTO; GS-9973) in subjects with relapsed or refractory hematologic malignancies

The secondary objectives of this study are as follows:

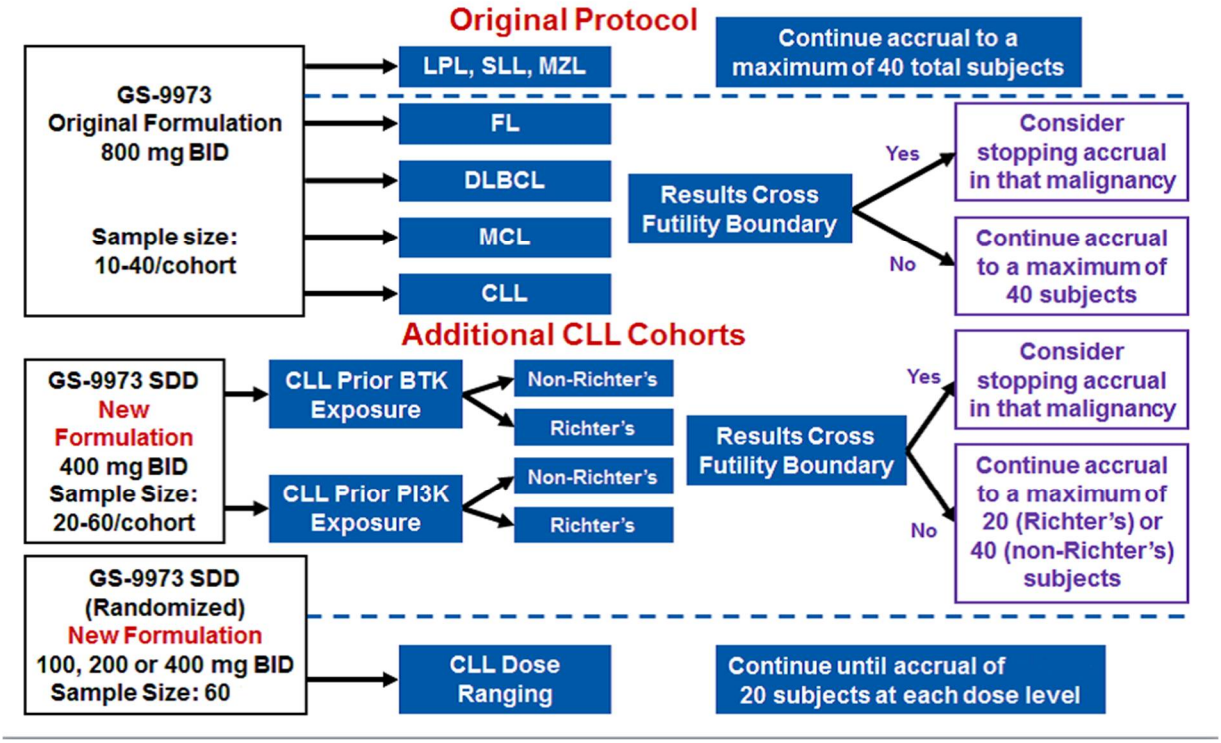
- To evaluate the safety and tolerability of ENTO in subjects with relapsed or refractory hematologic malignancies
- To evaluate ENTO exposures in subjects with relapsed or refractory hematologic malignancies

1.2. Study Design

1.2.1. Design Configuration

This is a Phase 2, open-label study evaluating the efficacy, safety, and tolerability of ENTO administered twice daily (BID) over multiple 28-day cycles in subjects with relapsed or refractory hematologic malignancies. Historically the study planned to investigate 5 cohorts of ENTO in subjects with chronic lymphocytic leukemia (CLL), mantle cell lymphoma (MCL), diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL), and a fifth cohort consisting of the non-FL indolent non-Hodgkin lymphomas (iNHL), ie, subjects with lymphoplasmacytoid lymphoma/Waldenström macroglobulinemia (LPL/WM), small lymphocytic lymphoma (SLL), or marginal zone lymphoma (MZL), with a mono-methanesulfonate salt at 800 mg bid of the original mono-mesylate (MM) formulation (Figure 1-1). After completion of enrollment of the original CLL cohort, the study was amended to include the addition of 3 CLL cohorts (1 dose finding prior B-Cell receptor (BCR) naïve cohort and 2 prior BCR exposure cohorts [ie, 1 prior BTK inhibitor and 1 prior PI3K inhibitor cohort]). All 3 additional cohorts receive a new formulation of ENTO designated spray dried dispersion (SDD). The SDD formulation had greater bioavailability and lesser drug-drug interactions (no H2 and reduce proton pump inhibitors (PPI)). As of protocol amendment 8, subjects receiving ENTO MM formulation are transitioned to the ENTO SDD formulation.

Figure 1-1. Study Schema



The 2 CLL cohorts with prior BCR exposure enroll based on the most recent progression followed BCR-exposure. The BCR naïve patient cohort designated as CLL dose ranging cohort are randomly assigned to one of 3 doses evaluating 100 mg, 200 mg, and 400 mg (200 mg x 2) BID dosing of ENTO SDD (Table 1-1).

Table 1-1. Dose Levels and Formulations

Cohort	Dose (BID)*	Formulation
CLL	800mg Amendment 8: 400mg	MM Amendment 8: SDD
MCL	800mg Amendment 8: 400mg	MM Amendment 8: SDD
DLBCL	800mg Amendment 8: 400mg	MM Amendment 8: SDD
FL	800 mg Amendment 8: 400mg	MM Amendment 8: SDD
Other iNHL (LPL/WM, SLL, and MZL)	800mg Amendment 8: 400mg	MM Amendment 8: SDD
CLL prior BCR inhibitor naïve	400mg 200mg 100mg	SDD SDD SDD
CLL Prior BTK inhibitor	400mg	SDD
CLL Prior PI3K inhibitor	400mg	SDD

*Note 800mg of MM is PK/PD equivalent of 400 mg SDD

1.2.2. CLL (non-dose-ranging cohorts), MCL, DLBCL, and FL cohorts

A Bayesian, continuous data review approach is used to update the estimates of progression-free survival (PFS) rates at 16 weeks (CLL after BCR targeted therapy, MCL, and DLBCL) or 24 weeks (CLL and FL) for a malignancy. The data reviews for the CLL prior BTK inhibitor exposure and CLL prior PI3K inhibitor exposure cohorts are conducted independently for Richter's and non-Richter's. The criterion used for the futility boundary is defined as highly likely (>90%) that the PFS rates at 16 weeks (CLL after BCR targeted therapy, MCL, and DLBCL) or 24 weeks (CLL and FL) are less than 0.2 given the available subjects' efficacy data.

