STATISTICAL ANALYSIS PLAN

Study Title:	A Phase 1b/2 Study of Entospletinib (GS-9973) Monotherapy and in Combination with Chemotherapy in Patients with Acute Myeloid Leukemia (AML)
Name of Test Drug:	Entospletinib (GS-9973)
Study Number:	GS-US-339-1559
Protocol Version:	Amendment 7
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Analysis Plan Author:	PPD

CONFIDENTIAL AND PROPRIETARY INFORMATION

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LIST OF ABBREVIATIONS

7+3	cytarabine and daunorubicin chemotherapy
AE	adverse event
ATC	Anatomical Therapeutic Chemical
AML	acute myeloid leukemia
BID	bis in die (twice a day)
BLQ	below the limit of quantitation
BMI	body mass index
BM-MNCs	bone marrow mononuclear cells
CI	confidence interval
CR	complete remission
CRc	cytogenetic complete remission
CRF	case report form
CRi	morphologic CR with incomplete blood count recovery
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DLT	dose limiting toxicity
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EFS	event free survival
ELN	European LeukemiaNet
ENTO	Entospletinib, GS-9973
EOS	end of study
ETA	early treatment assessment
FAB	French-American-British
FISH	fluorescent in situ hybridization
HLT	high-level term
HOXA9	Homeobox A9
ID	identification
IWRS	Interactive Web Response System
IV	intravenous
KM	Kaplan-Meier
LLT	lower-level term
LOQ	limit of quantitation
MedDRA	Medical Dictionary for Regulatory Activities
MEIS1	Myeloid Ecotropic Viral Integration Site 1
MLFS	morphologic leukemia free state
MLL	mixed lineage leukemia
MRD	minimal residual disease
MTD	maximum tolerated dose

OS	overall survival
PK	pharmacokinetic(s)
PR	partial remission
PT	preferred term
Q1	first quartile
Q3	third quartile
RFS	relapse - free survival
R/R	relapsed/refractory
SAP	statistical analysis plan
SAE	serious adverse event
SCT	stem cell transplant
SOC	system organ class
StD	standard deviation
TEAE	treatment-emergent adverse event
TF	treatment failure
TFLs	tables, figures, and listings
WBC	white blood cell
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-339-1559. This SAP is based on the study protocol amendment 7 dated 15 February 2018 and the electronic case report form (eCRF). This study was intended to evaluate the efficacy, safety, and tolerability of entospletinib (ENTO) in subjects with Acute Myeloid Leukemia (AML). Due to the lack of responses to ENTO monotherapy and the evolving treatment landscape for AML, the recruitment of Group B Phase 2 was permanently closed prior to the planned sample size being reached. The enrollments of other treatment groups/cohorts were either completed or terminated, and, as such, this study will be terminated early. The SAP will be finalized before database finalization. Any changes made after the finalization of the SAP will be documented in the CSR.

1.1. Study Objectives

The primary objectives of this study are as follows:

- To demonstrate the overall safety of ENTO in combination with standard dose cytarabine and daunorubicin chemotherapy (7+3) in subjects with previously untreated AML who are candidates for chemotherapy (fit subjects) and to assess the efficacy of ENTO at the recommended Phase 2 dose (RP2D) (Group A)

- To demonstrate the overall safety of ENTO in combination with hypomethylating agents (decitabine or azacitidine) in subjects with previously untreated AML who are not candidates for 7+3 (unfit subjects) and to assess the efficacy of ENTO at the RP2D (Group B)

- To demonstrate the overall safety of ENTO monotherapy in subjects with previously untreated AML who are not candidates for chemotherapy or in subjects with relapsed/refractory (R/R) AML with or without mixed-lineage leukemia (MLL) and to assess the efficacy of ENTO at the RP2D (Group C)

The secondary objectives of this study are as follows:

- To assess the qualitative and quantitative toxicities of ENTO monotherapy or ENTO in combination with chemotherapy in subjects with AML

- To document therapeutic response of subjects with AML treated with ENTO monotherapy or ENTO in combination with chemotherapy

The exploratory objective of this study is as follows:

- CCI [redacted]

1.2. Study Design

This is a Phase 1b/2 study evaluating the efficacy, safety, and tolerability of ENTO in subjects with AML. Subjects with AML will be dosed using a 3 + 3 design for the dose escalation phase. During the dose escalation phase, ENTO will be administered at a dose of 200 mg and 400 mg every 12 hours either in combination with chemotherapy for Group A or with a hypomethylating agent for Group B. ENTO will be administered at a dose of 400 mg and 800 mg every 12 hours as monotherapy for Group C.

Following completion of the dose escalation phase, the sponsor in consultation with the coordinating center has selected ENTO at a dose level of 400 mg every 12 hours for all dose expansion cohorts.

Figure 1-1. Study Schema

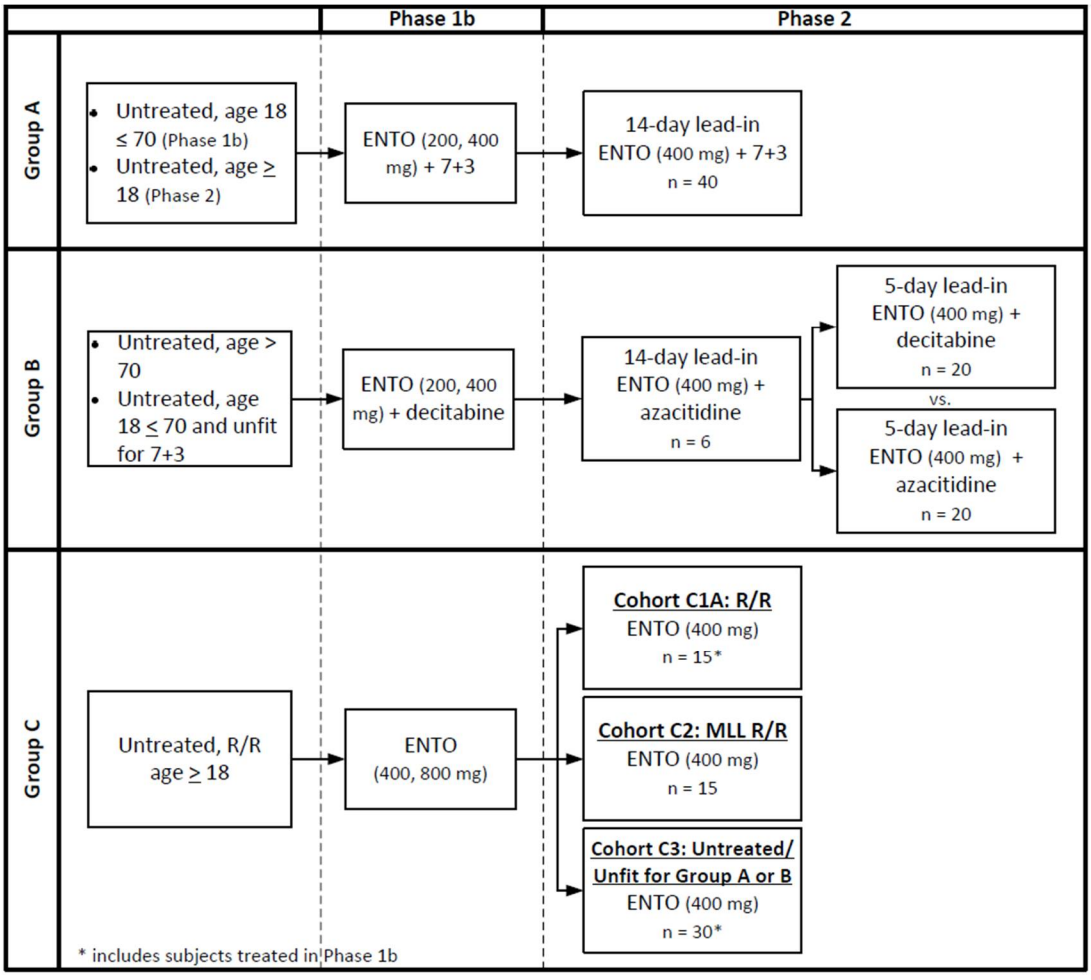

Table 1-1. Treatment Groups/Cohorts

Treatment Group/Cohort	Treatment	Primary Objective
Group A Phase 1b (Dose Escalation)	ENTO + Daunorubicin + Cytarabine (ENTO: 200 and 400 mg)	To determine maximum tolerated dose (MTD) and to demonstrate the overall safety of ENTO + Daunorubicin + Cytarabine in subjects with previously untreated AML
Group A Phase 2 (Dose Expansion)	ENTO + Daunorubicin + Cytarabine (ENTO: 400 mg)	To assess the efficacy of ENTO + Daunorubicin + Cytarabine in subjects with previously untreated AML
Group B Phase 1b (Dose Escalation)	ENTO + Decitabine (ENTO: 200 and 400 mg)	To determine MTD and to demonstrate the overall safety of ENTO + Decitabine in subjects with previously untreated AML
Group B Phase 2 Safety Run-in	ENTO + Azacitidine (ENTO: 400 mg)	To demonstrate the overall safety of ENTO + Azacitidine in subjects with previously untreated AML
Group B Phase 2 Randomization (Dose Expansion)	ENTO + Decitabine vs. ENTO + Azacitidine (ENTO: 400 mg)	To assess the efficacy of ENTO + Decitabine or Azacitidine in subjects with previously untreated AML
Group C Phase 1b (Dose Escalation)	ENTO Monotherapy (ENTO: 400 and 800 mg)	To determine MTD and to demonstrate the overall safety of ENTO monotherapy in subjects with R/R AML or previously untreated AML but unfit for Group A or B
Group C Phase 2 Cohort 1A (Dose Expansion)	ENTO Monotherapy (ENTO: 400 mg)	To assess the efficacy of ENTO monotherapy in subjects with R/R AML
Group C Phase 2 Cohort C2 (Dose Expansion)	ENTO Monotherapy (ENTO: 400 mg)	To assess the efficacy of ENTO monotherapy in subjects with R/R AML with MLL gene rearrangement
Group C Phase 2 Cohort C3 (Dose Expansion)	ENTO Monotherapy (ENTO: 400 mg)	To assess the efficacy of ENTO monotherapy in subjects with previously untreated AML and unfit for Group A or B

Group A Phase 1b (Dose Escalation)

Note: At the time of amendment 7, Group A Phase 1b had completed enrollment.

