STATISTICAL ANALYSIS PLAN

Study Title:	A Phase 1b Study to Investigate the Safety, Tolerability, and Pharmacokinetics of Entospletinib (ENTO) as Monotherapy in Japanese Subjects with Relapsed or Refractory Hematologic Malignancies and in Combination with Chemotherapy in Japanese Subjects with Previously Untreated Acute Myeloid Leukemia (AML)
Name of Test Drug:	Entospletinib (ENTO)
Study Number:	GS-US-429-4104
Protocol Version (Date):	Amendment 3 (23 August 2017)
Analysis Type:	Final
Analysis Plan Version:	Version 1.0
Analysis Plan Date:	24 May 2018
Analysis Plan Author:	PPD

CONFIDENTIAL AND PROPRIETARY INFORMATION

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LIST OF ABBREVIATIONS

AE	adverse event
AML	acute myeloid leukemia
ATC	Anatomical-Therapeutic-Chemical classification
BID	bis in die (twice a day)
BLQ	below the limit of quantitation
cm	centimeter
CR	complete remission
CRc	cytogenetic complete remission
CRi	morphologic CR with incomplete blood count recovery
CRF	case report form
CRO	contract research organization
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DBP	diastolic blood pressure
DLT	dose limiting toxicity
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form(s)
EFS	event free survival
ENTO	Entospletinib
EOS	end of study
EOT	end of treatment
ETA	early treatment assessment
FAB	French-American-British
FAS	full analysis set
FDA	(United States) Food and Drug Administration
HiDAC	high-dose cytarabine
g	gram
GCP	Good Clinical Practice (Guidelines)
Gilead	Gilead Sciences, Inc.
h, hr	hour
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

LFS	leukemia free survival
LLT	lower-level term
LOQ	lower limit of quantitation
mg	milligram
MedDRA	Medical Dictionary for Regulatory Activities
NCI	National Cancer Institute
NIH	National Institutes of Health
NE	not evaluable
ORR	objective response rate
OS	overall survival
PD	progressive disease
PK	pharmacokinetic(s)
PR	partial remission
PT	preferred term
Q1	first quartile
Q3	third quartile
StD	standard deviation
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
SE	standard error
SOC	system organ class
SOP	standard operating procedure
TEAE	treatment emergent adverse event
TF	Treatment failure
TFL	tables, figures and listings
TTR	time to response
uL	microliter
ULN	upper limit of the normal range
US	United States
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 a synoptic study report (CSR) for Study GS-US-429-4104. This SAP is based on Protocol GS-US-429-4104 Amendment 3 dated 23 August 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.

The study was originally designed to evaluate the safety, tolerability, and pharmacokinetics of entospletinib (ENTO) in 2 stages: (1) ENTO monotherapy (Group A) for relapsed or refractory hematologic malignancies; (2) ENTO in combination with cytarabine and daunorubicin (Group B) for AML. However, per the Sponsor's decision, only the monotherapy stage is conducted with full enrollment of Group A, and the study will be terminated early without opening enrollment in Group B. The decision to terminate the study was not due to any safety concerns. Therefore, a synoptic CSR will be generated, and this SAP describes the analyses for the monotherapy part (Group A) only.

1.1. Study Objectives

1.1.1. Primary Objectives

- To evaluate the safety and tolerability of ENTO monotherapy in Japanese subjects with relapsed or refractory hematologic malignancies
- To evaluate the safety and tolerability of ENTO in combination with cytarabine and daunorubicin (7+3) in Japanese subjects with previously untreated AML who are candidates for chemotherapy

1.1.2. Secondary Objectives

- To evaluate the pharmacokinetics (PK) of ENTO in Japanese subjects with relapsed or refractory hematologic malignancies
- To evaluate the PK of ENTO in Japanese subjects with previously untreated AML who are candidates for chemotherapy
- To evaluate the safety and tolerability of ENTO in combination with age-adjusted high-dose cytarabine (HiDAC) in Japanese subjects with previously untreated AML who are candidates for chemotherapy