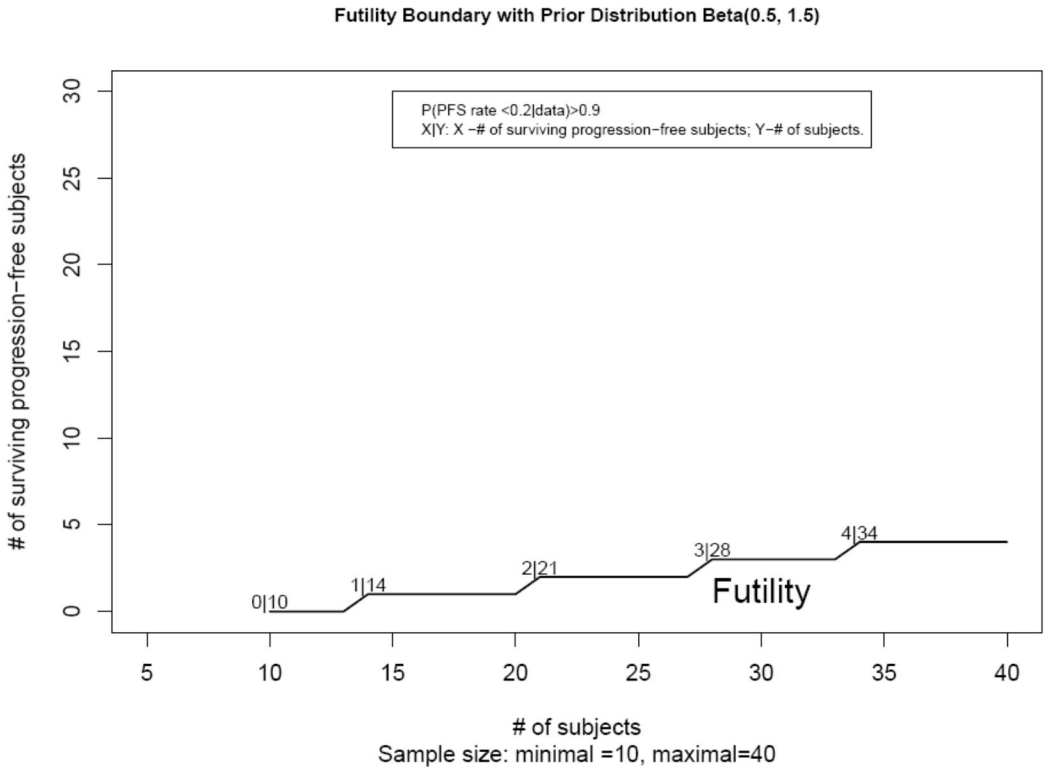
Futility assessment begins when the first 10 subjects' primary endpoints become available. Thereafter, continuous data reviews are conducted when a new primary endpoint becomes available.

- If the futility criterion is not met, subsequent subjects will be enrolled until a total of pre-defined number of subjects are recruited for a cohort.
- If the futility criterion is met, the sponsor will consider terminating enrollment to that malignancy, taking into account efficacy, drug exposure and subtype (for DLBCL), unless there are subjects who remain on treatment and have not yet reached 16 weeks (CLL after BCR targeted therapy, MCL, and DLBCL) or 24 weeks (CLL and FL). In this case, enrollment will be suspended until the next on-going subjects' primary endpoints become available, and another data review is conducted. If, after review of all available subjects, the futility boundary has still been crossed and the lack of drug exposure or for DLBCL, subtype does not explain the lack of activity, enrollment to that malignancy will be terminated.

The futility boundary is provided in Figure 1-2 with details in Section 2.1. The boundary is represented in terms of the total number of subjects and the number of progression-free subjects at Week 16 (CLL after BCR targeted therapy, MCL, and DLBCL) or Week 24 (CLL and FL). Subjects who withdraw or are lost to follow-up before Week 16 (CLL after BCR targeted therapy, MCL, and DLBCL) or week 24 (CLL and FL) will be considered as not achieving PFS for the analysis.

At each data review, if the observed ratio of the number of PFS at Week 16 (CLL after BCR targeted therapy, MCL and DLBCL) or Week 24 (CLL and FL) over the total number of subjects is at or below the futility boundary, the futility criterion has been met.

Figure 1-2. Futility Boundary with Prior Distribution Beta (0.5, 1.5)



1.2.3. CLL Dose Ranging Cohort

For the CLL dose ranging cohort, subjects are randomized in the ratio of 1:1:1 to receive 100 mg, 200 mg or 400 mg (200 mg x 2) of ENTO SDD BID. 20 subjects are planned to be treated at each of the three dose levels. Because the CLL dose raging cohort consists of 3 different dose levels each with approximately 20 subjects, the continuation data review of futility will not be conducted for this cohort.

1.2.4. Other iNHL (LPL/WM, SLL, and MZL) Cohort

Because the 'Other iNHL' cohort consists of 3 different histologies, the accrual continues to a maximum of 45 subjects without a Bayesian analysis.

2. TYPE OF PLANNED ANALYSIS

2.1. Final Analysis

After all subjects have completed the study, outstanding data queries have been resolved or adjudicated as unresolvable, and the data have been cleaned and finalized, the final analysis of the data will be performed. Due to the Sponsor's strategic plan, the final CSR will be in synoptic version.

3. GENERAL CONSIDERATIONS FOR DATA ANALYSES

Analysis results will be presented using descriptive statistics. For categorical variables, the number and percentage of subjects in each category will be presented; for continuous variables, the number of subjects (n), mean, standard deviation (StD) or standard error (SE), median, first quartile (Q1), third quartile (Q3), minimum, and maximum will be presented.

By-subject listings will be presented for all subjects in the All Enrolled Analysis Set and sorted by subject ID number, visit date, and time (if applicable). Data collected on log forms, such as AEs, will be presented in chronological order within the subject. The treatment group to which subjects are initially assigned will be used in the listings. Age, sex at birth, race, and ethnicity will be included in the listings, as space permits.

3.1. Analysis Sets

Analysis sets define the subjects to be included in an analysis. Analysis sets and their definitions are provided in this section. The analysis set will be identified and included as a subtitle of each table, figure, and listing.

3.1.1. All Enrolled Analysis Set

All Enrolled Analysis Set includes all subjects who received a study subject identification number in the study after screening. The All Enrolled Analysis Set will be used for subject enrollment summaries.

3.1.2. Full Analysis Set

The Full Analysis Set (FAS) includes all enrolled subjects who took at least one dose of study drug (ie, ENTO) with treatment group designated according to the planned treatment. This is the primary analysis set for efficacy analyses.

3.1.3. Safety Analysis Set

The Safety Analysis Set includes all subjects who took at least one dose of study drug (ie, ENTO) with treatment group designated according to the actual treatment. This is the primary analysis set for safety analyses.

3.1.4. Pharmacokinetic Analysis Sets

The Pharmacokinetic (PK) Analysis Set will include all enrolled subjects who took at least one dose of study drug (ie, ENTO) and have at least one nonmissing postdose concentration value reported by the PK laboratory. This is the primary analysis set for all PK analyses.

3.2. Subject Grouping

For summary tables, unless otherwise specified, subjects will be grouped by disease indications, prior treatment status, and dose levels as follows in Table 3-1, Table 3-2, and Table 3-3.

Table 3-1. Subject Grouping for Cohorts of CLL (except for the CLL Dose Ranging and the CLL after BCR Targeted Therapy Cohorts) and other Disease Indications

CLL N = xx	FL N = xx	DLBCL N = xx	MCL N=xx	Other iNHL N = xx	Total N=xx
xx	xx	xx	xx	xx	xx

Table 3-2. Subject Grouping for the CLL Dose Ranging Cohort

100mg BID N = xx	200mg BID N = xx	400mg BID N = xx	Total N=xx
xx	xx	xx	xx

Table 3-3. Subject Groupings for the CLL after BCR Targeted Therapy Cohorts

Non-Richters (Prior BTK Exposure) N = xx	Non-Richters (Prior PI3K Exposure) N = xx	Richters (Prior BTK Exposure) N = xx	Richters (Prior PI3K Exposure) N = xx	Total N = xx
xx	xx	xx	Xx	xx

3.3. Strata and Covariates

No planned analyses using strata and/or covariates.