ENTO will be administered at 2 dose levels for Group A during the dose escalation phase (see table below); the initial dosing level for the 1st cohort is defined as level 0.

Intra-subject dose escalation will not be allowed.

Group A Entospletinib Dose Escalation Table

Dose Level	Entospletinib	Daunorubicin	Cytarabine
0	200 mg	60mg/m^2	100mg/m^2
1	400 mg		

ENTO will be administered orally every 12 hours as a monotherapy lead-in on Days 1-14 (Cycle 0) and will be administered orally every 12 hours in combination with cytarabine (Days 1-7) and intravenous (IV) daunorubicin (Days 1-3) during induction chemotherapy for up to two 14-day cycles (Cycles 1 and 2). Subjects with residual disease detected at the Cycle 1 Day 14 bone marrow evaluation will proceed with Cycle 2 of induction chemotherapy.

A bone marrow aspirate will be collected at Screening, Cycle 1 Day 14 (and Cycle 2, if needed) or at the time of blood count recovery (whichever comes first), remission/relapse, and End of Study Treatment (if not performed within the last 2 weeks) for disease assessment and biomarker research.

Group A Phase 2 (Dose Expansion)

Note: At the time of amendment 7, Group A Phase 2 had completed enrollment.

Similar to Phase 1b, in Phase 2, ENTO 400 mg will be administered first as a 14-day lead-in monotherapy followed by ENTO in combination with 7+3 induction chemotherapy. Post-remission chemotherapy will be offered to subjects who achieve complete remission (CR)/ morphologic CR with incomplete blood count recovery (CRi) and do not require or cannot proceed to allogeneic stem cell transplantation (SCT). In addition, subjects who are awaiting a donor or transitioning to allogeneic SCT are allowed to receive post-remission chemotherapy per investigator discretion. Subjects who continue to maintain a CR/CRi after 3 or 4 cycles of post-remission chemotherapy will be offered maintenance therapy with ENTO 400 mg every 12 hours for up to 12 cycles. Extension of maintenance therapy may occur on an individual basis if approved by the Principal Investigator.

A bone marrow aspirate will be collected at Screening, at the end of the monotherapy lead-in period (ie, Cycle 0 Day 14 or after the minimum 5-days of ENTO) and prior to chemotherapy, Cycle 1 Day 14 (and Cycle 2, if needed) or at the time of blood count recovery, remission/relapse, and End of Study Treatment (if not performed within the last 2 weeks) for disease assessment and biomarker research. A bone marrow aspirate will also be collected during Post-remission on Cycle 2 Day 28 and Cycle 4 Day 28 and during Maintenance at the end of every 4 cycles on Day 28 (eg, Cycle 4 Day 28, Cycle 8 Day 28, etc.) or as clinically indicated for disease assessment and biomarker research. Subjects who achieve CR/CRi that is stable for 2 consecutive bone marrow evaluations are not required to have further bone marrow aspirate samples collected, unless clinically indicated.

Group B Phase 1b (Dose Escalation)

Note: At the time of amendment 7, Group B Phase 1b had completed enrollment.

ENTO will be administered at 2 dose levels for Group B during the dose escalation phase (see table below); the initial dosing level for the 1st cohort is defined as level 0. Intra-subject dose escalation will not be allowed.

Group B Entospletinib Dose Escalation Table

Dose Level	Entospletinib	Decitabine
0	200 mg	20 mg/m^2
1	400 mg	

ENTO will be administered orally every 12 hours as a monotherapy lead-in on Days 1-14 (Cycle 0) and will be administered orally every 12 hours on Days 1-28 in combination with decitabine on Days 1-10 of every 28-day cycle for at least 2 but no more than 4 cycles of induction chemotherapy. Subject will undergo a bone marrow aspiration and biopsy on Cycle 2 Day 28. Subjects who have a CR/CRi can proceed to SCT per investigator's discretion or to maintenance therapy with ENTO + decitabine. Subjects with persistent AML will receive 2 more cycles of induction chemotherapy and a bone marrow aspiration and biopsy will be performed at Cycle 4 Day 28. Subjects who have persistent leukemia at this time point will be considered a treatment failure and come off study. Subjects ineligible for SCT will have the option to receive maintenance therapy with ENTO + decitabine. Subjects who are intolerant of decitabine after completing 2 cycles will switch to ENTO monotherapy maintenance. Maintenance will continue as long as the subject experiences benefit and does not meet criteria for study treatment discontinuation. Extension of maintenance may occur on an individual basis if approved by the Principal Investigator.

A bone marrow aspirate will be collected at Screening, Cycle 0 Day 14 (must be prior to start of chemotherapy), induction Cycles 2 and 4 on Day 28, remission/relapse, and End of Study Treatment (if not performed within the last 2 weeks) for disease assessment and biomarker research. During ENTO + Hypomethylating agent maintenance and ENTO maintenance therapy, a bone marrow aspirate will be collected at the end of every 4 cycles on Day 28 (eg, Cycle 4 Day 28, Cycle 8 Day 28, etc.) or as clinically indicated for disease assessment and biomarker research. Subjects who achieve CR/CRi that is stable for 2 consecutive bone marrow evaluations are not required to have further bone marrow aspirate samples collected, unless clinically indicated.

Group B Phase 2 (Dose Expansion)

Note: At the time of amendment 7, Group B Phase 2 safety run-in had completed enrollment.

In Phase 2, the overall safety of ENTO in combination with a hypomethylating agent (decitabine or azacitidine) will be evaluated. As part of the safety run-in, ENTO in combination with azacitidine will be administered to 6 evaluable subjects. Following completion of the safety run-in (dose limiting toxicity (DLT) window), the azacitidine arm will be evaluated to determine if enrollment of the expansion cohort may proceed with azacitidine. If 2 or more subjects experience DLTs, all ongoing subjects in the safety run-in will be discontinued, the azacitidine arm will be dropped from the study, and subjects in the expansion phase will only receive ENTO in combination with decitabine.

If Phase 2 proceeds with an azacitidine arm, subjects will be randomized to receive ENTO in combination with either decitabine (Days 1-10) or azacitidine (Days 1-7) of every 28-day cycle for at least 2 but no more than 4 cycles of induction chemotherapy. Randomization will be stratified by age (≤ 75 or > 75 years) and by white blood cell (WBC) count ($\leq 5{,}000/\mu L$ or $> 5{,}000/\mu L$). If subjects are not eligible for SCT after 2 cycles of induction, subjects will have the option to receive maintenance therapy with ENTO in combination with decitabine (Days 1-5) or azacitidine (Days 1-7). Subjects who are intolerant of the hypomethylating agent after completing 2 cycles may switch to ENTO monotherapy maintenance. Maintenance may continue as long as the subject is experiencing benefit and does not meet the criteria for study treatment discontinuation. Extension of maintenance may occur on an individual basis if approved by the Principal Investigator.

A bone marrow aspirate will be collected at Screening, Cycle 0 Day 5 if circulating blasts have cleared, induction Cycles 2 and 4 on Day 28, remission/relapse, and End of Study Treatment (if not performed within the last 2 weeks) for disease assessment and biomarker research. During ENTO + Hypomethylating agent maintenance and ENTO maintenance therapy, a bone marrow aspirate will be collected at the end of every 4 cycles on Day 28 (eg Cycle 4 Day 28, Cycle 8 Day 28, etc.) or as clinically indicated for disease assessment and biomarker research. Subjects who achieve CR/CRi that is stable for 2 consecutive bone marrow evaluations are not required to have further bone marrow aspirate samples collected, unless clinically indicated.

Group C Phase 1b (Dose Escalation)

Note: At the time of amendment 7, Group C Phase 1b had completed enrollment.

