STATISTICAL ANALYSIS PLAN

Study Title:	A Phase 1b/2 Open-Label, Dose Escalation and Expansion Study Evaluating the Safety and Efficacy of Entospletinib (GS-9973) with Vincristine and Dexamethasone in Adult Subjects with Relapsed or Refractory Acute Lymphoblastic Leukemia (ALL)
Name of Test Drug:	Entospletinib (ENTO)
Study Number:	GS-US-339-1560
Protocol Version (Date):	Amendement 5
Protocol Date:	13 April 2018
Analysis Type:	Final
Analysis Plan Version:	Version 1.0
Analysis Plan Date:	03 December 2018
Analysis Plan Author:	PPD

CONFIDENTIAL AND PROPRIETARY INFORMATION

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LIST OF ABBREVIATIONS

AE	adverse event
ALL	acute lymphoblastic leukemia
ATC	Anatomical-Therapeutic-Chemical classification
BID	bis in die (twice a day)
BLQ	below the limit of quantitation
BMI	body mass index
CBC	complete blood count
CLL	chronic lymphocytic leukemia
cm	centimeter
CNS	central nervous system
CR	complete remission
CRi	Morphologic CR with incomplete blood count recovery
CRO	contract research organization
CRF	case report form
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DDI	drug-drug interaction
DLT	Dose limiting toxicities
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form(s)
EFS	event-free survival
EMD	extramedullary disease
ENTO	entospletinib
EOS	end of study
EOT	end of treatment
FAB	French-American-British
FAS	full analysis set
FDA	(United States) Food and Drug Administration
g	gram
GCP	Good Clinical Practice (Guidelines)
Gilead	Gilead Sciences, Inc.
HLGT	high-level group term
HLT	high-level term
HSCT	hematopoietic stem cell transplant
ID	identification
ICH	international conference on harmonisation
IV	intravenous
kg	kilogram

LLT	lower-level term
LOQ	lower limit of quantitation
mg	milligram
MedDRA	Medical Dictionary for Regulatory Activities
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NIH	National Institutes of Health
OS	overall survival
PK	pharmacokinetic(s)
PR	partial remission
PT	preferred term
PVE	Pharmacovigilance and Epidemiology
Q1	first quartile
Q3	third quartile
RFS	relapse-free survival
SAE	serious adverse event
SAP	statistical analysis plan
SE	standard error
SOC	system organ class
SOP	standard operating procedure
StD	standard deviation
Syk	Spleen tyrosine kinase
TEAE	treatment emergent adverse event
TFL	tables, figures and listings
uL	microliter
ULN	upper limit of the normal range
US	United States
VCR	vincristine
WHO	World Health Organization

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-339-1560. This SAP is based on the study protocol GS-US-339-1560 Amendment 5 dated 13 April 2018 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.

The study was originally designed to evaluate the safety, efficacy, tolerability, and pharmacokinetics (PK) of entospletinib (ENTO) in combination with vincristine (VCR) and dexamethasone in 2 stages: (1) Phase 1b dose-escalation; (2) Phase 2 expansion for relapsed or refractory Acute Lymphoblastic Leukemia (ALL). However, due to the low response rate to ENTO in combination with VCR and dexamethasone in Phase 1b portion, the Sponsor has decided to not proceed with the Phase 2 portion of this study. Subjects currently on study will continue to be treated and/or followed until the end of study criteria are met. A synoptic CSR will be generated, and this SAP describes the analyses for Phase 1b only.

1.1. Study Objectives

1.1.1. Primary Objectives

- To evaluate safety of ENTO in combination with VCR and dexamethasone in adult subjects with previously treated relapsed or refractory B-cell lineage ALL

1.1.2. Secondary Objectives

- To determine the recommended dose of ENTO in combination with VCR and dexamethasone in adult subjects with previously treated relapsed or refractory B-cell lineage ALL

- To evaluate the therapeutic response of ENTO in combination with VCR and dexamethasone in adult subjects with previously treated relapsed or refractory B-cell lineage ALL

1.1.3. Exploratory Objectives

1.2. Study Design

This is an open-label, Phase 1b dose-escalation and Phase 2 expansion study evaluating the safety, efficacy, tolerability, and PK of ENTO in combination with VCR and dexamethasone.