3.4. Examination of Subject Subsets

No planned subset analyses.

3.5. Multiple Comparisons

Not applicable.

3.6. Missing Data and Outliers

3.6.1. Missing Data

In general, missing data will not be imputed unless methods for handling missing data are specified. Exceptions are presented in this document.

The handling of missing or incomplete date for AE onset is described in Section 7.1.5.2, and for prior medication and concomitant medications in Section 7.4.

3.6.2. Outliers

Outliers will be identified during the data management and data analysis process, but no sensitivity analyses will be conducted. All data will be included in the data analysis.

3.7. Data Handling Conventions and Transformations

The following conventions will be used for the imputation of date of birth when it is partially missing or not collected:

- If only month and year of birth is collected, then "15" will be imputed as the day of birth
- If only year of birth is collected, then "01 July" will be imputed as the day and month of birth
- If year of birth is missing, then date of birth will not be imputed

In general, age (in years) collected at Study Day 1 (the first dosing date of study drug) will be used for analyses and presented in listings. If age at Study Day 1 is not available for a subject, age derived based on date of birth and the Day 1 visit date will be used instead. If an enrolled subject was not dosed with study drug, the enrollment date will be used instead of the Day 1 visit date. For screen failures, the date the first informed consent was signed will be used for the age derivation. Age required for longitudinal and temporal calculations and analyses (eg, estimates of creatinine clearance, age at date of AE) will be based on age derived from date of birth and the date of the measurement or event, unless otherwise specified.

Non-PK laboratory data that are continuous in nature but are less than the lower limit of quantitation (LOQ) or above the upper LOQ will be imputed as follows:

- A value that is 1 unit less than the LOQ will be used to calculate descriptive statistics if the datum is reported in the form of "< x" (where x is considered the LOQ). For example, if the values are reported as < 50 and < 5.0, values of 49 and 4.9, respectively, will be used to calculate summary statistics. An exception to this rule is any value reported as < 1 or < 0.1, etc. For values reported as < 1 or < 0.1, a value of 0.9 or 0.09, respectively, will be used to calculate summary statistics.
- A value that is 1 unit above the LOQ will be used to calculate descriptive statistics if the datum is reported in the form of "> x" (where x is considered the LOQ). Values with decimal points will follow the same logic as above.
- The LOQ will be used to calculate descriptive statistics if the datum is reported in the form of "≤ x" or "≥ x" (where x is considered the LOQ).

Concentration values that are below the limit of quantitation (BLQ) will be presented as "BLQ" in the concentration data listing. Values that are BLQ will be treated as 0 at predose time points, and one half the value of the LOQ at postdose time points for summary purposes. Concentration values that are BLQ will be imputed as one-half LOQ before log transformation.

3.8. Analysis Visit Windows

3.8.1. Definition of Study Day

Study day will be calculated from the first dosing date of study drug and derived as follows:

- For post-treatment study days: Assessment Date First Dosing Date + 1
- For days prior to the first dose: Assessment Date First Dosing Date

Therefore, Study Day 1 is the day of first dose of study drug administration.

Baseline is defined as the last non-missing record on or prior to the date/time of the first dose of study drug, unless otherwise specified.

3.8.2. Analysis Windows

The nominal visit and related date as recorded on the CRF will be used when data are summarized by visit and no analysis window will be derived. Any data relating to unscheduled visits will not be assigned to a particular visit or time point. In listings, both visit names and dates will be presented.

4. SUBJECT DISPOSITION

4.1. Subject Enrollment and Disposition

A summary of subject enrollment will be provided by the grouping specified in Section 3.2 based on All Enrolled Analysis Set. The summary will present the number and percentage of subjects enrolled. For each column, the denominator for the percentage calculation will be the total number of subjects analyzed for that column.

A summary of subject disposition will be provided based on All Enrolled Analysis Set. This summary will present the number and percentage of subjects in the following categories:

- Treated and Non-treated
- ENTO discontinuations and reasons
- Study discontinuations and reason

The denominator of the percentage calculation will be the total number of subjects in All Enrolled Analysis Set corresponding to that column.

The by-subject listings will be provided by subject identification (ID) number in ascending order to support the above summary tables.

4.2. Extent of Study Drug Exposure and Adherence

Extent of exposure to study drug will be examined by assessing the total duration of exposure to study drug and the level of adherence to the study drug specified in the protocol. The summaries will be based on Safety Analysis Set.

4.2.1. Duration of Exposure to Study Drug

Total duration of exposure to study drugs will be defined as last dosing date minus first dosing date plus 1, regardless of any temporary interruptions in study drug administration, and will be expressed in months using up to 1 decimal place (eg, 4.5 months). If the last study drug dosing date is missing, the following rules will be followed:

- If the study drug is permanently withdrawn, 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.
- If the study drug completion status is unknown, the earlier of the date of death or database lock date for analysis will be used.

The total duration of exposure to study drug will be summarized using descriptive statistics and using the number and percentage of subjects exposed for at least 1 day, 1, 2, 3, 4, 6, 9, 12 months, and every 6 months thereafter.

The number and percentage of subjects who have dose modification or dose interruption will also be summarized.

4.2.2. Adherence to Study Drug

By-subject listings of ENTO administration, accountability (dispenses and returns), and dose interruption/modification will be provided by subject ID number (in ascending order) and visit (in chronological order).

4.3. Protocol Deviations

Subjects who do not meet the eligibility criteria for study entry but are enrolled in the study will be summarized regardless of whether they are exempted by the sponsor or not. The summary will present the number and percentage of subjects who do not meet at least 1 eligibility criterion and the number of subjects who do not meet specific criteria based on the All Enrolled Analysis Set. A by-subject listing will be provided for those subjects who do not meet at least 1 eligibility (inclusion or exclusion) criterion. The listing will present the eligibility criterion (or criteria if more than 1 deviation) that subjects do not meet and related comments, if collected.

Protocol deviations occurring after subjects enter the study are documented during routine monitoring. The number and percentage of subjects with important protocol deviations by deviation reason (eg, nonadherence to study drug, violation of select inclusion/exclusion criteria) will be summarized for the All Enrolled Analysis Set. A by-subject listing will be provided for those subjects with important protocol deviation.

5. BASELINE CHARACTERISTICS

5.1. Demographics

Subject demographic variables (ie, age, sex, race, and ethnicity) and baseline characteristics (body weight [in kg], height [in cm], body mass index [BMI; in kg/m^2]) will be summarized using descriptive statistics for continuous variables and using number and percentage of subjects for categorical variables. The summary of demographic data will be provided for the FAS.

A by-subject demographic listing, including the informed consent date, will be provided by subject ID number in ascending order.

5.2. Other Baseline Characteristics

Other baseline characteristics include Karnofsky performance status and creatinine clearance (mL/min). These baseline characteristics will be summarized using descriptive statistics for continuous variables and using number and percentage of subjects for categorical variables. The summary of these baseline characteristics will be provided for the FAS. No formal statistical testing is planned.

A by-subject listing of other baseline characteristics will be provided by subject ID number in ascending order.

5.3. Medical History

Medical history will be collected at screening for the disease-specific and general conditions (ie, conditions not specific to the disease being studied).