ENTO will be administered at 2 dose levels for Group C during the dose escalation phase (see table below); the initial dosing level for the 1st cohort is defined as level 0.

Intra-subject dose escalation will not be allowed.

Group C ENTO Dose Escalation Table

Dose Level	ENTO
0	400 mg
1	800 mg

A bone marrow aspirate will be collected at Screening, at the end of Cycles 1 and 2, remission/relapse, and End of Study Treatment (if not performed within the last 2 weeks) for disease assessment and biomarker research. A bone marrow aspirate will also be collected every 4 cycles on Day 28 starting on Cycle 4 Day 28 of subsequent cycles (eg, Cycle 4 Day 28, Cycle 8 Day 28) or as clinically indicated for disease assessment and biomarker research. Subjects who achieve CR/CRi that is stable for 2 consecutive bone marrow evaluations are not required to have further bone marrow aspirate samples collected, unless clinically indicated.

Group C Phase 2 (Dose Expansion)

R/R and previously untreated subjects will be evaluated in separate cohorts during Phase 2 with ENTO monotherapy. ENTO 400 mg will be administered orally every 12 hours on Days 1-28 of every 28-day cycle as long as the subject is experiencing benefit and does not meet criteria for study treatment discontinuation.

A bone marrow aspirate will be collected at Screening, at the end of Cycles 1 and 2 on Day 28, remission/relapse, and End of Study Treatment (if not performed within the last 2 weeks) for disease assessment and biomarker research. A bone marrow aspirate will also be collected on Day 28 of every 4 cycles beginning on Cycle 4 Day 28 of subsequent cycles (eg, Cycle 4 Day 28, Cycle 8 Day 28) for disease assessment and biomarker research or as clinically indicated. Subjects who achieve CR/CRi that is stable for 2 consecutive bone marrow evaluations are not required to have further bone marrow aspirate samples collected, unless clinically indicated.

Cohort C1A: This cohort is designed to enroll 6 R/R AML subjects first. Nine Group C Phase 1b subjects who were R/R AML and received at least 21 days of ENTO (400 mg or 800 mg) and Cohort C1A subjects will be pooled to provide an adequate sample size (n=15) for the following futility analysis for subjects with R/R AML. If 5 or more of the initial 15 subjects achieve CR/CRi after 1-2 cycles, an additional 15 subjects will be enrolled. However, if less than 5 of the initial 15 subjects achieve CR/CRi after 1-2 cycles, then treatment would be considered futile. At the time of amendment 7, futility has been met and, thus, Cohort C1A will not move forward (ie, will not enroll any subjects).

Cohort C2: This cohort is designed to enroll 15 subjects with R/R AML subjects with MLL gene rearrangement.

Cohort C3: This cohort is designed to enroll 27 previously untreated AML subjects who are unfit (eg, very elderly, have multiple comorbidities, and a poor Eastern Cooperative Oncology Group (ECOG) performance status) for chemotherapy or hypomethylating agent, or refuse either of these 2 treatment options. Three Group C Phase 1b subjects who were previously untreated AML, unfit for Group A or B, and received at least 21 days of ENTO (400 mg or 800 mg), and Cohort C3 subjects will be pooled to provide an adequate sample size (n=30) for the efficacy analysis for subjects with previously untreated AML and unfit for Group A or B. Amendment 7 identifies early enrollment closure of this cohort.

The study procedures for all treatment groups/cohorts are presented in Appendix 2 of the study protocol.

1.3. Sample Size and Power

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. For example, 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.

In Phase 1b, each group will enroll up to 12 subjects, assuming 2 planned dose levels for escalation are tested with up to 6 subjects per level. Assuming 10% of the subjects are unevaluable during dose escalation, up to 14 subjects may be enrolled in each group for a total of up to 42 subjects. In Group B, an additional 6 subjects will be enrolled to evaluate the safety of ENTO in combination with azacitidine prior to the dose expansion.

In the Group A Phase 2, approximately an additional 40 subjects will be enrolled. Table 1-2 provides the 90% confidence interval (CI) of 40 subjects for the assumed composite complete remission rate. This sample size ensures a narrow CI (~ 7-14% distance from the point estimates). The complete remission rate of standard chemotherapy (7+3) has been reported as 52% in the CALGB study of over 1000 subjects.

Table 1-2. Exact 90% CIs of Composite Complete Remission Rate for a Cohort Size of 40 in Group A

Assumed Composite Complete Remission Rate of Entospletinib + 7+3	Exact 90% CI
70%	(56% – 82%)
80%	(67% – 90%)
90%	(79% – 97%)

In the Group B Phase 2, approximately 40 additional subjects will be randomized in a 1:1 manner to either treatment arm ENTO + decitabine or ENTO + azacitidine. Randomization will be stratified by age (≤ 75 years or > 75 years) and WBC (≤ 5,000/uL or > 5,000/uL). Assuming a composite complete remission rate of 50% for both treatment arms, the 90% CI would be 30% to 70% with a sample size of 20. The composite complete remission rate of standard chemotherapy is reported as 20% to 30%. Evaluation between the treatment arms will be based on the totality of clinical data.

Approximately 63 additional subjects will be enrolled in Group C dose expansion.

A total of 15 initial subjects, including 9 subjects in Group C Phase 1b who were R/R AML and received at least 21 days of ENTO (400 mg or 800 mg) and 6 subjects in Cohort C1A, will be pooled for evaluation of futility in subjects with R/R AML. An additional 15 subjects will be enrolled if greater or equal to 5 (out of 15) CR/CRi are observed. This futility boundary will provide a high chance (84%) of early stopping of the trial if the composite complete remission rate is undesirable (20%) and a low chance (22%) of early stopping if the composite complete remission rate is clinically meaningful (40%).

The sample size is 15 for Cohort C2. This sample size is based on practical considerations. The sample size is 30 for previously untreated AML (unfit for Group A or B), including 3 subjects in Group C Phase 1b who were previously untreated AML, unfit for Group A or B, and received at least 21 days of ENTO (400 mg or 800 mg), and 27 subjects in Cohort C3, which will provide adequate precision of efficacy estimates. Table 1-3 provides the 90% CI of 30 subjects for the assumed composite complete remission rate.

Table 1-3. Exact 90% CIs of Composite Complete Remission Rate for a Cohort Size of 30 in Subjects with Previously Untreated AML (Unfit for Group A or B)

Assumed Composite Complete Remission Rate of ENTO Monotherapy in Subjects with Previously Untreated AML (Unfit for Group A or B)	Exact 90% CI
30%	(17% – 47%)
50%	(34% – 66%)
70%	(53% – 83%)

Therefore, a total of approximately 54 subjects (including 14 in Phase 1b and 40 in Phase 2) in Group A, approximately 60 subjects (including 14 in Phase 1b, 6 in the safety run-in of ENTO + azacitidine, and 40 in Phase 2) in Group B, and approximately 77 subjects (including 14 in Phase 1b and 63 in Phase 2) in Group C will be enrolled for the duration of the study.

2. TYPE OF PLANNED ANALYSIS

2.1. Interim Analysis

No formal interim analysis is planned.

2.2. Final Analysis

After all subjects have discontinued/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.

2.3. Follow-up Analysis

No follow-up analysis is planned.

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 or All Randomized Analysis Set. Data collected on log forms, such as adverse events (AEs), will be presented in chronological order within the subject. The treatment group to which subjects were randomized or initially assigned will be used in the listings.

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.

For each analysis set, the number and percentage of subjects eligible for inclusion will be summarized by treatment group, phase, and dose level, treatment arm, or cohort if applicable, as elaborated in Table 3-2 in Section 3.2.

A listing of reasons for exclusion from analysis sets will be provided by subject.

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 and were not screen failures.

The All Enrolled Analysis Set will be used for by-subject listings for all treatment groups/cohorts except for Group B Phase 2 randomization.

3.1.2. All Randomized Analysis Set

All Randomized Analysis Set includes all subjects in Group B Phase 2 who were randomized.

The Randomized Analysis Set will be used for by-subject listings for Group B Phase 2 randomization.

3.1.3. Full Analysis Set

The Full Analysis Set (FAS) includes all subjects who received at least 1 dose of study drug with treatment designated according to the planned treatment.

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

3.1.4. Safety Analysis Set

The Safety Analysis Set includes all subjects who took at least 1 dose of study drug. This analysis set will be used for safety analyses.

3.1.5. DLT Analysis Set

The DLT assessment window for each group is as follows:

- Group A Phase 1b: begins on Cycle 0 Day 1 and ends 28 days from Cycle 1 Day 1 or 28 days from Cycle 2 Day 1 (if Cycle 2 is needed); for subjects with < 5% blasts in the bone marrow, the DLT window may be expanded for hematologic toxicity recovery as noted in Section 3.2 of the study protocol

- Group B Phase 1b/Phase 2 Safety Run-in: begins on Cycle 0 Day 1 and ends 28 days from Cycle 1 Day 1

- Group C Phase 1b: 28 days (Cycle 1); for subjects with < 5% blasts in the bone marrow the DLT window may be expanded for hematologic toxicity recovery as noted in Section 3.2 of the study protocol

The DLT Analysis Set includes all subjects in the Safety Analysis Set who

- received 21 days of ENTO (applicable to all groups) and all doses of cytarabine and daunorubicin in Group A Phase 1b, decitabine in Group B Phase 1b, or azacitidine in Group B Phase 2 safety run-in during the DLT assessment window; or

- experienced a DLT during the DLT assessment window.