The study was originally designed for 2 stages sequentially: (1) Phase 1b dose escalation; (2) Phase 2 expansion. However, due to the low response rate to ENTO in combination with VCR and dexamethasone in Phase 1b portion, per the Sponsor's decision, it has been decided not to proceed with the dose expansion (ie, Phase 2) portion of this study.

There are four dose levels in the dose escalation phase (Table 1-1) where subjects in cohorts of 3 to 6 are sequentially enrolled into one of the dose levels using a 3+3 dose escalation design (Table 1-2). The starting dose level for the first cohort is defined as Dose Level 1.

Table 1-1 Entospletinib/Vincristine Dose Escalation

Dose Level	Entospletinib (ENTO)	Vincristine (VCR)
1	200 mg BID	0.5 mg per dose
2	400 mg BID	0.5 mg per dose
3	400 mg BID	1 mg per dose
4	400 mg BID	2 mg per dose

BID = twice per day

Dose Escalation: Induction (Lead-in, Cycle 1 and Cycle 2)

Lead-in (ENTO Monotherapy): Beginning on Day -7 of Lead-In, ENTO will be administered orally twice daily (BID) for 7 days as a single agent.

Cycle 1 and Cycle 2 (ENTO, VCR, dexamethasone, CNS prophylaxis)

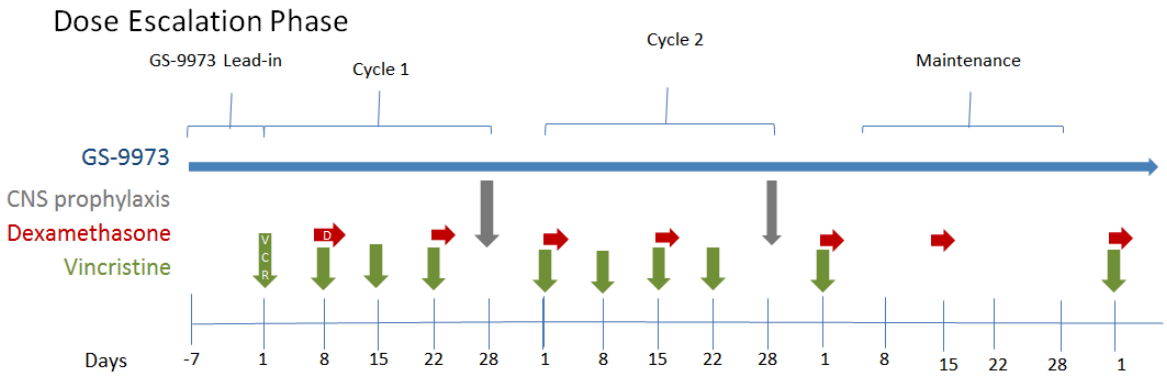
ENTO will be continuously administered orally BID in combination with chemotherapy for the duration of the study treatment.

VCR will be administered on Days 1, 8, 15 and 22 of each 28-day cycle for Cycle 1 and 2 only.

Dexamethasone (20 mg twice daily for 4 days) will be administered orally during Cycle 1 on Days 8-11 and Days 22-25 and during Cycle 2 on Days 1-4 and Days 15-18.

CNS prophylaxis per institutional standard will be given on Day 28 (±3 days) of Cycle 1 and Cycle 2.

Dose Escalation treatment schedule is outlined in the schema below:



Bone marrow (BM) aspirate/biopsy will be performed during screening (within 28 days prior to the start of study treatment), Cycle 1 on Day 8 and during both Cycle 1 and Cycle 2 on Day 28.