Disease-specific medical history will be summarized by the number and percentage of subjects with each prepopulated condition. The summary will be provided for the FAS. No formal statistical testing is planned. Time since diagnosis (years) will be calculated by (date of the first dosing date of study drug date of diagnosis)/365.25. Time since diagnosis will be summarized using summary statistics for a continuous variable. Disease stage at diagnosis and at screening will be summarized using summary statistics for a categorical variable. No formal statistical testing is planned. A by-subject listing of disease-specific medical history will be provided by subject ID number in ascending order.

In deriving the time since diagnosis, all partial dates of diagnosis and last regimen will be identified, and the partial dates will be imputed as follows:

- If day and month are missing but year is available, then the imputed day and month will be 01 Jan.
- If day is missing but the month and year are available, then the imputed day will be the first day of the month.
- Partial date will not be imputed if the year is missing.

General medical history data will not be coded but will be listed only. A by-subject listing of general medical history will be provided by subject ID number in ascending order.

5.4. Prior Anticancer Therapy

Number of prior regimens and time since the completion of the last regimen will be summarized using descriptive statistics based on the FAS. A partial completion date will be imputed using the algorithm defined in Section 5.3.

For the cohorts of CLL after BCR Targeted Therapy, prior BCR therapy, time since treatment failure, treatment failure reason, and best clinical response will be summarized.

A by-subject listing of prior anticancer therapy will be provided by subject ID number in ascending order.

6. EFFICACY ANALYSES

6.1. Primary Efficacy Endpoint

6.1.1. Definition of the Primary Efficacy Endpoint

The primary efficacy endpoint of this study is PFS rate at 16 weeks (CLL after BCR targeted therapy, MCL, and DLBCL) or 24 weeks (CLL and iNHL). PFS is defined as the interval from the first dose of ENTO to the earlier of the first documentation of definitive disease progression or death from any cause.

The determination of NHL response and progression (defined in the Protocol Section 6.20) is based on standardized criteria {Cheson 2007, Rourke 2010} as specifically modified for this study to reflect the biology of the diseases under study and the pharmacology of ENTO and the methods to be used in evaluation. The determination of CLL response and progression (defined in the Protocol Section 6.21) is based on standardized IWCLL criteria {Hallek 2008} as specifically modified for this study considering the pharmacology of ENTO and the methods to be used in evaluation.

In accordance with the Gilead Protocol 339-0102 Imaging Charter, if there is uncertainty regarding whether there is true progression, the subject may continue study treatment and remain under close observation (eg, evaluated at 4-week intervals). If subsequent evaluations suggest that the subject is experiencing progression, then the date of progression should be the time point at which progression was first identified. A single PD determination followed by a determination that indicated either no change or improvement in disease prior to the single PD observation will not be considered as PD.

Subjects without progression or death will be censored at the last adequate post-baseline tumor assessment time. If subjects receive other anti-cancer therapy or have ≥ 2 consecutive missing post-baseline tumor assessments immediately before documented progression or death, they will be censored at the last adequate post-baseline tumor assessment time before starting anti-cancer therapy or before ≥ 2 consecutive missing tumor assessments whichever is earlier. If subjects don't have adequate baseline tumor assessment or adequate post-baseline tumor assessment, they will be censored on the date of Study Day 1 unless subjects die before or on the 2nd scheduled post-baseline tumor assessment without receiving other anti-cancer therapy. Please see Appendix 2 for details on PFS event and censoring time derivation.

The findings of the IRC will be considered primary for analyses of PFS rate. The findings of investigator assessment will be provided in the listing.

6.1.2. Analysis of the Primary Efficacy Endpoint

The primary analysis of PFS will be performed using the Kaplan-Meier (KM) method based on IRC response assessments for the FAS. Medians, Q1, Q3 of the PFS distributions, and the proportion of subjects who are progression-free at Week 16 (for CLL after BCR targeted therapy, MCL, and DLBCL) and Week 24 (for CLL and iNHL) from the first dosing date will be

provided along with corresponding 95% confidence intervals (CIs). The loglog transformation will be used to compute the CIs.

PFS rate of the CLL prior BTK inhibitor exposure and CLL prior PI3K inhibitor exposure cohorts will be estimated separately. PFS rate of the CLL dose ranging cohort will be estimated by dose levels.

6.2. Secondary Efficacy Endpoint

6.2.1. Definition of Secondary Efficacy Endpoints

Same as the primary efficacy endpoint analysis, the response assessments by IRC will be used for the secondary efficacy endpoints' analyses based on the FAS. The response assessments after other anti-cancer therapy (if they are available) won't be included for secondary efficacy endpoints analyses.

- Objective response rate (ORR).

Best overall response (BOR) of complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD), not evaluable (NE), no disease (ND), and not applicable (NA) is allowed. For subjects with LPL/WM, a very good partial response (VGPR) or minor response (MR) is also allowed. Again, a single PD determination followed by a determination that indicated either no change or improvement in disease prior to the single PD observation will not be considered as PD.

ORR is defined as the proportion of subjects with BOR during ENTO therapy of CR or PR (or VGPR or MR for subjects with LPL/WM). Subjects who do not have sufficient baseline tumor assessment, whose on-study tumor status information is not adequate for response status assessment or who received new anti-cancer therapy prior to achieving CR or PR (or VGPR or MR for subjects with LPL/WM), will be considered as non-responders.

- Duration of response (DOR).

DOR is defined as the interval from the first time when the objective response (CR or PR [or VGPR or MR for subjects with LPL/WM]) is achieved to the earlier of the first documentation of definitive disease progression or death from any cause.

- Time to response (TTR).

TTR is defined as the interval from the first dose of ENTO to the first time when the response (CR or PR [or VGPR or MR for subjects with LPL/WM]) is achieved.

6.2.2. Analysis Methods for Secondary Efficacy Endpoints

6.2.2.1. Objective Response Rate

ORR and 95% CIs will be summarized. The number and proportion of subjects whose best overall response were evaluated as CR, PR, VGPR, MR, SD, PD, NE, ND, and NA will also be tabulated.

Both IRC and investigator's response assessments will be presented in by-subject listings.

6.2.2.2. Duration of Response

DOR analysis will be conducted in the responding subjects of FAS set. Responding subjects are those who achieve a CR or PR (or VGPR/MR for LPL/WM subjects). The censoring rule is same as PFS analyses (see Appendix 2).

DOR will be summarized using the KM method. The KM estimates of the DOR survival function will be presented. The median of DOR will be provided along with the corresponding 95% CIs. Additionally, the Q1 and Q3 will also be provided. The log-log transformation will be used to compute the CIs.

6.2.2.3. Time to Response

TTR analysis will be conducted in the responding subjects in FAS. Responding subjects are those who achieve a CR or PR (or VGPR/MR for LPL/WM subjects). TTR will be summarized using descriptive statistics.

6.3. Changes from Protocol-Specified Efficacy Analyses

The study final CSR is determined in synoptic version. The sensitivity analyses will not be performed.

7. SAFETY ANALYSES

7.1. Adverse Events and Deaths

7.1.1. Adverse Event Dictionary

Clinical and laboratory adverse events (AEs) will be coded using the current version of MedDRA. System organ class (SOC), high-level group term (HLGT), high-level term (HLT), preferred term (PT), and lower-level term (LLT) will be provided in the AE dataset.

