CLINICAL STUDY PROTOCOL

Study Title:	A Phase 1b/2 Study of Entospletinib (GS-9973) Monotherapy and in Combination with Chemotherapy in Patients with Acute Myeloid Leukemia (AML)
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404
IND Number:	116416
EudraCT Number:	2016-003353-16
Clinical Trials.gov Identifier:	NCT02343939
Indication:	Acute Myeloid Leukemia
Protocol ID:	GS-US-339-1559
Gilead Medical Monitor:	Name: PPD Telephone: PPD E-mail: PPD
Protocol Version/Date:	Original: 05 December 2014 Amendment 1: 21 January 2015 Amendment 2: 12 May 2015 Amendment 3: 24 November 2015 Amendment 4: 05 August 2016 Amendment 5: 14 February 2017 Amendment 6: 04 August 2017 Amendment 7: 15 February 2018

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PROTOCOL SYNOPSIS
Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404

Study Title:	A Phase 1b/2 Study of Entospletinib (GS-9973) Monotherapy and in Combination with Chemotherapy in Patients with Acute Myeloid Leukemia (AML)
IND Number:	116416
Study Centers Planned:	Estimated 25 centers. Ohio State University (OSU) will be the coordinating center. The Phase 2 portion of the study will include centers in North America and Germany.
Objectives:	The primary objectives are: • To demonstrate the overall safety of entospletinib (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 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: • 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 when treated with ENTO monotherapy or ENTO in combination with chemotherapy The exploratory objective of this study is: • CCI [redacted]

Study Design:

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.

Group A Phase 1b (Dose Escalation)

Note: At the time of this amendment, 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 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.

Group A Phase 2 (Dose Expansion)

Note: At the time of this amendment, 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 CR/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.

Group B Phase 1b (Dose Escalation)

Note: At the time of this amendment, 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.

Group B Phase 2 (Dose Expansion)

Note: At the time of this amendment, 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 (DLT window, Section 3.2), 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 (≤ 5,000/μL or > 5,000/μL). 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.

Group C Phase 1b (Dose Escalation)

Note: At the time of this amendment, 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

Group C Phase 2 (Dose Expansion)

Note: At the time of this amendment, Cohort C1A had completed enrollment (n=15). This amendment identifies the closure of Cohort C3 to further enrollment (n=12).

	Relapsed/refractory 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. **Cohort C1A:** This cohort is designed to enroll 15 relapsed/refractory AML subjects. 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 this time, 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 relapsed/refractory AML subjects with MLL gene rearrangement. **Cohort C3:** This cohort is designed to enroll previously untreated AML subjects who are unfit (eg, very elderly, have multiple comorbidities, and a poor ECOG/performance status) for chemotherapy or hypomethylating agent, or refuse either of these 2 treatment options. This amendment identifies enrollment closure of this cohort.
Number of Subjects Planned:	Approximately 190 subjects
Target Population:	Subjects with Acute Myeloid Leukemia
Duration of Treatment:	Subjects may continue receiving ENTO until treatment failure, planned completion of treatment, start of new therapy, unacceptable toxicity, withdrawal of consent by subject, or withdrawal from study by investigator.
Safety Review:	Safety data will be reviewed continuously during the course of the study. The Cancer Therapy Evaluation Program (CTEP) Active Version of the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 will be utilized for Adverse Event (AE) reporting.
Main Diagnosis and Disease Eligibility Criteria:	AML (de novo, therapy related [t-AML], or secondary AML) All groups will build on ENTO backbone <u>Group A</u> • Subjects age ≥ 18 years with previously untreated AML by World Health Organization (WHO) criteria, excluding acute promyelocytic leukemia (M3), who are able and should receive up to 2 cycles of induction chemotherapy with 7+3 as determined by the treating physician

Group B

- Subjects age > 70 years with previously untreated AML by WHO criteria, excluding acute promyelocytic leukemia (M3)
- Subjects age ≤ 70 years with previously untreated AML by WHO criteria, excluding acute promyelocytic leukemia (M3), who refuse or are unable to receive 7+3 as determined by the treating physician

Group C Phase 1b (Dose Escalation)

- Subjects age ≥ 18 years with relapsed/refractory AML by WHO criteria, excluding acute promyelocytic leukemia (M3)
- Subjects with previously untreated AML by WHO criteria, excluding acute promyelocytic leukemia (M3), and who would have met disease eligibility criteria for Group A or B but refuse or are unable to receive 7+3 or decitabine chemotherapy as determined by the treating physician

Group C Phase 2 (Dose Expansion)

- Cohort C1A: Subjects age ≥ 18 years with relapsed or refractory AML by WHO criteria, excluding acute promyelocytic leukemia (M3)
- Cohort C2: Subjects age ≥ 18 years with relapsed/refractory AML with MLL
- Cohort C3: Subjects with previously untreated AML by WHO criteria, excluding acute promyelocytic leukemia (M3), and who would have met disease eligibility criteria for Group A or B but refuse or are unable to receive chemotherapy and hypomethylating agent as determined by the treating physician

See Section 4 for complete eligibility criteria.

Test Product, Dose, and Mode of Administration:

ENTO is available as 200 mg strength tablets and will be administered orally every 12 hours while in a fasted state. During dose escalation, 200, 400, or 800 mg of ENTO will be administered. There is no intra-subject dose escalation.

The recommended Phase 2 dose is ENTO 400 mg.

Please refer to the respective packaging inserts for daunorubicin, cytarabine, decitabine, and azacitidine for more information.

Criteria for Evaluation:

Safety: Grading of adverse events and laboratory abnormalities. The CTEP Active Version of the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 will be utilized for Adverse Event (AE) reporting. 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.