Imaging (computerized tomography [CT] with contrast or Positron Emission Tomography (PET) scan should be performed for subjects with extramedullary disease (EMD) if these are the only sites of evaluable disease (no BM involvement) to evaluate disease status and response, at screening, Cycle 1 Day 8 and Day 28, and Cycle 2 Day 28. Imaging will be evaluated using the NCCN guidelines version 2.2016 (Patients with no BM involvement and only EMD will not require BM aspirate/biopsy on cycle 1 day 8 and day 28, and cycle 2 day 28).

Up to 6 subjects will be dosed per dose level. Dose escalation will be performed based on assessments of Dose Limiting Toxicities (DLTs) and other adverse events data obtained within the DLT window (ENTO Lead-in and Cycle 1; study day 1 through day 35). Subjects with complete remission (CR), morphologic CR with incomplete blood count recovery (CRi), or partial remission (PR) on Day 28 of Cycle 1 bone marrow, and /or subjects who in the investigator's opinion have obtained clinical benefit from Cycle 1 induction, will continue to Cycle 2 of induction.

During the DLT assessment window, subjects who fail to complete 21 days of GS-9973 or fail to receive sufficient exposure (> 50% of planned total dose) to VCR and dexamethasone for reasons other than treatment-related toxicity will not be evaluable for DLT assessment and an additional (replacement) subjects may be enrolled to that dose level in order to provide adequate safety data for dose escalation decisions.

Decision to open the next higher dose level to enrollment or expand the current cohort will be determined by the sponsor in consultation with study Principal Investigators (PIs).

The maximum tolerated dose (MTD) is defined as the highest tested dose associated with an observed DLT rate of < 33% during the DLT window. A minimum of 6 subjects need to be treated at a dose level before this dose level can be determined as MTD or recommended dose.

Table 1-2 Dose Escalation/DLT Guidelines

Number of subjects with DLT at a given level	Escalation Decision Rule
0 out of 3	Enroll 3 subjects at the next higher dose level. If this dose level is the highest dose level, it will be declared the maximally administered dose, and enroll 3 additional subjects at this dose level.
1 out of 3	Enter 3 additional subjects at this dose level. If 0 of these 3 subjects experience DLT, proceed to the next higher dose level. If 1 or more of them experience DLT, then dose escalation is stopped, and this dose is declared the maximally administered dose. Three additional subjects will be entered at the next lower dose level if only 3 subjects were treated previously at that dose.
≥ 2 out of 3	Dose escalation will be stopped. This dose level will be declared the maximally administered dose (highest dose administered). Three additional subjects will be entered at the next lower dose level if only 3 subjects were treated previously at that dose.
≤1 out of 6 at highest dose level below the maximally administered dose	This is the maximum tolerated dose (MTD) and generally the recommended dose. At least 6 subjects must be enrolled at MTD or the recommended dose.

Maintenance:

It is anticipated that most subjects who are transplant eligible will receive hematopoietic stem cell transplant (HSCT) therapy with curative intent if a CR is reached. In the absence of a suitable alternative therapeutic option, subjects who obtain clinical benefit (at least PR) after completing both cycles of induction therapy in dose escalation may continue ENTO at the assigned dose level during maintenance for up to 36 cycles. Subjects will continue ENTO and VCR at their assigned dose. ENTO will continue to be taken orally twice daily with VCR to be administered on Day 1 of each 28-day cycle and dexamethasone 20 mg total dose daily (either a divided dose of 10 mg twice daily or a single dose of 20 mg once daily) on Days 1-4 and Days 15-18 of each 28-day cycle.

Bone marrow evaluations and additional central nervous system (CNS) directed therapy can be performed as clinically indicated during maintenance.