7.1.2. Adverse Event Severity

Adverse events are graded by the investigator as Grade 1, 2, 3, 4, or 5 according to CTCAE Version 4.03{U.S. Department of Health and Human Services 2010}. The severity grade of events for which the investigator did not record severity will be categorized as "missing" for tabular summaries and data listings. The missing category will be listed last in summary presentation.

Severity of adverse events will be determined by the investigator as mild, moderate, or severe. The severity of events for which the investigator did not record severity will be categorized as "missing" for tabular summaries and data listings. The missing category will be listed last in summary presentation.

7.1.3. Relationship of Adverse Events to Study Drug

Related AEs are those for which the investigator selected "Related" on the AE CRF to the question of "Related to Study Treatment." Relatedness will always default to the investigator's choice, not that of the medical monitor. Events for which the investigator did not record relationship to study drug will be considered related to study drug for summary purposes. However, by-subject data listings will show the 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 Adverse Events

Treatment-emergent adverse events (TEAEs) are defined as 1 or both of the following:

- Any AEs with an onset date on or after the study drug start date and no later than 30 days after permanent discontinuation of study drug

- Any AEs leading to premature discontinuation of study drug.

7.1.5.2. Incomplete Dates

If the onset date of the AE is incomplete and the AE stop date is not prior to the first dosing date of study drug, then the month and year (or year alone if month is not recorded) of onset determine whether an AE is treatment emergent. The event is considered treatment emergent if both of the following 2 criteria are met:

- The AE onset is the same as or after the month and year (or year) of the first dosing date of study drug, and

- The AE onset date is the same as or before the month and year (or year) of the date corresponding to 30 days after the date of the last dose of study drug

An AE with completely missing onset and stop dates, or with the onset date missing and a stop date later than the first dosing date of study drug, will be considered to be treatment emergent. In addition, an AE with the onset date missing and incomplete stop date with the same or later month and year (or year alone if month is not recorded) as the first dosing date of study drug will be considered treatment emergent.

In case when the AE onset date is incomplete and needs to be imputed, the following algorithm will be followed:

- If the 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.

- If the 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.

7.1.6. Summaries of Adverse Events and Deaths

Treatment-emergent AEs will be summarized based on the Safety Analysis Set.

7.1.6.1. Summaries of AE Incidence by Severity

The number and percentage of subjects who experienced at least 1 TEAE will be provided and summarized by SOC, and PT. For the AE categorizes described below, summaries will be provided by SOC, PT, and maximum severity (if applicable):

- TEAEs

- TEAEs of Grade 3 or higher

- TE treatment-related AEs

- TE Treatment-related AEs with Grade 3 or higher

- TE SAEs
- TE treatment-related SAEs
- TEAEs leading to discontinuation of study drug
- TEAEs leading to death
- TEAEs leading to dose interruption of study drug
- TEAEs leading to dose reduction of study drug

A brief, high-level summary of AEs described above will be provided by treatment group and by the number and percentage of subjects who experienced the above AEs.

Multiple events will be counted only once per subject in each summary. Adverse events will be summarized and listed first in alphabetic order of SOC and then by PT in descending order of total frequency within each SOC. For summaries by severity, the most severe severity will be used for those AEs that occurred more than once in a given subject during the study.

In addition to the above summary tables, TEAEs, TEAEs of Grade 3 or higher, TE treatment-related AEs, and TE SAEs will be summarized by PT only in descending order of total frequency.

In addition, data listings will be provided for the following:

- All AEs, indicating whether the event is treatment emergent
- All SAEs
- Deaths
- All AEs leading to death
- All AEs leading to discontinuation of study drug
- All AEs leading to dose interruption of study drug
- All AEs leading to dose reduction of study drug

7.1.6.2. Summary of Deaths

A summary (number and percentage of subjects) of deaths will be provided by presenting the following categories:

- All deaths
- Deaths within 30 days of the last dosing of study drug
- Deaths beyond 30 days of the last dosing of study drug

7.2. Laboratory Evaluations

Laboratory data collected during the study will be analyzed and summarized using both quantitative and qualitative methods. Summaries of laboratory data will be provided for the Safety Analysis Set and will include data collected up to the last dose of study drug plus 30 days for subjects who have permanently discontinued study drug, or all available data at the time of the database snapshot for subjects who were ongoing at the time of an interim analysis. The analysis will be based on values reported in conventional units. When values are below the LOQ, they will be listed as such, and the closest imputed value will be used for the purpose of calculating summary statistics as specified in Section 3.7. Hemolized test results will not be included in the analysis, but they will be listed in by-subject laboratory listings.

A by-subject listing for laboratory test results will be provided by subject ID number and visit in chronological order for hematology and serum chemistry separately. Values falling outside of the relevant reference range and/or having a severity grade of 1 or higher on CTCAE severity grade will be flagged in the data listings, as appropriate.

7.2.1. Graded Laboratory Values

CTCAE Version 4.03 will be used to assign toxicity grades (0 to 4) to laboratory results for analysis. Grade 0 includes all values that do not meet the criteria for an abnormality of at least Grade 1. For laboratory tests with 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 the central lab normal ranges with in-house macro. For 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 laboratory values will be listed.

7.2.1.1. Treatment-Emergent Laboratory Abnormalities

Treatment-emergent laboratory abnormalities are defined as values that increase at least 1 toxicity grade from baseline at any postbaseline time point, up to and including the date of last dose of study drug plus 30 days for subjects who permanently discontinued study drug, or the last available date in the database snapshot for subjects who were still on treatment at the time of an interim analysis. If the relevant baseline laboratory value is missing, any abnormality of at least Grade 1 observed within the time frame specified above will be considered treatment emergent.

7.2.1.2. Summaries of Laboratory Abnormalities

The following summaries (number and percentage of subjects) for laboratory abnormalities will be provided by lab test:

- Baseline grade (Grade 0 to 4 separately, Grade 3 or 4, Grade 1 to 4, and Missing)
- Worst treatment-emergent laboratory abnormalities postbaseline grade (Grade 1 to 4 separately, Grade 3 or 4, and Grade 1 to 4)

The summary of the baseline abnormalities will use the number of subjects in the Safety Analysis Set as the denominator. The summary of the worst treatment-emergent laboratory abnormalities postbaseline is the number of subjects with nonmissing postbaseline values up to 30 days after the last dosing date of the study drug.

A by-subject listing of treatment-emergent Grade 3 or 4 laboratory abnormalities will be provided by subject ID number and visit in chronological order. This listing will include all test results that were collected throughout the study for the lab test of interest, with all applicable severity grades displayed.

7.2.2. Shift in Relative to the Baseline

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

7.3. Body Weight and Vital Signs

A by-subject listing of body weight and vital signs will be provided by subject ID number and visit in chronological order. High or low values for vital signs will be flagged.

7.4. Prior and Concomitant Medications

Medications collected at screening and during the study will be coded using the current version of the World Health Organization (WHO) Drug dictionary.

7.4.1. Prior Medications

Prior medications are defined as any medications taken before a subject took the first study drug.

Prior medications will be summarized by Anatomical Therapeutic Chemical (ATC) drug class Level 2 and preferred name using the number and percentage of subjects for each treatment group and overall. A subject reporting the same medication more than once will be counted only once when calculating the number and percentage of subjects who received that medication. The summary will be ordered alphabetically by ATC medical class and then by preferred term in order of descending overall frequency within each ATC medical class. For drugs with the same frequency, sorting will be done alphabetically.