1.2. Study Design

This is a Phase 1b, open-label, multicenter study evaluating the safety, tolerability, and PK of ENTO as monotherapy in Japanese subjects with relapsed or refractory hematologic malignancies and in combination with cytarabine and daunorubicin (7+3) in Japanese subjects

with previously untreated AML. The study was originally designed for 2 stages sequentially: (1) ENTO monotherapy in subjects with relapsed or refractory hematologic malignancies (Group A); (2) ENTO in combination with cytarabine and daunorubicin (7 + 3) in subjects with untreated AML (Group B). Up to 24 subjects will be dosed in 2 groups using a rolling 6 design to evaluate 12 subjects for DLT assessment. However, per the Sponsor's decision, it was decided to only enroll subjects into Group A. The planned dose levels for Group A are:

Dose Level	Entospletinib
-1	200 mg twice daily
0	400 mg twice daily

The first 6 subjects in Group A will be enrolled at dose level 0 (400 mg twice daily BID). Subjects will receive ENTO BID on Days 1-28 of every 28-day cycle and will continue on study treatment as long as the subject is experiencing clinical benefit and does not meet criteria for study treatment discontinuation. When the sixth evaluable subject has completed the DLT assessment window (begins on Cycle 1 Day 1 and ends on Cycle 1 Day 28), the safety review team will evaluate the safety data from all enrolled subjects. During the DLT assessment window, subjects who fail to complete a total of 21 days of ENTO for reasons other than a DLT will not be evaluable for DLT assessment and may be replaced in a timely manner as determined by the Gilead Medical Monitor, the Japanese CRO Medical Monitor, and the Principal Investigator.

- If 0 or 1 out of the 6 subjects experiences a DLT, Group B will open and 6 subjects will be enrolled in Group B at dose level 0

- If ≥ 2 out of the 6 subjects experience a DLT, 6 additional subjects will be enrolled in Group A at the reduced dose level -1 (200 mg BID) and Group B will not open.

The schedules of study procedure are provided in Appendix 1.

1.3. Sample Size and Power

There is no formal efficacy or safety hypothesis to be tested in this study, and therefore no formal size calculation was performed.

The rolling 6 design is implemented for the study. The first 6 subjects will be enrolled at dose level 0 in Group A. During the DLT assessment window, if 0 or 1 out of these 6 subjects experience DLTs in Group A, Group B will open and 6 subjects will be enrolled at dose level 0 in Group B. However, if 2 or more subjects experience DLTs in Group A, 6 additional subjects will be enrolled at dose level -1 in Group A and Group B will not open. Subjects who discontinue early for a non-DLT defined reason during the DLT assessment window will not be evaluable for DLT and may be replaced. The aforementioned subjects are DLT evaluable subjects.

With consideration for subject replacement, up to 24 subjects will be enrolled to the study.

2. TYPE OF PLANNED ANALYSIS

2.1. Interim Analysis

No formal interim analyses are planned in this Phase 1b study.

2.2. Final Analysis

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

3. GENERAL CONSIDERATIONS FOR DATA ANALYSES

As the study was terminated early with only 9 subjects enrolled, the synoptic CSR will only include listings for efficacy analyses. Both summarized tables and listings will be provided for safety analyses.

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. Full Analysis Set

Full Analysis Set (FAS) includes all subjects who took at least 1 dose of study drug (ENTO).

This analysis set will be used in the analyses of subject characteristics, drug exposure, safety, and efficacy.

3.1.2. Dose-Limiting Toxicity (DLT) Analysis Set

DLT Analysis Set includes all subjects in the FAS who meet at least one of the following criteria:

- Receive at least 21 days of ENTO 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.

3.1.3. Pharmacokinetic Analysis Sets

The Pharmacokinetic (PK) Analysis Sets include all subjects in the FAS who have necessary baseline and at least 1 non-missing post-treatment assessments.

3.2. Subject Grouping

Due to the early termination of the study, only one dose is evaluated. Subjects will be presented under ‘400 mg BID’ dose level for FAS, DLT Analysis Set, and PK Analysis Sets.

3.3. Strata and Covariates

Not applicable.

3.4. Examination of Subject Subgroups

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 of Study Day 1, 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 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
- 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 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 ENTO 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 FAS.

4.2.1. Exposure to Study Drug

Total duration of exposure to study drug 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 total duration of exposure to ENTO will be summarized using descriptive statistics and using the number and percentage of subjects exposed for at least 1 day, 14 days, 28 days, and 2, 3, 6, 9 months, etc.

The number of cycles subjects were exposed to study drug will be summarized using descriptive statistics, as well as the number and percentage of subjects exposed to a given cycle category (eg, Cycle X).