1.3. Sample Size and Power

The study implements 3+3 design. Sequential dose-escalation is consistent with usual oncologic paradigms for dose ranging. The intent is to limit the number of subjects who are exposed to excessively toxic doses of a drug in an early phase evaluation of an anticancer agent. The trial employs the standard National Cancer Institute (NCI) definition of MTD (starting dose associated with DLT in < 33.3% of subjects during the DLT assessment window) to determine

dose escalation. The cohort size and dose-escalation rules establish a low probability of increasing the dose if the true rate of DLT is high while there is a high likelihood of escalating or proceeding to the next cohort of the study if the true underlying probability of DLT is low. Table 1-3 shows the probability of escalating to the next dose level or proceeding to the next stage, based on the true rate of DLT at the current dose level. If the true underlying probability of DLT is low (eg, < 10%) at the current dose level, there is a high probability (> 0.91) of dose escalation to the next dose level. Conversely, if the true underlying proportion of DLT is high (eg, > 60%) at the current dose level, there is a low probability (< 0.08) of escalation to the next dose level.

Table 1-3 Probability of Dose Escalation (N=3+3)

True Incidence of DLT	Probability of Escalating
10%	0.91
20%	0.71
30%	0.49
40%	0.31
50%	0.17
60%	0.08

Assuming that 4 planned dose levels are tested for escalation and 3, 3, 6 and 6 subjects are tested at each dose level, respectively (18 subjects for escalation), and assuming 10% subjects are not evaluable during dose escalation, 20 subjects will be enrolled during dose escalation.

2. TYPE OF PLANNED ANALYSIS

2.1. Interim Analysis

No formal interim analyses are planned in this study. The GSI study team and the investigators will collectively discuss study conduct and accumulating safety and other data.

2.2. Final Analysis

Final study reporting is expected to occur after all subjects have discontinued the study.

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 Full Analysis Set and sorted by subject identification (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. The analysis set will be identified and included as a subtitle of each table, figure, and listing.

3.1.1. All Enrolled Analysis Set

The All Enrolled Analysis Set includes all subjects who receive a study identification number in the study after screening.

3.1.2. Full Analysis Set

The Full Analysis Set (FAS) includes all subjects who receive at least 1 dose of study treatment.

This analysis set will be used in the analyses of subject characteristics and efficacy.

3.1.3. Safety Analysis Set

The Safety Analysis Set includes all subjects who receive at least 1 dose of study treatment.

This analysis set will be used in the drug exposure and safety analyses.

3.1.4. Dose-Limiting Toxicity Analysis Set

Dose-Limiting Toxicity (DLT) Analysis Set includes all subjects in the Safety Analysis Set who meet at least one of the following criteria:

- Receive at least 21 days of ENTO, >50% of planned total dose of VCR and dexamethasone during the DLT assessment window (refer to Section 1.2)
- Experience a DLT during the DLT assessment window

This analysis set will be used for analyses related to DLT.

3.1.5. Pharmacokinetic (PK) Analysis Sets

The Pharmacokinetic Analysis Sets include all enrolled subjects who took at least 1 dose of study drug and have at least 1 nonmissing postdose concentration value reported by the PK laboratory. This is the primary analysis set for all PK analyses.

This analysis set will be used in the analysis of ENTO plasma pharmacokinetic.

3.2. Subject Grouping

Unless otherwise specified, subjects will be grouped by dose level and overall for all analyses.

3.3. Strata and Covariates

Not applicable.

3.4. Examination of Subject Subsets

Not applicable.

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 medication 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

In general, age (in years) on the first dosing date of study drug will be used for analyses and presentation in listings. For enrolled subjects who are not dosed with any study drug, the enrollment date will be used instead of the first dosing date of study drug. For screen failures, the date the informed consent was signed will be used for age calculation. If only the birth year is collected on the CRF, “01 July” will be used for the unknown birth day and month for the purpose of age calculation. If only birth year and month are collected, “01” will be used for the unknown birth day.

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).

Plasma 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 pre-dose time points, and one-half the value of the LOQ at post-baseline time points.

The following conventions will be used for the presentation of summary and order statistics:

- If at least 1 subject has a concentration value of BLQ for the time point, the minimum value will be displayed as "BLQ."