For the purposes of analysis, any medication with a start date prior to the first dosing date of study drug will be included in the prior medication summary regardless of when the stop date is. If a partial start date is entered the medication will be considered prior unless the month and year (if day is missing) or year (if day and month are missing) of the start date are after the first dosing date. Medications with a completely missing start date will be included in the prior medication summary, unless otherwise specified.

Summaries will be based on the Safety Analysis Set. No formal statistical testing is planned.

7.4.2. Concomitant Medications

Concomitant medications are defined as medications taken while a subject took study drug. Use of concomitant medications will be summarized by ATC drug class Level 2 and preferred name using the number and percentage of subjects for each treatment group. A subject reporting the same medication more than once will be counted only once when calculating the number and percentage of subjects who received that medication. The summary will be ordered alphabetically by ATC medical class and then by preferred term in descending overall frequency within each ATC medical class. For drugs with the same frequency, sorting will be done alphabetically.

For the purposes of analysis, any medications with a start date prior to or on the first dosing date of study drug and continued to be taken after the first dosing date, or started after the first dosing date but prior to or on the last dosing date of study drug will be considered concomitant medications. Medications started and stopped on the same day as the first dosing date or the last dosing date of study drug will also be considered concomitant. Medications with a stop date prior to the date of first dosing date of study drug or a start date after the last dosing date of study drug will be excluded from the concomitant medication summary. If a partial stop date is entered, any medication with the month and year (if day is missing) or year (if day and month are missing) prior to the date of first study drug administration will be excluded from the concomitant medication summary. If a partial start date is entered, any medication with the month and year (if day is missing) or year (if day and month are missing) after the study drug stop date will be excluded from the concomitant medication summary. Medications with completely missing start and stop dates will be included in the concomitant medication summary, unless otherwise specified. Summaries will be based on the Safety Analysis Set. No formal statistical testing is planned.

All 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.

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. Electrocardiogram (ECG) Results

Twelve (12)-lead ECGs reporting ventricular rate, PR, QRS, QT, and QTc intervals will be obtained at screening, safety monitoring visits and, if clinically indicated, during the course of the study.

ECG data including heart rate-corrected QT intervals (ie. corrected by Bazett's formula (QTcB) and Fridericia's formula (QTcF), will be presented in a by-subject listing sorted by subject ID number and exam date in chronological order. QTcB and QTcF will be derived as following formulas:

- Bazett formula: QTcB QT / $(RR)^{1/2}$
- Fridericia formula: QTcF QT / $(RR)^{1/3}$

where QT is measured in milliseconds, and RR 60/Heart Rate (beats/min).

A by-subject listing of ECG results will be provided by subject ID number and visit in chronological order.

7.6. Post Treatment Anti-Cancer Therapies

All post treatment anti-cancer therapies (other than those allowed per-protocol) will be provided in a by-subject listing sorted by subject ID number and administration date in chronological order.

A summary of post treatment anti-cancer therapies will not be provided.

7.7. Changes from Protocol-Specified Safety Analyses

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

8. PHARMACOKINETIC (PK) ANALYSES

Plasma samples will be collected for concentrations of ENTO at protocol specified time points. Concentration of ENTO in plasma will be determined using a validated bioanalytical assay.

8.1. Statistical Analysis Methods

8.1.1. Plasma Concentration

Individual subject concentration data will be listed and summarized using descriptive statistics. Summary statistics (n, mean, StD, coefficient of variation [%CV], median, min, max, Q1, and Q3) will be presented by time point. Moreover, the geometric mean, 95% CI of the natural log-transformed values will be presented.

Individual concentration data listings and summaries will include all subjects in PK Analysis Set. The sample size for each time point will be based on the number of subjects with nonmissing concentration data at that time point. The number of subjects with concentration BLQ will be presented for each time point. For summary statistics, BLQ values will be treated as 0 at predose and one-half of the lower LOQ for postdose time points.

The listing of PK plasma concentrations sampling details by subject including deviations in scheduled and actual draw time and procedures will be provided.

9. PHARMACODYNAMIC (PD) ANALSES

In the synoptic CSR, the following exploratory endpoints of PD will not be provided:

- CCI [redacted]
- [redacted]

10. REFERENCES

U.S. Department of Health and Human Services. Common Terminology Criteria for Adverse Events (CTCAE). Version 4.0 (Published: May 28, 2009). v4.03 (Published: June 14, 2010) NIH Publication No. 09-5410. 2010.

Cheson BD, Pfistner B, Juweid ME, Gascoyne RD, Specht L, Horning SJ, et al. Revised response criteria for malignant lymphoma. J Clin Oncol 2007;25 (5):579-86.

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.

Rourke M, Anderson KC, Ghobrial IM. Review of clinical trials conducted in Waldenstrom macroglobulinemia and recommendations for reporting clinical trial responses in these patients. Leuk Lymphoma 2010;51 (10):1779-92.

11. SOFTWARE

SAS® Software Version 9.4 or higher, 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. Schedule of Assessments

Study Phase	Screening	Cycle 1 (28 days)	Subsequent Cycles (28 days)	Safety Monitoring Visits	Tumor Response Assessments	Disease Progression or EOS[c]	30-Day Follow Up
Cycle Day	**Screening**	**1**	**1**	**Varies[a]**	**Q8 or 12 wks or 6 months[b]**	**N/A**	
Window	**-35**		**±2 days**	**±2 days**		**N/A**	
Study Assessments							
Informed Consent	X						
Medical History	X						
Physical Exam[d]	X	X	X	X		X	
Vital Signs[e]	X	X	X	X		X	
12-lead ECG	X			X			
Karnofsky Performance Status	X	X	X	X		X	
Prior/Concomitant Meds	X	X	X	X		X	
AEs[f]	X	X	X	X		X	X
CT or MRI	X[g]				X[h]	X[i]	
Bone Marrow Biopsy and Aspirate					X[j]	X[j]	
DLBCL Subtyping[k]		X					
Collect Archival Tumor Tissue (if available)		X[l]					
Complete Subject/Visit info in IxRS	X	X	X			X	

Study Phase	Screening	Cycle 1 (28 days)	Subsequent Cycles (28 days)	Safety Monitoring Visits	Tumor Response Assessments	Disease Progression or EOS[c]	30-Day Follow Up
Cycle Day	**Screening**	**1**	**1**	**Varies[a]**	**Q8 or 12 wks or 6 months[b]**	**N/A**	
Window	**-35**		**±2 days**	**±2 days**		**N/A**	
Sample Collection							
Chemistry	X	X	X[x]	X		X	
Beta-2-microglobulin		X	X			X	
Hematology	X	X	X[x]	X		X	
Coagulation	X	X	X[x]	X		X	
Urinalysis	X	X	X				
HBV, HCV and HIV Virology	X						
Pregnancy Test[n]	X	X	X	X		X	
GS-9973 Plasma Concentration[o, p, v]		X	X	X		X	
Buccal Swab[u]		X					
CCI							
Serum monoclonal IgM SPEP/IFE and cryoglobulin testing[q]		X			X		
Study Drug Dosing							
GS-9973 up to 800 mg BID Fasting or 100, 200 or 400 mg GS-9973 SDD BID Fasting		X				X	
Dispense Study Drug		X	X				
Study Drug Compliance[r]		X	X			X	
Collect Used/Unused Study Drug[w]			X			X	
For CLL, SLL and MCL subjects only							