The number and percentage of subjects, who had dose reduction or interruption, and the reason, will also be summarized.

4.2.2. Adherence to Study Drug

A by-subject listing of study drug accountability (dispenses and returns) 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 treatment group 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.

Age will be calculated by the formula:

Age (in years) = (date of first dose – date of birth+1) / 365.25 (round down to an integer)

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, cytogenetics, genetic risk group classification, and type of hematologic malignancy. 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 by subject ID number in ascending order.

5.4. Prior Anti-Cancer Therapy

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

6. EFFICACY ANALYSES

Assessment of clinical response in subjects with hematologic malignancies other than AML will be according to the latest set of published response criteria. Assessment of clinical response in subjects with AML will be according to the modified International Working Group criteria and will include findings on examination of blood, bone marrow and physical examination.

Clinical response will be evaluated by investigator assessments. All efficacy endpoints will be analyzed by treatment group using FAS.

6.1. Primary Efficacy Endpoints

Not applicable.

6.2. Secondary Efficacy Endpoints

Not applicable.

6.3. Exploratory Efficacy Endpoints

6.3.1. Definition of Exploratory Efficacy Endpoints

CCI [redacted]

6.3.2. Analysis Methods of Exploratory Efficacy Endpoints

CCI [redacted]

6.3.3. Changes from Protocol-Specified Efficacy Analyses

CCI [redacted]

7. SAFETY ANALYSES

Safety analyses are conducted using FAS, 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 21.0) 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 those for which the investigator selected "Related" on the AE CRF to the question of "Related to Study Treatment Entospletinib". 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 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 then Gilead Drug Safety and Public Health 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 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

The number and percentage of subjects who experienced at least 1 TEAE will be provided and summarized by SOC, PT, and maximum severity as follows:

- All TEAEs
- Grade 3 or higher TEAEs
- ENTO-related TEAEs
- ENTO-related Grade 3 or higher TEAEs
- Serious TEAEs
- ENTO-related Serious TEAEs
- TEAEs leading to ENTO discontinuation

- TEAEs leading to ENTO reductions
- TEAEs leading to ENTO interruptions
- 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. All deaths occurred in the study will also be included.

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 SAEs
- Deaths
- TEAEs leading to ENTO discontinuation

7.1.7. Dose Limiting Toxicity

Dose limiting toxicity (DLT) will be analyzed based on the 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

Central laboratory assessment will be used for safety analysis. Laboratory data collected during the study will be analyzed and summarized using both quantitative and qualitative methods. 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.

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.

7.2.1. Graded Laboratory Values

CTCAE Version 4.03 will be used for assigning 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.

For parameters for which a CTCAE scale does not exist, the frequency of subjects with values below, within, and above the normal ranges will be summarized.

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 post-baseline 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 to be treatment emergent.

7.2.1.2. Summaries of Laboratory Abnormalities

Summary (number and percentage of subjects) of baseline and worst post-baseline treatment-emergent laboratory abnormalities will be provided by lab test. Subjects will be categorized according to the most severe post-baseline 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. Shifts Relative to the Baseline Value

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

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 considered as prior medication 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.

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 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 based on FAS analysis set.

7.5. Electrocardiogram and MUGA Scan

Electrocardiogram (ECG) and MUGA data will not be presented in the synoptic CSR since ECGs and MUGA scan were not assessed in this study other than as part of the screening process for potential new subjects.

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

8.1. PK Sample Collection

Intensive PK samples are collected on Day 8 of Cycle 1 at 0 (pre-dose), 1, 2, 3, 4, 6, 8, and 12 hours post-dose of ENTO.

Sparse PK samples are collected at pre-dose and 2 hours post-dose of ENTO on (1) Days 1, 14, and 28 of Cycle 1; (2) Day 28 of Cycle 2 and subsequent cycles.

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

8.2. Statistical Analysis Methods

8.2.1. Plasma Concentration

Plasma PK sampling details by subject including nominal collection time, actual dosing time and actual collection time, calculated time postdose of sample collection, differences in scheduled and actual draw times, sample age, and sample ENTO concentration will be provided in the listing.