Subjects who expired prior to the end of DLT assessment window without experiencing a DLT will be considered not evaluable for DLT.

The DLT Analysis Set will be used for analyses related to DLT.

3.1.6. Pharmacokinetic Analysis Set

The Pharmacokinetic (PK) Analysis Set includes all enrolled/randomized 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.

Table 3-1 summarizes the applicable treatment group(s)/cohort(s) for each analysis set.

Table 3-1. Analysis Sets

Analysis Set	Treatment Group/Cohort
All Enrolled Analysis Set	Group A Phase 1 and Phase 2 Group B Phase 1b and Phase 2 Safety Run-in Group C Phase 1b and Phase 2 Cohort 1A/C2/C3
All Randomized Analysis Set	Group B Phase 2 Randomization
FAS	All Treatment Groups/Cohorts
Safety Analysis Set	All Treatment Groups/Cohorts
DLT Analysis Set	Group A Phase 1b Group B Phase 1b and Phase 2 Safety Run-in Group C Phase 1b
PK Analysis Set	All Treatment Groups/Cohorts

3.2. Subject Grouping

For analyses based on the FAS, subjects will be grouped according to the treatment to which they were assigned or randomized:

- For the dose escalation of each treatment group, subjects will be grouped according to the ENTO dose level first received.
- For all dose expansion cohorts, all the subjects were assigned to a dose level of 400 mg.
- For Group B Phase 2 randomization, subjects will be grouped according to the treatment to which they were randomized.

For analyses based on the Safety Analysis Set and the PK Analysis Set, subjects will be grouped according to the actual treatment received. The actual treatment received will differ from the assigned/randomized treatment only when their actual treatment differs from assigned/randomized treatment for the entire treatment duration.

As all treated subjects in this study received the assigned/randomized treatment, the FAS will be the same as the Safety Analysis Set for all treatment groups/cohorts.

Table 3-2 shows the column headers of the summary tables for all treatment groups/cohorts. Column "Total" is not applicable to the efficacy summary tables for Group B Phase 2 randomization and Group C Phase 2.

Table 3-2. Column Headers of the Summary Tables

Treatment Group/Cohort	Column Header			
Group A Phase 1b	Dose Level 0 200 mg BID	Dose Level 1 400 mg BID	Total	
Group A Phase 2	Dose Level 1 400 mg BID			
Group A (Phase 1b + Phase 2)	Dose Level 0 200 mg BID	Dose Level 1 400 mg BID	Total	
Group B Phase 1b	Dose Level 0 200 mg BID	Dose Level 1 400 mg BID	Total	
Group B Phase 2 Safety Run-in	Dose Level 1 400 mg BID			
Group B Phase 2 Randomization	ENTO (400 mg) + Decitabine	ENTO (400 mg) + Azacitidine	Total	
Group C Phase 1b	Dose Level 0 400 mg BID	Dose Level 1 800 mg BID	Total	
Group C Phase 2	Cohort C1A ENTO (400 mg BID)	Cohort C2 ENTO (400 mg BID)	Cohort C3 ENTO (400 mg BID)	Total
Group C (Phase 1b + Phase 2)	Dose Level 0 400 mg BID	Dose Level 1 800 mg BID	Total	

In addition, in Group C, Phase 1b subjects who meet the following criteria will be pooled with Phase 2 Cohort C1A or Cohort C3 as described in Section 1.2:

- Pooled analysis (1): Group C Phase 1b subjects who were R/R AML and received at least 21 days of ENTO (400 mg or 800 mg) and Group C Phase 2 Cohort C1A (400 mg) will be pooled to provide an adequate sample size for futility analysis for subjects with R/R AML.

- Pooled analysis (2): Group C Phase 1b subjects who were previously untreated AML, unfit for Group A or B, and received at least 21 days of ENTO (400 mg or 800 mg), and Group C Phase 2 Cohort C3 will be pooled to provide an adequate sample size for efficacy analyses for subjects with previously untreated AML and unfit for Group A or B.

Only efficacy analyses will be done for the pooled Group C cohorts. Summary will be based on FAS.

Table 3-3 presents the titles and column headers of the summary tables for the pooled analyses of Group C.

Table 3-3. Pooled Analyses of Group C

Pooled Analysis	Title	Column Header		
(1)	Pooled Analysis of Group C Phase 1b and Phase 2 of Cohort C1A (All Doses) in R/R AML	Dose Level 0 400 mg BID	Dose Level 1 800 mg BID	Total
(2)	Pooled Analysis of Group C Phase 1b and Phase 2 of Cohort C3 (All Doses) in Untreated AML	Dose Level 0 400 mg BID	Dose Level 1 800 mg BID	Total

3.3. Strata and Covariates

In Group B Phase 2 randomization, approximately 40 subjects were planned to be randomly assigned to treatment arm ENTO + decitabine or ENTO + azacitidine via the interactive web response system (IWRS) in a 1:1 ratio using a stratified randomization schedule. Stratification will be based on the following variables:

- Age: ≤ 75 years vs > 75 years
- WBC: ≤ 5,000/uL vs > 5,000/uL

Here age will be calculated as (date of randomization – date of birth+1) / 365.25. Subject with age at randomization ≤ 75 years or > 75 years will be assigned to "Age ≤ 75 years" or "Age > 75 years" respectively.

If there are discrepancies in the value used for stratification assignment between the IWRS and the clinical database, the value collected in the clinical database will be used for the summary.

No covariates will be included in the efficacy analyses.

3.4. Examination of Subject Subgroups

Primary efficacy endpoints will be examined in the following subgroups:

- Age (applicable to Groups A and C)
  - — < 60 years
  - — ≥ 60 years

- Age (applicable to Group B)
  - ≤ 75 years
  - > 75 years
- European LeukemiaNet (ELN) Risk Group
  - Favorable
  - Intermediate-I
  - Intermediate-II
  - Adverse
- Age and ELN risk group (applicable to Group A)
- AML Type
  - De novo AML
  - Secondary AML

  Note that the CRF didn't collect AML type directly and this will be derived from the AML subtype collected in the CRF Form "Staging". Subject with the WHO classification subtype "AML with myelodysplasia-related changes" will be considered as "Secondary AML". Subjects with other WHO classification subtypes as well as all the French-American-British (FAB) classification subtypes will be considered as "De novo AML". See Appendix 1 for the list of FAS and WHO classification subtypes.
- MLL
  - With MLL
  - Without MLL
- FLT3-ITD Mutation (applicable to Groups A and B)
  - FLT3-ITD+
  - FLT3-ITD-

- NPM1 Mutation (applicable to Groups A and B)
  - NPM1+
  - NPM1-

For Group B Phase 2 randomization cohort, subgrouping of subjects based on randomization stratification factors will be explored for subgroup analyses as well.

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.

For missing last dosing date of study drug, imputation rules are described in Section 4.2.1. The handling of missing or incomplete dates for disease diagnosis is described in Section 5.3, for SCT and new anticancer therapy in Section 6.1.2, for death in Section 6.2.2, for AE onset in Section 7.1.5.2, and for prior 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 collected at Day 1 (the first dosing date of study drug) (in years) will be used for analyses and presented in listings. If age at Day 1 is not available for a subject, then 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 any study drug, the randomization or 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 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).

If methods based on the assumption that the data are normally distributed are not adequate, analyses may be performed on transformed data or nonparametric analysis methods may be used, as appropriate.

Sparse PK concentration values that are below the limit of quantitation (BLQ) will be presented as "BLQ" in the data listing.

3.8. Analysis Visit Windows

3.8.1. Definition of Baseline and Study Day

Baseline is defined as the last observation prior to the first dose of study drug, unless otherwise specified.

Study Day 1 is defined as the day of first dose of study drug. Study day will be calculated from the first dosing date of study drug and derived as follows:

- For post-dose study days: Assessment Date – First Dosing Date + 1

- For days prior to the first dose: Assessment Date – First Dosing Date

3.8.2. Analysis Visit Windows

The nominal visit as recorded on the CRF will be used when data are summarized by visit. Any data relating to unscheduled visits will not be assigned to a particular visit or time point. However, the following exceptions will be made:

- An unscheduled visit prior to the first dosing of study drug may be included in the calculation of the baseline value, if applicable.
- Unscheduled visits after the first dosing of study drug will be included in determining the maximum postbaseline toxicity grade.
- The analysis window for Morphologic Leukemia-free State (MLFS) rate at Cycle 1 Day 14 is defined as Cycle 1 Day 1 + 13 (± 2) days.

3.8.3. Selection of Data in the Event of Multiple Records in an Analysis Visit Window

Depending on the statistical analysis method, single values may be required for each analysis window. For example, change from baseline by visit usually requires a single value, whereas a time-to-event analysis would not require 1 value per analysis window.