Study Phase	Screening	Cycle 1 (28 days)	Subsequent Cycles (28 days)	Safety Monitoring Visits	Tumor Response Assessments	Disease Progression or EOS[c]	30-Day Follow Up
Cycle Day	**Screening**	**1**	**1**	**Varies[a]**	**Q8 or 12 wks or 6 months[b]**	**N/A**	
Window	**-35**		**±2 days**	**±2 days**		**N/A**	
Cytokines and Chemokines		X[m]	X[m]	X[m]		X	
CTC Molecular Characterization		X		X[s]		X	
CTC RNA[w]		X[w]	X[w]			X[w]	
CLL ONLY: Pharmacodynamic Measurements (BAT Assay)		X[t]					
CLL ONLY: Pharmacogenomic Testing		X		X[s]		X	

a Days 8, 15, and 22 of Cycle 1 and Day 15 of Cycle 2

b Tumor assessments will be performed every 8 weeks during the first 24 weeks of the study and then every 12 weeks thereafter regardless of cycle number and regardless of dose interruptions. Tumor assessments may be performed at other timepoints during the treatment phase as clinically indicated (to assess tumor progression). After week 72 scans will occur at least every 6 months (± 4 weeks). The same evaluation procedures must be used throughout the study for each subject. Scans should be of high quality and digitalized in the DICOM format to allow for reading at a centralized facility.

c If a subject stops study drug for a reason other than progressive disease and consistent with good medical practice, they will be followed as per the scheduled imaging in Section 6.5 with additional CBC (hematology) at time of assessments.

d Complete physical examination will be performed at Screening and at Disease Progression or EOS. A modified physical examination capturing changes from prior exams will be performed at other visits. Weight should be measured (in kilograms) at each physical examination. Height will be measured (in centimeters) at Screening only.

e Vital signs (including blood pressure, respiratory rate, pulse, oxygen saturation by pulse oximetry and temperature) should be taken after the subject has been sitting for at least 5 minutes.

f Adverse events will be assessed once ICF is signed, pre and post dose during applicable clinic visits, and 30 (±7) days following completion of the subject's last dose of study drug. Subjects should be contacted by phone (or in person, if necessary) 30 days (± 7 days) after the subject's last dose of study drug to assess AEs. Subjects should specifically be asked about the development of any adverse events since stopping the study.

g CT or MRI scans of neck, chest, abdomen, and pelvis taken as part of standard medical practice up to 35days prior to Day 1 of Cycle 1 visit are acceptable for use at the Screening. Subjects with LPL/WM who previously failed screening for this study, due to an absence of lymphadenopathy on CT or MRI scans, do not need to be re scanned if the scans were performed within 16 weeks of first study drug administration to meet eligibility criteria.

h At all timepoints after Screening imaging of the chest, abdomen, and pelvis will be required. Imaging of the neck is required at each follow up time point if the neck scan was positive at baseline or if palpable neck lymphadenopathy appears during the course of the study.

i Tumor evaluations should be conducted at the End of Study Visit if not conducted in the previous 4 weeks. If a subject permanently discontinues study drug prior to objective documentation of progression, investigators should continue further follow up at the ~8 or ~12 week intervals until progression is documented.

j A bone marrow biopsy and aspirate will be collected for all subjects who achieve a CR for confirmatory purpose. For CLL subjects a bone marrow biopsy/aspirate will be collected to confirm a 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 bone marrow biopsy/aspirate (See Sections 6.18 and 6.20).

k If the subject has DLBCL, subtyping is required. Submission of 15 unstained slides is required for subtyping if the subtype is not already known. Subjects for whom tissue is not available but the subtype is already known may be included if approved by the Medical Monitor following discussion with the investigator.
l Fifteen recently prepared unstained slides from archival tumor tissues will be collected. Efforts to acquire tissue sample should begin on Day 1 of Cycle 1.
m Collect on Cycle 1 Day 1, Cycle 1 Day 8, Cycle 2 Day 1 and Cycle 12, Day 1 only
n For females of childbearing potential, a serum pregnancy test will be performed at Screening and urine pregnancy tests will be performed on Days 1 of each Cycle and Day 15 of Cycles 1 & 2 and at EOS.
o Record the approximate number of hours between the last 2 doses of GS 9973 and the time the blood samples for plasma concentration were obtained
p GS 9973: PK samples will be collected on Day 1 of Cycle 1 pre dose, 1.5 hours post dose and 4 hours post dose; on Day 1 of Cycles 2 6 pre dose (12 hours post last dose).
q GS 9973 SDD: PK samples will be collected on Day 1 of Cycle 1 pre dose, 1.5 hours post dose and 4 hours post dose; on Day 8 of Cycle 1 pre dose, 1.5 hours post dose and 4 hours post dose; on Days 15 and 22 of Cycle 1 pre dose and 1.5 hours post dose; and on Day 1 of subsequent cycles pre dose and 1.5 hours post dose.
r Subjects with LPL/WM only. This procedure should be conducted on the Day 1 visit occurring during the week window allotted for tumor response assessments.
s Includes date/time of last dose of GS 9973 (excluding Day 1 of Cycle 1)
t Collect on Cycle 2, Day 15 only
u On Day 1 of Cycle 1, samples will be collected pre dose, 1.5 hours post dose (± 10 minutes) and 4 hours post dose ((± 10 minutes); on cycle 1 day 8 (predose and 4 hours post dose) and cycle 1 day 15 (predose)
v For CLL dose ranging, CLL prior BTK inhibitor exposure, or CLL prior PI3K inhibitor exposure cohorts only
w Excluding subjects off study drug at time of progression
x Samples will be collected pre dose on Cycle 1 Day 1, Cycle 12 Day 1 and at Disease Progression or EOS only
y May be collected up to 2 days prior to the Day 1 visit

Appendix 2. PFS Definition and Derivation Diagram

Progression-free survival (PFS) is defined as the interval from the first dosing date of study drug to the earlier of the first documentation of definitive disease progression or death from any cause.

Definitive disease progression for NHL is defined in the Protocol Section 6.20 based on standardized criteria {Cheson 2007, Rourke 2010} as specifically modified for this study to reflect the biology of the diseases under study and the pharmacology of study drug and the methods to be used in evaluation. The determination of CLL response and progression is defined in the Protocol Section 6.21 based on standardized IWCLL criteria {Hallek 2008} as specifically modified for this study considering the pharmacology of ENTO and the methods to be used in evaluation. The progression should be identified by relevant radiographic imaging assessments and pertinent clinical data by IRC and investigators. For this study, the IRC assessments will be used as primary PFS analyses. The date of definitive progression will be the time point at which progression is first identified. The death from any cause to be considered as PFS event should occur within the time window of 2 consecutive scheduled post-baseline tumor assessments after the last tumor assessment.

Subjects without progression or death will be censored at the last adequate post-baseline tumor assessment time. The adequate tumor assessments for determining censoring dates include complete response (CR), partial response (PR), minor response (MR), stable disease (SD), progressive disease (PD), and very good partial response (VGPR) or minor response (MR) for subjects with LPL/WM. Non-evaluable (NE), not assessed, and not applicable are considered as not adequate.

Subjects will be censored on the date of Study Day 1 if

- no adequate baseline tumor assessment is available and subject didn't die before or on the 2nd scheduled post-baseline tumor assessment without receiving anti-cancer therapy;
- or if no adequate post-baseline tumor assessment is available and subjects didn't die
- or if no adequate post-baseline tumor assessment is available and subjects died after the 2nd scheduled tumor assessment.