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. Study Procedures Table: Group A (ENTO Monotherapy)

Study Phase	Screening	Cycle 1				Subsequent Cycles		Remission/Relapse	End of Treatment (EOT)	30-day Follow-Up	Long Term Follow-up
Study Day	**Screening**	**1**	**8**	**14**	**28**	**1**	**28**				
Window (day)	**-14**	**NA**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±7**	**±7**	**± 4 weeks**
General and Safety Assessments											
Informed Consent	X										
Medical & Medication History	X										
Adverse Events/Concomitant Medications	X	X	X	X	X	X	X		X	X	
Smoking status[a]	X	X				X					
Physical Exam	X	X		X		X			X		
Vital Signs[b]	X	X	X	X	X	X			X		
Height and Weight[c]	X	X				X			X		
ECG	X										
ECHO/MUGA	X										
Performance Status	X	X		X		X			X		
Chest X-ray	X										
Overall survival, treatments, and other malignancies											X (every 6 months)
Study Treatment											
ENTO Administration[d]		X	X	X	X	X	X				
Laboratory Assessments											
Chemistry[e]	X	X	X	X	X		X		X		
Hematology	X	X	X	X	X		X	X	X		
Coagulation	X			X	X		X		X		
Urinalysis	X										
Serum Pregnancy Test and FSH[f]	X										
Urine Pregnancy Test[g]		X				X			X		
HIV/HBV/HCV	X										
Sparse PK[h]		X		X	X		X				
Intensive PK[i]			X								
Disease Assessment[j]	X				X			X	X		

Study Phase	Screening	Cycle 1				Subsequent Cycles		Remission/Relapse	End of Treatment (EOT)	30-day Follow-Up	Long Term Follow-up
Study Day	**Screening**	**1**	**8**	**14**	**28**	**1**	**28**				
Window (day)	**-14**	**NA**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±7**	**±7**	**± 4 weeks**
Bone Marrow Assessments											
Biopsy[k]	X				X			X	X		
Aspirate[k]	X				X			X	X		

a Collect smoking status at screening and Day 1 of each cycle.
b Vital signs include measurement of blood pressure, respiratory rate, pulse, temperature, and oxygen saturation level.
c Height and weight will be measured at screening. Only weight will be measured on Day 1 of each cycle and at EOT.
d ENTO will be administered BID on Days 1-28 for every 28 day-cycle as long as the subject is experiencing benefit and does not meet criteria for study treatment discontinuation. The subject may continue on ENTO monotherapy as long as the subject is experiencing benefit and does not meet criteria for study treatment discontinuation.
e Include Total CPK at screening, Day 28 of every cycle, and EOT.
f A negative serum pregnancy test is required for female subjects (unless surgically sterile or menopausal) at screening and a negative urine pregnancy test is required on Cycle 1 Day 1 prior to dose. Female subjects with medically documented ovarian failure must also have serum FSH levels within the institutional postmenopausal range at screening.
g For females of childbearing potential, urine pregnancy tests will be done on Day 1 of each cycle and at EOT.
h Peripheral blood samples for sparse PK will be obtained on Cycle 1 Days 1, 14 and 28, and Day 28 of subsequent cycles at pre-dose and 2hrs post-dose of ENTO.
i Peripheral blood samples for intensive PK will be obtained on Cycle 1 Day 8 at 0 (pre-dose), 1, 2, 3, 4, 6, 8, and 12 hours post-dose of ENTO.
j Subjects with hematologic malignancies other than AML will undergo the appropriate clinical, radiographic, laboratory procedures for disease assessment per the standard of care/institutional practice at screening (within 21 days before the first administration of study treatment), at the end of Cycle 1 on Day 28, as clinically indicated after Cycle 1, remission/relapse, and EOT (if not performed within the last 2 weeks).
k Subjects with AML will undergo a bone marrow biopsy and aspirate (~8mL) for disease assessment at screening (within 21 days before the first administration of study treatment), at the end of Cycle 1 on Day 28, as clinically indicated after Cycle 1, remission/relapse, and EOT (if not collected within the last 2 weeks). Biopsy will be used in the event the aspirate cannot be collected or analyzed. Subjects with AML with cytogenetic and molecular mutations at screening must have cytogenetic and molecular mutation testing repeated at Cycle 1 Day 28, remission/relapse, and EOT.

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ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy hh:mm:ss)
PPD	Clinical Pharmacology eSigned	25-Sep-2018 18:44:46
PPD	Clinical Research eSigned	01-Oct-2018 19:37:45
PPD	Biostatistics eSigned	01-Oct-2018 22:41:10