- If more than 25% of the subjects have a concentration data value of BLQ for a given time point, the minimum and Q1 values will be displayed as "BLQ."

- If more than 50% of the subjects have a concentration data value of BLQ for a given time point, the minimum, Q1, and median values will be displayed as "BLQ."

- If more than 75% of the subjects have a concentration data value of BLQ for a given time point, the minimum, Q1, median, and Q3 values will be displayed as "BLQ."

- If all subjects have concentration data values of BLQ for a given time point, all order statistics (minimum, Q1, median, Q3, and maximum) will be displayed as "BLQ."

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 treatment, unless otherwise specified.

3.8.2. Analysis Windows

The nominal visit as recorded on the CRF will be used when data are summarized by visit and no analysis window will be derived.

4. SUBJECT DISPOSITION

4.1. Subject Enrollment and Disposition

A summary of subject enrollment will be provided by dose level for each country and overall based on all enrolled subjects. 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 by dose level based on FAS. This summary will present the number and percentage of subjects in the following categories:

- ENTO discontinuation
  - — Reasons of ENTO discontinuation
- VCR discontinuation
  - — Reasons of VCR discontinuation
- Dexamethasone discontinuation
  - — Reasons of dexamethasone discontinuation
- CNS prophylaxis discontinuation
  - — Reasons of CNS prophylaxis discontinuation
- Included in the DLT analysis set
- Study discontinuation
  - — Reasons of study discontinuation

The denominator for the percentage calculation will be the total number of subjects in FAS corresponding to that column.

A data listing of all enrolled subject enrollment to describe the site, subject number, date of first and last dose and dose level of ENTO, analysis set inclusion (FAS and DLT analysis sets), reasons for all study drugs' discontinuation, and reasons for study discontinuation will be provided.

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 Drugs

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 weeks using up to 1 decimal place (eg, 4.5 weeks).

The duration of exposure to ENTO, VCR, dexamethasone, and CNS prophylaxis will be summarized respectively using descriptive statistics. Besides, the number and percentage of subjects exposed to each drug will be presented as follows:

- ENTO: at least 1 day, 14 days, 21 days, 28 days, and 2, 3, 6, 9 months, etc.
- VCR: Cycle 1, Cycle 2, Maintenance Cycle 1, Maintenance Cycle 2, etc.
- Dexamethasone: Cycle 1, Cycle 2, Maintenance Cycle 1, Maintenance Cycle 2, etc.
- CNS prophylaxis: Cycle 1, Cycle 2

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

4.2.2. Adherence (Compliance) with Study Drugs

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

4.3. Protocol deviations

Subjects who did not meet the eligibility criteria for study entry, but enrolled in the study will be identified regardless of whether they were exempted by the sponsor or not. A by-subject listing will be provided for those subjects who did 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 did not meet and related comments, if collected.

Protocol deviations occurring after subjects entered the study are documented during routine monitoring. A by-subject listing will be provided for those subjects with important protocol deviation.

5. BASELINE CHARACTERISTICS

The baseline characteristics will be presented by dose level and overall based on FAS.

5.1. Demographics

Subject demographic variables (ie, age, sex, race, and ethnicity) will be summarized using descriptive statistics for age, and using number and percentage of subjects for sex, race, and ethnicity.

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 body weight (in kg), height (in cm), body mass index (BMI; in kg/m^2), ECOG status, and cytogenetics. BMI will be calculated by the formula:

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

Other baseline characteristics will be summarized using descriptive statistics.

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 disease-specific and general conditions (ie, conditions not specific to the disease being studied). General medical history data will not be coded.

A by-subject listing of disease-specific (including hematologic malignancy type, date of initial diagnosis, and detailed diagnosis) and general medical history will be provided separately by subject ID number in ascending order.

5.4. Prior Anticancer Therapy

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

6. EFFICACY ANALYSES

Efficacy will be evaluated per the response criteria in NCCN guidelines on ALL Version 2, 2016. The major criteria for judging response will include physical examination and examination of blood and bone marrow. All laboratory studies that are abnormal prior to study will be repeated to document the degree of maximal response.