If multiple valid, nonmissing, continuous measurements exist in an analysis window, records will be chosen based on the following rules if a single value is needed:

- For baseline, if there are multiple measurements with the same time or no time recorded on the same day, the average of these measurements (for continuous data) will be used.
- For postbaseline values:
  - The record closest to the nominal day for that visit will be selected.
  - If there are 2 records that are equidistant from the nominal day, the later record will be selected.
  - If there is more than 1 record on the selected day, the average will be taken, unless otherwise specified.

If multiple valid, nonmissing, categorical measurements exist in an analysis window, records will be chosen based on the following rules if a single value is needed:

- For baseline, if there are multiple records with the same time or no time recorded on the same day, the value with the lowest severity will be selected (eg, normal will be selected over abnormal for safety electrocardiogram [ECG] findings).

- For postbaseline visits, if there are multiple records with the same time or no time recorded on the same day, the value with the worst severity within the window will be selected (eg, abnormal will be selected over normal for safety ECG findings).

4. SUBJECT DISPOSITION

4.1. Subject Enrollment and Disposition

A summary of subject enrollment will be provided by treatment group, phase, and dose level, treatment arm, or cohort if applicable, as elaborated in Table 3-2 in Section 3.2, for each investigator within a country. 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 similar enrollment table will be provided by randomization stratum for Group B Phase 2 randomization. If there are discrepancies in the value used for stratification assignment between the IWRS and the clinical database, the value collected in the clinical database will be used for the summary. A listing of subjects with discrepancies in the value used for stratification assignment between the IWRS and the clinical database at the time of data finalization will be provided.

The randomization schedule used for Group B Phase 2 randomization will be provided as an appendix to the CSR.

A summary of subject disposition will be provided by treatment group, phase, and dose level, treatment arm, or cohort if applicable, as elaborated in Table 3-2 in Section 3.2. This summary will present the number of subjects enrolled/randomized, and the number of subjects in each of the categories listed below:

- Full Analysis Set
- Safety Analysis Set
- Not Treated with ENTO

  Treated with ENTO

  — Completed ENTO dosing as specified per protocol

  — Prematurely discontinued ENTO with reasons
- Not Treated with cytarabine (applicable to Group A only)

  Treated with cytarabine (applicable to Group A only)

  — Completed cytarabine dosing as specified per protocol

  — Prematurely discontinued cytarabine with reasons

- Not Treated with daunorubicin (applicable to Group A only)

  Treated with daunorubicin (applicable to Group A only)

  — Completed daunorubicin dosing as specified per protocol

  — Prematurely discontinued daunorubicin with reasons

- Not Treated with decitabine or azacitidine (applicable to Group B only)

  Treated with decitabine or azacitidine (applicable to Group B only)

  — Completed decitabine or azacitidine dosing as specified per protocol

  — Prematurely discontinued decitabine or azacitidine with reasons

- Study Completion Status

  — Completed the protocol-planned duration of the study

  — Prematurely discontinued study with reasons

For the status of study drug and study completion and reasons for premature discontinuation, the number and percentage of subjects in each category will be provided. The denominator for the percentage calculation will be the total number of subjects in the All Enrolled Analysis Set or All Randomized Analysis Set corresponding to that column. A summary of subject disposition with all treatment groups combined will also be provided, presenting the number of subjects screened, the number of subjects enrolled/randomized, the number of subjects in the FAS, the number of subjects in the Safety Analysis Set, and the number of subjects in different study completion statuses. In addition, flowcharts will be provided to depict the disposition.

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

- Reasons for discontinuing study treatment or study
- Reasons for screen failure (will be provided by screening ID number in ascending order)
- Lot number

Listings of ID numbers of the subjects who will be included in the pooled analyses of Group C 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 ENTO, the number of treatment cycles, the level of adherence to ENTO, and the number of doses of chemotherapy if applicable. The following analyses will be presented by treatment group, phase, and dose level, treatment arm, or cohort if applicable, as elaborated in Table 3-2 in Section 3.2. Summaries will be provided for the Safety Analysis Set.

4.2.1. Exposure to ENTO

Total duration of exposure to ENTO will be defined as (last dosing date of ENTO - first dosing date of ENTO + 1), regardless of temporary interruptions in ENTO administration, and will be expressed in weeks using up to 1 decimal place (eg, 4.5 weeks). If the last study drug dosing date is missing, the latest date among the study drug end date, clinical visit date, laboratory sample collection date, and vital signs assessment date that occurred during the on-treatment period will be used.

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, and 1, 2, 3, 6, 9, 12, and 15 months (if appropriate).

The number of induction cycles for Groups A and B and the number of cycles for Group C will be summarized using descriptive statistics. The number and percentage of subjects exposed to a given cycle category for induction therapy for Groups A and B, ENTO monotherapy for Group C, post-remission therapy for Group A Phase 2, and ENTO + Hypomethylating agent maintenance for Group B will be presented. The number and percentage of subjects who received ENTO monotherapy maintenance will also be summarized for Groups A and B.

The number and percentage of subjects who had dose reduction will be summarized.

4.2.2. Adherence to ENTO

The presumed total number of doses administered to a subject will be determined by the data collected on the drug accountability CRF using the following formula:

Total Number of Doses Administered =

$$\left(\sum \text{No. of Doses Dispensed}\right) - \left(\sum \text{No. of Doses Returned}\right)$$

The level of on-treatment adherence to the study drug regimen will be determined by the total amount of study drug administered relative to the total amount of study drug expected to be administered during a subject's actual on-treatment period based on the study drug regimen. Investigator-prescribed interruption and reductions as specified in the protocol will be taken into account. If there are treatment periods that bottles are not returned or the return information is missing, these periods will be excluded from the on-treatment adherence calculation for both total amount of study drug administered and study drug expected to be administered. If subjects never returned any bottle, the adherence will be set as missing.

The level of on-treatment adherence will be expressed as a percentage using the following formula:

$$\text{On-Treatment Adherence (\%)} = \left(\frac{\text{Total Amount of Study Drug Administered}}{\text{Study Drug Expected to be Administered on Treatment}} \right) \text{x } 100$$

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

No formal statistical testing is planned.

By-subject listings of ENTO administration and accountability will be provided separately by subject ID number and visit (in chronological order).

4.2.3. Exposure to Chemotherapy

The exposure to each of the chemotherapies will be summarized by the number of doses received using descriptive statistics. The number and percentage of subjects for each distinct number of doses will be provided.

By-subject listings of chemotherapy administration will be provided.

4.3. Protocol Deviations

Subjects who did not meet the eligibility criteria for study entry, but enrolled in the study will be summarized regardless of whether they were exempted by the sponsor or not. The summary will present the number and percentage of subjects who did not meet at least 1 eligibility criterion and the number of subjects who did not meet specific criteria based on the All Enrolled Analysis Set or All Randomized Analysis Set. 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. The number and percentage of subjects with important protocol deviations by deviation categories will be summarized for the All Enrolled Analysis Set or All Randomized Analysis Set. The deviation categories are as follows:

- IC=Informed consent
- EN=Eligibility Criteria
- XM=Excluded concomitant medication
- NW=Not withdrawn, despite meeting withdrawal criteria
- TA=Wrong treatment or incorrect dose
- TC=Other treatment compliance issue
- OS=Off schedule procedure
- MD=Missing data
- OT=Other

A by-subject listing will be provided for those subjects with important protocol deviation.

5. BASELINE CHARACTERISTICS

The following analyses will be presented by treatment group, phase, and dose level, treatment arm, or cohort if applicable, as elaborated in Table 3-2 in Section 3.2. Summaries will be provided for the 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, ethnicity, and age groups (<65 years vs >=65 years; and the age group defined in Section 3.4 if applicable).

A by-subject demographic listing will be provided.

5.2. Other Baseline Characteristics

Other baseline characteristics include body weight (in kg), height (in cm), body mass index (BMI; in kg/m^2), bone marrow blasts (in %), ECOG performance status, cytogenetics (normal or abnormal), ELN risk group, de novo/secondary AML, MLL status, and molecular mutation assessment. Bone marrow blasts will be based on the blasts in bone marrow aspirate. If blasts in bone marrow aspirate are not available, blasts in bone marrow biopsy will be used. These baseline characteristics will be summarized using descriptive statistics for continuous variables and using number and percentage of subjects for categorical variables.

By-subject listings of other baseline characteristics will be provided.

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).

A summary of disease-specific medical history will be provided. AML classification at screening will be presented by the FAB and the WHO classification subtypes. Subtypes will be summarized using summary statistics for a categorical variable. Time since AML diagnosis (weeks) will be calculated as (date of first dose of study drug – date of diagnosis)/7. Time since AML diagnosis will be summarized by using summary statistics for continuous variables.

General medical history data will not be coded.

By-subject listings of disease-specific and general medical history will be provided.

In deriving the time since AML diagnosis, partial dates of diagnosis 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.

5.4. Prior Anticancer Therapy

For Group C, number of prior regimens and time since the completion of last regimen will be summarized using descriptive statistics. A partial completion date will be imputed using the algorithm defined in Section 5.3.