Subjects will be censored on the date of last adequate post-baseline tumor assessment, or Study Day 1 if the last adequate post-baseline tumor assessment doesn't exist, for the following situations:

- who do not have documented progression or die, or
- who start new anti-cancer therapy before documented progression, or
- who start new anti-cancer therapy before death without documented progression, or
- who have ≥ 2 consecutive missing post-baseline tumor assessments immediately before documented progression, or

- who have ≥ 2 consecutive missing post-baseline tumor assessments immediately before death without documented progression

Table 13-1 below lists detailed event/censoring scheme for PFS derivation and the derivation diagram lists all decisions on event/censoring indicators and time.

Table 13-1. Event/Censoring Scheme of Analysis for PFS

PFS Derivation Step	Situation	Date of Progression or Censoring	Outcome
1	No adequate baseline tumor assessments and subjects didn't die before or on the 2nd scheduled post-baseline tumor assessment	Study Day 1*	Censored
1	No adequate baseline tumor assessments and subjects died before or on the 2nd scheduled post-baseline tumor assessment without receiving anti-cancer therapy	Date of death	Event
1	No adequate baseline tumor assessments, subjects died before or on the 2nd scheduled post-baseline tumor assessment and received anti-cancer therapy	Study Day 1*	Censored
2	No adequate post-baseline tumor assessments and subjects did not die	Study Day 1	Censored
2	No adequate post-baseline tumor assessments and subjects died after the 2nd scheduled post-baseline tumor assessment	Study Day 1	Censored
2	No adequate post-baseline tumor assessments and subjects died before or on the 2nd scheduled post-baseline tumor assessment without receiving anti-cancer therapy	Date of death	Event
2	No adequate post-baseline tumor assessments, subjects died before the 2nd scheduled post-baseline tumor assessment and received anti-cancer therapy	Study Day 1	Censored
3	Documented progression and didn't receive anti-cancer therapy or have ≥ 2 consecutive missing post-baseline tumor assessments immediately before documented progression	Date of the first documented progression	Event
3	Death without progression and within the time window of 2 consecutive scheduled post-baseline tumor assessments after the last tumor assessment and didn't receive anti-cancer therapy or have ≥ 2 consecutive missing post-baseline tumor assessments immediately before death	Date of death	Event
3	No documented progression or death and didn't receive anti-cancer therapy or have ≥ 2 consecutive missing post-baseline tumor assessments	Date of the last adequate post-baseline tumor assessment	Censored

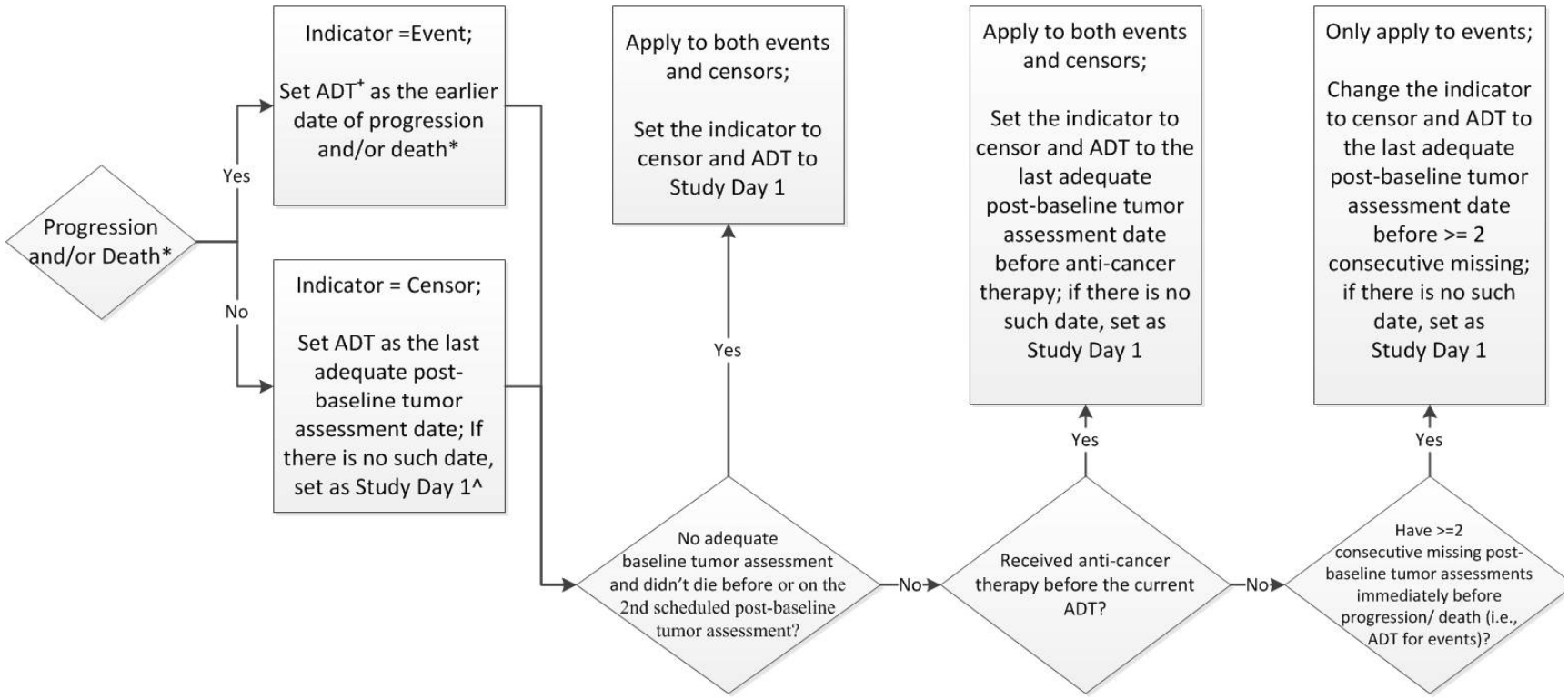
PFS Derivation Step	Situation	Date of Progression or Censoring	Outcome
4	Start new anti-cancer therapy without or before documented progression or death or have ≥ 2 consecutive missing post-baseline tumor assessments immediately before documented progression or death	The later one of 1) Date of the last adequate post-baseline tumor assessment on/prior to the new anti-cancer therapy start date and/or the consecutive missing 2) Study Day 1	Censored

* Study Day 1 is the day of first dose of study drug administration.

When the date of initiation of anti-cancer therapy other than the study treatment is incomplete or missing, the following algorithm will be followed:

- If the day is missing but the month and year are available, then the imputed day will be the first day of the month.
- If day and month are missing but year is available, then the imputed day and month will be 01Jan or the last day of the month for the last adequate disease assessment if they have the same year, whichever is later.

Progression Free Survival Derivation Diagram



* Death should occur within the time window of 2 consecutive scheduled post-baseline tumor assessments from the last tumor assessment.

+ ADT: Analysis date

^ Study Day 1 is the randomization date of the randomized studies, or the 1st dosing date of the non-randomized studies.

GS-US-339-0102 CSR Statistical Analysis Plan_v1.0

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy hh:mm:ss)
PPD	Clinical Research eSigned	17-Sep-2019 17:37:29
PPD	Biostatistics eSigned	17-Sep-2019 21:25:26