For subjects with extramedullary disease (EMD) if these are the only sites of evaluable disease (no BM involvement) to evaluate disease status and response, imaging (computerized tomography (CT) with contrast or positron emission tomography (PET)) should be performed. Imaging will be evaluated using NCCN guideline Version 2, 2016.

Clinical response will be evaluated with investigator assessments. All efficacy endpoints will be analyzed by dose level using FAS.

6.1. Primary Efficacy Endpoints

Not applicable.

6.2. Secondary Efficacy Endpoints

6.2.1. Definition of the Secondary Efficacy Endpoints

- Overall Remission (CR or CRi) rate at end of induction - defined as the proportion of subjects who achieve complete remission (CR) or complete remission with incomplete hematologic recovery (CRi) at the end of induction

- Complete remission (CR) rate at the end of induction - defined as the proportion of subjects who achieve CR at the end of induction

- Partial response (PR) rate at end of induction - defined as the proportion of subjects who achieve a partial response of marrow or by imaging criteria for patients with extramedullary disease (NCCN guidelines version 2.2016) as the best response

- Overall Response (CR, CRi, or PR) rate at end of induction - defined as the proportion of subjects who achieve a complete remission (CR), complete remission with incomplete hematologic recovery (CRi) or partial response (PR) at end of induction

6.2.2. Analysis Methods for Secondary Efficacy Endpoints

Overall Remission (CR/CRi) rate, CR rate, PR rate, and Overall Response rate (CR, CRi, or PR) on or prior to other anticancer therapy and HSCT (if there is) at the end of induction will be summarized by dose level and overall. The number and percentage of subjects will be presented.

A by-subject listing of response assessment and EMD assessment will be provided by subject ID number (in ascending order) and visit (in chronological order).

7. SAFETY ANALYSES

Safety analyses will be conducted using Safety Analysis Set, unless otherwise specified.

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 (ie, Version 20.1) of Medical Dictionary for Regulatory Activities (MedDRA). System organ class (SOC), high-level group term (HLGT), high-level term (HLT), preferred term (PT), and lower-level term (LLT) will be 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 toxicity criteria specified in the Common Toxicity Criteria for Adverse Events (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 and the missing category will be listed last in data presentation.

7.1.3. Relationship of Adverse Events to Study Drug

Related AEs are defined as AEs marked by investigators as 'Related' on the AE CRF to the questions of 'Related to Study Treatment GS-9973 SDD', 'Related to Study Treatment Dexamethasone', 'Related to Study Treatment Vincristine', 'Related to Study Treatment Cytarabine Arabinoside', and 'Related to Study Treatment CNS Prophylaxis'. Relatedness will always default to the investigator's choice, not that of the medical monitor. Events for which the investigator did not record relationships to study treatment will be considered related to study treatment for summary purposes. However, by-subject data listings will show the relationship as missing.

7.1.4. Serious Adverse Events (SAEs)

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 then Gilead Pharmacovigilance and Epidemiology (PVE) Department before data finalization.

7.1.5. Treatment-Emergent Adverse Events

7.1.5.1. Definition of Treatment-Emergent Adverse Events

AEs which meet at least one of the following criteria are defined as Treatment-Emergent Adverse Events (TEAEs):

- Any AEs with onset dates on or after the start of study treatment and up to 30 days after the permanent discontinuation of the study treatment
- Any AEs leading to permanent discontinuation of study treatment

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 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 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, HLT, PT, and treatment group. For other AEs described below, summaries will be provided by SOC, PT, and maximum severity:

- TEAEs
- TEAEs of Grade 3 or higher
- Treatment-related TEAEs by study drugs (ie ENTO, VCR, dexamethasone, CNS prophylaxis)
- Treatment-related Grade 3 or higher TEAEs by study drugs