The prior anticancer therapies, the last regimens subjects received prior to study entry, and the best response to the last regimen will also be summarized.

6. EFFICACY ANALYSES

Assessment of clinical response will be made according to the International Working Group criteria for AML {Cheson 2003}, which is documented in Appendix 5 of the study protocol. The major criteria for judging response assessment include physical examination and examination of blood and bone marrow.

Efficacy analysis will be presented by treatment group, phase, and dose level, treatment arm, or cohort if applicable, as elaborated in Table 3-2 in Section 3.2. In addition, the pooled analyses of Group C for efficacy specified in Sections 6.1, 6.2, and 6.3 will be present by dose level and total as elaborated in Table 3-3 in Section 3.2. Summaries will be provided for the FAS.

6.1. Primary Efficacy Endpoints

6.1.1. Definition of the Primary Efficacy Endpoints

- Complete remission rate at induction completion: defined as the proportion of subjects who achieved morphologic complete remission (CR) at induction completion. Note that CR includes a subcategory of cytogenetic CR (CRc)

- Composite complete remission rate at induction completion: defined as the proportion of subjects who achieved morphologic complete remission (CR) or morphologic complete remission with incomplete blood count recovery (CRi) at induction completion

- Overall response rate at induction completion: defined as the proportion of subjects who achieved morphologic complete remission (CR), morphologic complete remission with incomplete blood count recovery (CRi), or partial remission (PR) at induction completion

6.1.2. Analysis of the Primary Efficacy Endpoints

Complete remission rate, composite complete remission (CR/CRi) rate, and overall response (CR/CRi/PR) rate at induction completion for Groups A and B will be summarized and the corresponding 95% exact CIs based on Clopper-Pearson method will be presented.

Response at induction completion is defined as the best response across the time points that occurred after day 1 of last cycle of induction therapy, and prior to the earliest of cycle 1 day 1 of post-remission or maintenance therapy, date of SCT and date of other anticancer therapy (excluding SCT and conditioning regimen (listed in Appendix 2)). Best response is the best outcome according to the ranking below by decreasing favorable level:

1) Cytogenetic Complete Remission [CRc]

2) Morphologic Complete Remission [CR]

3) Morphologic Complete Remission with Incomplete Blood Count Recovery [CRi]

4) Partial Remission [PR]

5) Morphologic Leukemia-free State [MLFS]

6) Relapse

7) Other

The category "Other" includes 3 subcategories: Treatment Failure [TF], Early Treatment Assessment [ETA], and No Assessment Done. For subjects who had response assessment in the last cycle but didn't achieve any of the first 6 categories listed above at induction completion, TF will be the response at induction completion for those who received 2 induction cycles in Group A or received >= 2 induction cycles in Group B, and ETA will be the response at induction completion for those who only received <= 1 induction cycle. All subjects in "Other" will be considered as nonresponders and will be included in the denominator when calculating the remission rates at induction completion.

Complete remission rate, composite complete remission (CR/CRi) rate, and overall response (CR/CRi/PR) rate per best overall response ever achieved during the treatment for Group C will be summarized and the corresponding 95% exact CIs based on Clopper-Pearson method will be presented.

Best overall response is defined as the best response across all time points prior to SCT and other anticancer therapy (excluding SCT and conditioning regimen). Best response is the best outcome according to the ranking below by decreasing favorable level:

1) Cytogenetic Complete Remission [CRc]

2) Morphologic Complete Remission [CR]

3) Morphologic Complete Remission with Incomplete Blood Count Recovery [CRi]

4) Partial Remission [PR]

5) Morphologic Leukemia-free State [MLFS]

6) Other

The category "Other" includes 2 subcategories: Treatment Failure [TF] and No Assessment Done. All subjects in "Other" will be considered as nonresponders and will be included in the denominator when calculating the remission rates per best overall response.

As a sensitivity analysis, complete remission rate, composite complete remission (CR/CRi) rate, and overall response (CR/CRi/PR) rate per best overall response ever achieved during the treatment will be summarized for Groups A and B. The category "Other" includes 3 subcategories: Treatment Failure [TF], Early Treatment Assessment [ETA], and No Assessment Done. For subjects who had response assessment but didn't achieve any of the first 5 categories

listed above as the best overall response, TF will be the best overall response for those who received 2 induction cycles in Group A or received >= 2 induction cycles in Group B, and ETA will be the best overall response for those who only received <= 1 induction cycle. All subjects in "Other" will be considered as nonresponders and will be included in the denominator when calculating the remission rates per best overall response.

As an example, assuming a subject in Group A received two induction cycles and discontinued all study drugs, if subject achieved PR at end of Cycle 1 but relapsed at end of Cycle 2, the best overall response is PR while the response assessment at induction completion is relapse.

When the date of initiation of SCT/anticancer 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 last 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.

The following subgroup analyses will be provided for primary analysis:

- Age (<60 years, >=60 years; applicable to Groups A and C)
- Age (≤75 years, >75 years; applicable to Group B)
- ELN risk group (Favorable, Intermediate -I, Intermediate -II, Adverse)
- De novo and Secondary AML
- Age and ELN risk group (applicable to Group A)
- With and without MLL
- FLT3-ITD mutation (applicable to Groups A and B)
- NPM1 mutation (applicable to Groups A and B)

For Group B phase 2 randomization, similar analyses will be provided by randomization stratum if there is sufficient sample size in the subgroup. The denominator for the percentage of subjects in the stratum will be the total number of randomized subjects. If there are discrepancies in the value used for stratification assignment between the IWRS and the clinical database, the value collected in the clinical database will be used for the summary.

Data listings for the clinical responses will be presented.

6.2. Secondary Efficacy Endpoints

6.2.1. Definition of Secondary Efficacy Endpoints

- Event free survival (EFS) - defined for all subjects and it is measured from the start of the study therapy until the date of treatment failure, AML relapse or death from any cause, whichever occurs first

- Overall survival (OS) – defined as the interval from the start of the study therapy to the death from any cause

Every attempt will be made to ensure that complete death dates are recorded. In those rare instances where complete death dates are not recorded, the following algorithm will be used:

- 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 last known alive date + 1, whichever is later.

- If day and month are missing but year is available, then the imputed date will be 01Jan of that year or the last known alive date + 1, whichever is later.

6.2.2. Analysis of the Secondary Endpoints

Subjects will be considered as treatment failure if having at least one efficacy assessment prior to SCT and other anticancer therapy (excluding SCT and conditioning regimen) but none of these efficacy assessments is CRc, CR, CRi, or PR; date of treatment failure will be the date of last adequate efficacy assessment prior to SCT and other anticancer therapy (excluding SCT and conditioning regimen). The events and censoring rules are detailed in Table 6-1. Of note, other anti-cancer therapy excludes SCT and conditioning regimen in this table, and the criteria are hierarchical: subjects who meet the criteria on the top will be excluded from the criteria on the bottom.

Table 6-1. Event/Censoring Rules for EFS

Criteria	Event or Censored	Date of Event/Censoring
Relapse, no other anti-cancer therapy or prior to the start of other anti-cancer therapy, and • had SCT prior to relapse, OR • no SCT prior to relapse, and days from last response assessment prior to relapse to relapse was within the following window (2 consecutive response assessments): For Group A: — <=60 days (2 cycles (including the time waiting for	Event	Date of first relapse

count recovery) + 4 days) if didn't receive post-remission cycle — <=120 days (4 cycles + 8 days) if received post-remission cycle but didn't receive ENTO mono maintenance cycle — <=240 days (8 cycles + 16 days) if received ENTO mono maintenance cycle		
For Group B: — <=120 days (4 cycles + 8 days) if didn't receive maintenance cycle — <= 240 days (8 cycles + 16 days) if received maintenance cycle For Group C: — <= 60 days (2 cycles + 4 days) if received <= 2 cycles — <= 120 days (4cycles + 8 days) if received 3-4 cycles — <= 240 days (8 cycles + 16 days) if received > 4 cycles		
Treatment failure, and days from last response assessment prior to treatment failure or first dosing date, whichever is later, to treatment failure was within the window defined above	Event	Date of treatment failure
Death without treatment failure/relapse/other anti-cancer therapy, and • had SCT, OR • no SCT, and days from the date of last assessment or first dosing date, whichever is later, to the date of death was within the window defined above	Event	Date of death
No postbaseline assessment, no death	Censored	Date of first dose
No treatment failure/relapse/death	Censored	Date of last response assessment (and prior to other anti-cancer therapy if any) or first dosing date, whichever is later

Other anti-cancer therapy started prior to treatment failure/relapse/death	Censored	Date of last response assessment prior to other anti-cancer therapy or first dosing date, whichever is later
Days from last response assessment prior to treatment failure/relapse/death or first dosing date, whichever is later, to treatment failure/relapse/death was not within the window defined above	Censored	Date of last response assessment prior to treatment failure/relapse/death or first dosing date, whichever is later

Censoring Rules for OS:

- For a subject who is not known to have died by the end of study follow-up, OS is censored on the date the subject was last known to be alive.

For EFS or OS in months, the calculation is based on the following formula:

(date of event/censoring- date of first dose + 1)/30.4375.

EFS and OS will be analyzed using Kaplan-Meier (KM) methods. The KM estimate of the survival function will be computed and the results will be presented using KM curves. The median will be provided along with the corresponding 95% CI. Additionally, the 25% and 75% percentiles for these endpoints will also be provided.

Follow up time for OS will be summarized as continuous variable with descriptive statistics.

- For a subject who is not known to have died by the end of study follow-up, duration of OS follow up in months = (date of last known to be alive – date of first dose + 1)/30.4375
- For the remaining subjects, duration of OS follow up in months = (date of follow-up cutoff – date of first dose + 1)/30.4375

Data listing for EFS and OS will be presented.

6.3. Exploratory Efficacy Endpoints

6.3.1. Definition of the Exploratory Efficacy Endpoints

- CCI [redacted]

- CCI [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

6.3.2. Analysis of the Exploratory Efficacy Endpoints

CCI [redacted]

[redacted]

[redacted]

Table 6-2. Event/Censoring Rules for RFS

Criteria	Event or Censored	Date of Event/Censoring
Relapse, no other anti-cancer therapy or prior to the start of other anti-cancer therapy, and • had SCT prior to relapse, OR • no SCT prior to relapse, and days from last response assessment prior to relapse to relapse was within the following window (2 consecutive response assessments): For Group A: — <=60 days (2 cycles (including the time waiting for count recovery) + 4 days) if didn't receive post-remission cycle — <=120 days (4 cycles + 8 days) if received post-remission cycle but didn't receive ENTO mono maintenance cycle — <=240 days (8 cycles + 16 days) if received ENTO mono maintenance cycle For Group B: — <=120 days (4 cycles + 8 days) if didn't receive maintenance cycle — <= 240 days (8 cycles + 16 days) if received maintenance cycle For Group C: — <= 60 days (2 cycles + 4 days) if received <= 2 cycles — <= 120 days (4cycles + 8 days) if received 3-4 cycles — <= 240 days (8 cycles + 16 days) if received > 4 cycles	Event	Date of first relapse

Death without relapse/other anti-cancer therapy, and • had SCT, OR • no SCT, and days from the date of last assessment or first dosing date, whichever is later, to the date of death was within the window defined above	Event	Date of death
No relapse/death	Censored	Date of last response assessment (and prior to other anti-cancer therapy if any) or first dosing date, whichever is later
Other anti-cancer therapy started prior to relapse/death	Censored	Date of last response assessment prior to other anti-cancer therapy or first dosing date, whichever is later
Days from last response assessment prior to relapse/death or first dosing date, whichever is later, to relapse/death was not within the window defined above	Censored	Date of last response assessment prior to relapse/death or first dosing date, whichever is later

Remission duration will be analyzed using cumulative incidence by considering competing risks. Relapse (the first situation in Table 6-2) is considered as the event of interest. Death without relapse (the second situation in Table 6-2) is a competing risk as death eliminates the occurrence of relapse. The other situations described in Table 6-2 are considered as censored. There are three statuses: 0=censored, 1=relapse, and 2=death without relapse. SAS 9.4 PROC LIFETEST with statement TIME and option EVENTCODE=1 will be used. The estimates of the cumulative incidence of relapse (CIR) at 1, 3, 6, 12, 18, and 24 months (if appropriate) will be reported with the associated 95% CIs.

TTR will be summarized using descriptive statistics.

Data listing of TTR, RFS, and remission duration will be presented.

TTC will not be analyzed as data are not intensively measured/collected.

MRD rates will not be summarized as data are not measured/collected at all visits. A by-subject listing of MRD level will be provided.

The number and percentage of subjects who underwent SCT will be summarized and the corresponding 95% exact CI will be presented. In addition, the same analysis will be performed for subjects who underwent SCT at induction completion, post-remission, and maintenance completion, if applicable. A by-subject listing of SCT will be provided.

6.4. Other Efficacy Measures

Spaghetti plots of blasts (%) in bone marrow aspirate through the induction cycles for Group A and Group B and all cycles for Group C will be provided. For visits at which blasts in bone marrow aspirate are not available, blasts in bone marrow biopsy will be used. Since different subjects will be treated for different time periods per cycle and different number of cycles, the x-axis of the spaghetti plot, which is the study day, will be adjusted as follows to distinguish bone marrow results among the cycles:

Group A

For results in Cycle 1: Relative Day to Cycle 1 Day 1 + 15

For results in Cycle 2: Relative Day to Cycle 2 Day 1 + 102

Group B

For results in Cycle 1: Relative Day to Cycle 1 Day 1 + 16

For results in Cycle 2: Relative Day to Cycle 2 Day 1 + 61

For results in Cycle 3: Relative Day to Cycle 3 Day 1 + 106

For results in Cycle 4: Relative Day to Cycle 4 Day 1 + 151

A by-subject listing of bone marrow assessments, including both bone marrow aspirate and bone marrow biopsy, will be provided.

By-subject listings of ECOG performance status, cytogenetics, fluorescent in situ hybridization (FISH) analysis, and molecular mutation will be provided separately.

6.5. Changes From Protocol-Specified Efficacy Analyses

TTC will not be analyzed as data are not intensively measured/collected.

MRD rates will not be summarized as data are not measured/collected at all visits. A by-subject listing of MRD level will be provided.

7. SAFETY ANALYSES

Safety analysis will be presented by treatment group, phase, and dose level, treatment arm, or cohort if applicable, as elaborated in Section 3.2. Dose level for phase 1b is defined as the initial dose level a subject actually received.

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 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. 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 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 GS-9973", "Related to Study Treatment Cytarabine", "Related to Study Treatment Daunorubicin", "Related to Study Treatment Decitabine", or "Related to Study Treatment Azacitidine". 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 AEs met the definitions of SAE 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 before database 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

AEs with incomplete onset dates will be identified and the incomplete dates will be imputed for TEAE determination. The imputation rules are as follows:

- 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.

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.

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

- TEAEs
- Grade 3 or higher TEAE
- TEAEs related to ENTO
- TE SAEs

- TE SAEs related to ENTO
- TEAEs leading to ENTO discontinuation
- TEAEs leading to ENTO dose reduction or interruption

For AEs described below, summaries will be provided by SOC and PT:

- TEAEs
- TEAEs related to ENTO
- TE SAEs
- TE SAES related to ENTO
- TEAEs leading to ENTO discontinuation
- TEAEs leading to death

A brief, high-level summary of TEAEs described above will be provided by the number and percentage of subjects who experienced the above TEAEs. This summary table will also include TEAE related to chemotherapy (Groups A and B), Grade 3 or higher TEAE related to ENTO, Grade 3 or higher TEAE related to chemotherapy (Groups A and B), TE SAEs related to chemotherapy (Groups A and B), TEAEs leading to chemotherapy discontinuation (Groups A and B), TEAE leading to chemotherapy dose reduction or interruption (Groups A and B), and death.

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 HLT within each SOC (if applicable) 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 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
- SAEs
- Deaths
- TEAEs leading to ENTO discontinuation

7.1.6.2. Summary of Deaths

A summary (number and percentage of subjects) of deaths will be provided. The 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

The attribution of death will also be summarized.

7.1.7. Dose Limiting Toxicity

DLT will be analyzed with the DLT Analysis Set.

A listing of the DLT AEs will be provided by treatment group, dose level, subject ID, DLT category, preferred term, associated severity grade, and date of onset/resolution, if available.

A summary of DLT will be presented by SOC and PT.

7.2. Laboratory Evaluations

Local 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. 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 time point in chronological order for hematology, serum chemistry, coagulation, urinalysis, and serology separately. Values falling outside of the relevant reference range and/or having a severity grade of 1 or higher on the CTCAE severity grade will be flagged in the data listings, as appropriate.

7.2.1. Summaries of Numeric Laboratory Results

Descriptive statistics will be provided for each laboratory test specified in the study protocol as follows:

- Baseline values
- Values at each postbaseline visit
- Postbaseline maximum value
- Postbaseline minimum value
- Change from baseline to postbaseline maximum value
- Change from baseline to postbaseline minimum value

A baseline laboratory value will be defined as the last measurement obtained on or prior to the date/time of first dose of study drug. Change from baseline to a postbaseline visit will be defined as the visit value minus the baseline value. The mean, median, Q1, Q3, minimum, and maximum values will be displayed to the reported number of digits; StD values will be displayed to the reported number of digits plus 1.

In the case of multiple values in an analysis window, data will be selected for analysis as described in Section 3.8.3.

7.2.2. 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.

7.2.2.1. 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.

7.2.2.2. Summaries of Laboratory Abnormalities

The summary (number and percentage of subjects) for 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.

For all summaries of laboratory abnormalities, the denominator is the number of subjects with nonmissing postbaseline values up to 30 days after last dosing date.

A by-subject listing of treatment-emergent laboratory abnormalities will be provided by subject ID number and time point 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.