- TE SAEs
- TE treatment-related SAEs by study drugs
- TEAEs leading to treatment discontinuation by study drugs
- TEAEs leading to treatment reductions or interruptions by study drugs
- TEAEs leading to death
- TEAEs leading to study discontinuations

A brief, high-level summary of AEs described above will be provided 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, data listings will be provided for the following:

- All AEs, indicating whether the event is treatment emergent
- All AEs of Grade 3 or higher
- All SAEs
- Deaths
- All AEs leading to study treatment discontinuation by study drugs

7.1.6.2. 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
- Deaths within 30 days of the last dosing of study drug
- Deaths beyond 30 days of the last dosing of study drug

7.1.7. Dose Limiting Toxicity

Dose limiting toxicity (DLT) will be analyzed using DLT analysis set.

A listing of the DLT AEs will be provided by dose level, subject identification, actual dose amount prior to or on the start date of the AE, DLT terms from the investigators, CTCAE terms, and associated severity grade, if available.

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. 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, serum chemistry, and urinalysis 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.

No formal statistical testing is planned.

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 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 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. 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

Summaries (number and percentage of subjects) of baseline and worst postbaseline treatment-emergent laboratory abnormalities will be provided by lab test. Subjects will be categorized according to the most severe postbaseline abnormality grade for a given lab test.

A by-subject listing will include all laboratory results with flags to indicate treatment emergent laboratory abnormalities.

7.2.2. 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 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

Prior and concomitant medications will be coded based on World Health Organization Drug Dictionary (WHO DRUG) Version Q32017 into Anatomical-Therapeutic-Chemical classification (ATC) codes.

7.4.1. Prior Medications

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

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 considered as prior medication, unless otherwise specified.

All prior medications will be provided in a by-subject listing sorted by subject ID number and administration date in chronological order based on FAS analysis set.

7.4.2. Concomitant Medications

Concomitant medications are defined as medications taken while a subject took study drug.

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 not be considered as concomitant. 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 not be considered as concomitant medication. 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 not be considered as concomitant medication. Medications with completely missing start and stop dates will be considered as concomitant medication, unless otherwise specified.

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

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 based on FAS analysis set.

7.5. Electrocardiogram Results

Electrocardiogram is not planned to be assessed for the study.

7.6. Other Safety Measures

No additional safety measures are specified in the protocol.

7.7. Changes From Protocol-Specified Safety Analyses

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

8. PHARMACOKINETIC ANALYSES

Pharmacokinetic peripheral blood samples are obtained pre-dose during Lead-in on Day -7; Cycle 1 on Day 1, 8, 28 and Cycle 2 on Day 28. PK blood samples will also be collected 1.5 hours post-dose of ENTO (±30 minutes) during Lead-in on Day -7; Cycle 1 on Days 1, 8, 28 and Cycle 2 on Day 28.

Concentrations of ENTO in plasma will be determined using a validated bioanalytical assay.

8.1. Statistical Analysis Methods

8.1.1. Plasma Concentration

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

9. 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.

10. SOFTWARE

SAS® Software Version 9.4 or higher, SAS Institute Inc., Cary, NC, USA.

11. SAP REVISION

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

12. APPENDICES

Appendix 1 Schedule of Assessments

Study Phase	Screening (-28 days)	ENTO Lead-in*	Cycle 1					Cycle 2					Maintenance**					End of Treatment	30 Day Follow-Up
Cycle Day	**Screening**	**-7**	**1**	**8**	**15**	**22**	**28**	**1**	**8**	**15**	**22**	**28**	**1**	**8**	**15**	**22**	**28**		
Study Day		**1**	**8**	**15**	**22**	**29**	**35**												
Study Assessments																			
Informed Consent	X																		
General and Safety Assessments																			
Physical Exam and weight[a]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital Signs[b]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AE/Concomitant Meds[c]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Medical History	X																		
HBV, HCV, and HIV Virology	X																		
Smoking status	X	X	X					X					X						
Disease Assessments																			
ECOG	X	X	X					X					X					X	
Laboratory Assessments																			
Bone marrow aspirate and biopsy[d]	X			X			X					X						X	
Hematology[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Serum Chemistry & Liver Function Testing	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Urinalysis	X		X					X					X					X	
Urine or Serum Pregnancy Test or FSH[f]	X	X	X					X					X					X	
Pharmacokinetic Sampling[g]		X	X	X			X					X							

Study Phase	Screening (-28 days)	ENTO Lead-in*	Cycle 1					Cycle 2					Maintenance**					End of Treatment	30 Day Follow-Up
Cycle Day	**Screening**	**-7**	**1**	**8**	**15**	**22**	**28**	**1**	**8**	**15**	**22**	**28**	**1**	**8**	**15**	**22**	**28**		
Study Day		**1**	**8**	**15**	**22**	**29**	**35**												
CSF (for PK sampling)[h]							X					X							
PPD																			
Imaging																			
CT or PET[k] (Investigator's discretion, for EMD subjects only)	X			X			X					X							
Investigational Product and Auxiliary																			
ENTO[l]		X	X				X	X				X	X				X		
IV Vincristine[m]			X	X	X	X		X	X	X	X		X						
Dexamethasone[n]				X		X		X		X			X		X				
CNS Prophylaxis per institutional standard[o]							X					X							

* For Dose Escalation only
** During Maintenance Cycle 1, all visits are required. Starting from Maintenance Cycle 2, Day 1 is required and Day 8/15/22/28 visits are per the Investigator's discretion.
a Complete physical examination will be performed at Screening which includes height. A modified physical examination capturing changes from prior exams will be performed at other visits.
b 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.
c Following consent, adverse events will be assessed pre-and post-dose during each clinic visit, 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 be asked specifically if there are any AEs since stopping the study.
d Bone marrow aspirate/biopsy will be taken during Screening; Cycle 1 on Day 8 and Day 28; Cycle 2 on Day 28. PPD
e CBC with differential including PT/INR and PTT.
f For female subjects of childbearing potential, serum testing performed at screening only. Urine pregnancy test will be performed at Lead-in on Day -7 of (escalation) or during Cycle 1 on Day 1 (expansion). Pregnancy tests will be performed on a Day 1 of each cycle thereafter.
g Pharmacokinetic peripheral blood samples will be obtained pre-dose during Lead-in on Day -7; Cycle 1 on Day 1, 8, 28 and Cycle 2 on Day 28. PK blood samples will also be collected 1.5 hours post-dose of ENTO (±30 minutes) during Lead-in on Day -7; Cycle 1 on Days 1, 8, 28 and Cycle 2 on Day 28. CNS prophylaxis administration is independent of PK time point.

h CSF samples will be collected for pharmacokinetic analysis during Cycles 1 and Cycle 2 on Day 28 (prior to CNS prophylaxis administration).

PPD

PPD

k Subjects with EMD only, with no BM involvement will not require BM aspirate/biopsy

l Treatment with ENTO will be continuous. ENTO should be dispensed on Day 28 to include cycle break drug coverage, if necessary.

m Vincristine will be administered during Cycles 1 and Cycle 2 on Days 1, 8, 15, 22 and during Maintenance on Day 1 of each cycle.

n Dexamethasone (20 mg BID; dosed for 4 days) will be dispensed during Cycle 1 on Day 8 and Day 22 and during Cycle 2 on Day 1 and Day 15. During Maintenance, dexamethasone (20 mg QD or 10 mg BID; dosed for 4 days) will be dispensed on Day 1 and Day 15 of each cycle.

o CNS prophylaxis per institutional standard during Cycle 1 and Cycle 2 on Day 28 (± 3 days).

SAP CSR GS-US-339-1560_ v1.0

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy hh:mm:ss)
PPD	Clinical Research eSigned	11-Jan-2019 00:43:50
PPD	Biostatistics eSigned	11-Jan-2019 01:19:08