7.2.3. Shift in CTCAE Grade Relative to Baseline

Shift tables will be presented by showing change in CTCAE grade from baseline to the worst postbaseline grade up to 30 days after last dosing date. The percentage will be based on subjects with values available at both baseline and postbaseline.

7.2.4. Graphics of Numeric Laboratory Results

Spaghetti plots of circulating blasts (%), neutrophils, platelets, and WBC through the induction treatment for Group A and Group B and all cycles for Group C will be provided. Since different subjects will be treated for different time periods per cycle and different number of cycles, the x-axis of the spaghetti plot, which is the study day, will be adjusted following the algorithms in Section 6.4 to distinguish laboratory results among the cycles.

7.3. Body Weight and Vital Signs

Descriptive statistics will be provided for body weight and vital signs as follows:

- Baseline value
- Values at each postbaseline visit
- Postbaseline maximum value
- Postbaseline minimum value
- Change from baseline to postbaseline maximum value
- Change from baseline to postbaseline minimum value

A baseline value will be defined as the last available value collected on or prior to the date/time of first dose of study drug. Change from baseline to a postbaseline visit will be defined as the postbaseline value minus the baseline value. Body weight and vital signs measured at unscheduled visits will be included for the baseline value selection.

In the case of multiple values in an analysis window, data will be selected for analysis as described in Section 3.8.3. No formal statistical testing is planned.

A by-subject listing of vital signs will be provided by subject ID number and time point in chronological order. Body weight will be included in the vital signs listing.

7.4. Prior and Concomitant Medications

Medications collected at screening and during the study will be coded using the current version of the 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. 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 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 Results

Electrocardiogram (ECG) was performed at screening and may be performed at the Investigator's discretion following enrollment.

A by-subject listing for ECG assessment results will be provided by subject ID number and time point in chronological order.

7.6. Other Safety Measures

Platelet transfusions through induction cycles will be summarized for each induction cycle for Groups A and B. For Group C, platelet transfusions will be summarized for each cycle. Number of platelet transfusions per subject and number of platelet transfusions per week will be presented using descriptive statistics. For each cycle,

$$\text{Number of platelet transfusions per week} = \frac{\text{Number of platelet transfusions within the cycle}}{\text{Number of days of the cycle}} \times 7$$

For the last cycle, the number of days of cycle will be calculated as the date of last dose of the study drug – the start date of the cycle+1.

Summaries will be based on the Safety Analysis Set.

A by-subject listing of different types of transfusions required through the study will be provided.

A by-subject listing will be provided for the results of all pregnancy tests conducted in the study.

On-treatment and post-treatment anticancer therapies will be listed for applicable subjects.

7.7. Changes From Protocol-Specified Safety Analyses

For Groups A and B, safety data will not be presented by the lead-in ENTO therapy phase and the induction chemotherapy phase separately due to no washout period.

8. PHARMACOKINETIC (PK) ANALYSES

8.1. PK Sample Collection

PK blood samples will be collected on

Group A:

- Phase 1b: Cycle 0 Days 1, 8, and 14 at pre-dose and 2 hour post-dose of ENTO; Cycle 1 Days 3 and 7 at pre-dose, 2 hours, and 4 hours post-dose of ENTO; Cycle 1 Day 14 at pre-dose and 2 hours post-dose of ENTO

- Phase 2: Cycle 0 Days 1, 8, and 14 at pre-dose and 2 hour post-dose of ENTO; Cycle 1 (and 2, if needed) Day 3 at pre-dose, 2 hours, and 4 hours post-dose of ENTO; Intensive PK on Cycle 1 Day 7 at pre-dose, 1, 2, 3, 4, 6, 8, and 12 hours post-dose of ENTO; Cycle 1 Day 14 at pre-dose and 2 hours post-dose of ENTO; Day 5 and Day 28 of each Post-Remission cycle at pre-dose and 2 hours post-dose of ENTO; Day 28 of each Maintenance cycle at pre-dose and 2 hours post-dose of ENTO

Group B:

- Phase 1b and Phase 2 Safety Run-in: Cycle 0 Days 1, 8, and 14 at pre-dose and 2 hour post-dose of ENTO; Induction Cycle 1 Day 8 at pre-dose, 2 hours, and 4 hours post-dose of ENTO; Day 8 of subsequent induction cycles at pre-dose and 2 hours post-dose of ENTO; Day 28 of every induction cycle at pre-dose and 2 hours post-dose of ENTO; Day 28 of every Entospletinib + Hypomethylating agent Maintenance cycle at pre-dose and 2 hours post-dose of ENTO; Day 28 of every Entospletinib Maintenance cycle at pre-dose and 2 hours post-dose of ENTO

- Phase 2 Randomization: Cycle 0 Days 1 and 5 at pre-dose and 2 hour post-dose of ENTO; Induction Cycle 1 Day 8 at pre-dose, 2 hours, and 4 hours post-dose of ENTO; Day 8 of subsequent induction cycles at pre-dose and 2 hours post-dose of ENTO; Day 28 of every induction cycle at pre-dose and 2 hours post-dose of ENTO; Day 28 of every Entospletinib + Hypomethylating agent Maintenance cycle at pre-dose and 2 hours post-dose of ENTO; Day 28 of every Entospletinib Maintenance cycle at pre-dose and 2 hours post-dose of ENTO

Group C:

- Phase 1b: Cycle 1 Days 1, 8, 14, and 28 at pre-dose and 2 hours post-dose of ENTO

- Phase 2: Cycle 1 Days 1, 8, 14, and 28, and Day 28 of each subsequent cycle at pre-dose and 2 hours post-dose of ENTO

8.2. ENTO Plasma Concentrations Analysis

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

8.3. Statistical Analysis Methods

The following listing will be provided:

- ENTO plasma concentrations and PK sampling details by subject including deviations in scheduled and actual draw times and procedures

No PK parameters will be generated.

9. BIOMARKER ANALYSES

Baseline bone marrow mononuclear cells (BM-MNCs) from bone marrow aspirates will be analyzed for mRNA expression of Homeobox A9 (HOXA9)/Myeloid Ecotropic Viral Integration Site 1 (MEIS1) using a custom Nanostring assay. Expression data will be first normalized using the NanoStringNorm R package with 18 housekeeping genes. HOXA9/MEIS1 expression will then be compared to that in pooled BM-MNCs from healthy donors (n=20). Subjects will be classified into HOXA9/MEIS1 high and low groups using a cutoff of 3-fold higher than a pooled healthy donor samples:

- HOXA9/MEIS1 status=high: sample/normal >= 3 for both HOXA9 and MEIS1
- HOXA9/MEIS1 status=low: sample/normal < 3 for either HOXA9 or MEIS1

The following analyses will be performed by HOXA9/MEIS1 status for Group A subjects who are in the FAS and have baseline HOXA9/MEIS1 expression data:

- Complete remission rate, composite complete remission (CR/CRi) rate, and overall response (CR/CRi/PR) rate at induction completion will be summarized and the corresponding 95% exact CIs based on Clopper-Pearson method will be presented.
- EFS and OS will be analyzed using KM methods and KM curves will be provided.

In addition, a by-subject level listing of HOXA9/MEIS1 expression values, classified HOXA9/MEIS1 status, response at induction completion, EFS, and OS will be provided for these subjects.

10. REFERENCES

Cheson BD, Bennett JM, Kopecky KJ, Buchner T, Willman CL, Estey EH, et al. Revised recommendations of the International Working Group for Diagnosis, Standardization of Response Criteria, Treatment Outcomes, and Reporting Standards for Therapeutic Trials in Acute Myeloid Leukemia. J Clin Oncol 2003;21 (24):4642-9.

11. SOFTWARE

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

12. APPENDICES

Appendix 1. List of FAB/WHO Classification Subtypes

FAB Classification	WHO Classification
M0: Undifferentiated acute myeloblastic leukemia	AML with certain genetic abnormalities
M1: Acute myeloblastic leukemia with minimal maturation	AML with myelodysplasia-related changes
M2: Acute myeloblastic leukemia with maturation	AML related to previous chemotherapy or radiation
M3: Acute promyelocytic leukemia (APL)	• AML not otherwise specified: • AML with minimal differentiation (M0) • AML without maturation (M1) • AML with maturation (M2) • Acute myelomonocytic leukemia (M4) • Acute monocytic leukemia (M5) • Acute erythroid leukemia (M6) • Acute megakaryoblastic leukemia (M7) • Acute basophilic leukemia • Acute panmyelosis with fibrosis
M4: Acute myelomonocytic leukemia	
M4 eos: Acute myelomonocytic leukemia with eosinophilia	
M5: Acute monocytic leukemia	
M6: Acute erythroid leukemia	
M7: Acute megakaryoblastic leukemia	

Appendix 2. List of Conditioning Regimen

Conditioning Regimen (Preferred Term)
ANTITHYMOCYTE IMMUNOGLOBULIN
BUSULFAN
CYCLOPHOSPHAMIDE
ETOPOSIDE
FLUDARABINE
MELPHALAN
MELPHALAN HYDROCHLORIDE
THIOTEPA