Efficacy: Assessment of clinical response will be made according to the modified International Working Group criteria. The major criteria for evaluating response assessment will include physical examination and examination of blood and bone marrow.

Pharmacokinetics/ Biomarkers: CCI [redacted].

Endpoints:

Primary Endpoints:

Safety

- Occurrence of adverse events and laboratory abnormalities defined as DLTs for ENTO in combination with standard dose cytarabine and daunorubicin in subjects with previously untreated AML (Group A)
- Occurrence of adverse events and laboratory abnormalities defined as DLTs for ENTO in combination with hypomethylating agent in subjects with previously untreated AML who are unable to receive 7+3 chemotherapy (Group B)
- Occurrence of adverse events and laboratory abnormalities defined as DLTs for ENTO as a single agent in subjects with relapsed/refractory AML with or without MLL or previously untreated AML (Group C)

Efficacy

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

Secondary Endpoints:

Exposure

- Drug administration and duration of exposure of study treatment

Safety

- Occurrence of AEs and laboratory abnormalities not defined as DLTs

Efficacy

- Event free survival (EFS) – defined for all subjects and 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 death from any cause.

Exploratory Endpoints:

CCI

Statistical Methods: Appropriate data analysis sets will be defined. The full analysis set (FAS) will include data from all subjects who receive ≥ 1 dose of study drug. Other data sets will be defined and will include data from subjects who have the necessary baseline and on-study measurements to provide interpretable results for specific parameters of interest.

Subject characteristics and study results will be described and summarized by group and dose level for the relevant analysis sets. Descriptive summaries will be prepared to show sample size, mean, standard deviation (StD), 95% confidence intervals (CIs) on the mean, median, minimum, and maximum for continuous variables and counts, percentages, and 95% CIs on the percentage for categorical variables.

Based on the FAS, information regarding study treatment administration, study drug compliance, safety variables, efficacy variables, and post-study therapies will be described and summarized. Using data from the relevant evaluable data sets, study drug plasma concentrations will also be described and summarized.

Sample Size Calculation

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.

Assuming 2 planned dose levels for escalation are tested with up to 6 subjects per level and assuming 10% of subjects are unevaluable during dose escalation, up to 14 subjects will be enrolled in each group in phase 1b. In Group B, 6 subjects will be enrolled to evaluate the safety of ENTO in combination with azacitidine prior to enrollment of the expansion cohort.

In Group B, following the safety run-in, approximately 40 subjects will be randomized in a 1:1 manner to ENTO in combination with decitabine or ENTO in combination with azacitidine.

In Group C2, approximately 15 subjects will be enrolled.

See detailed sample size calculation in Section 8.9.

Note: This amendment identifies the closure of Cohort C3 to further enrollment (n=12).

This study will be conducted in accordance with the guidelines of Good Clinical Practice (GCP) including archiving of essential documents.

GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

°C	degrees Celsius
°F	degrees Fahrenheit
7+3	cytarabine and daunorubicin chemotherapy
ADR	adverse drug reaction
AE	adverse event
AKT	protein kinase B (PKB)
ALC	absolute lymphocyte count
ALT	alanine aminotransferase
AM	morning
AML	acute myeloid leukemia
ANC	absolute neutrophil count
ARA-C	cytarabine arabinoside
ARA-CTP	ARA-C triphosphate
ARA-CMP	ARA-C monophosphate
AST	aspartate aminotransferase
ATP	adenosine triphosphate
AUC	area under the concentration versus time curve
AUC_{tau}	area under the plasma concentration versus time curve over the dosing interval (tau)
B-ALL	acute B-lympho blastic leukemia
BAT	basophil activation test
BCR	B-cell receptor
BID	bis in die (twice a day)
BLNK	B-cell linker protein
BM	Bone Marrow
BTK	bruton tyrosine kinase
BUN	blood urea nitrogen
C_{max}	maximum observed concentration of drug
CBC	complete blood count
CFR	(United States) Code of Federal Regulations
CI	confidence interval
CLL	chronic lymphocytic leukemia
CNS	central nervous system
cm/s	centimeter per second
CR	complete remission
CRc	cytogenetic complete remission
CRi	morphologic CR with incomplete blood count recovery
CRO	contract research organization
CT	computed tomography

CTA	clinical trial application
CTC	circulating tumor cells
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DLBCL	diffuse large B-cell lymphoma
dCMP	deoxycytidine monophosphate
DCR	disease control rate
DDI	drug to drug interaction
DICOM	Digital Imaging and Communication in Medicine
dL	deciliter
DLT	dose limiting toxicity
DNA	deoxyribonucleic acid
DOR	duration of response
PVE	Pharmacovigilance and Epidemiology
EC	ethics committee
EC_{50}	50% effective inhibitory concentration
ECG	electrocardiogram
eCRF	electronic case report form(s)
EDC	electronic data capture
EOS	end of study
EFS	event free survival
ENTO	Entospletinib, GS-9973
EU	European
FDA	(United States) Food and Drug Administration
FISH	fluorescent in situ hybridization
FL	follicular lymphoma
FLIPI	follicular lymphoma international prognostic index
FSH	follicle stimulating hormone
g	gram
GCP	Good Clinical Practice (Guidelines)
G-CSF	granulocyte colony-stimulating factor
GM-CSF	granulocyte-macrophage colony-stimulating factor
GSI	Gilead Sciences, Inc.
h, hr	hour
H2RA	histamine 2 receptor antagonist
HBc	hepatitis B core
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
β-HCG	beta human chorionic gonadotropin
HCV	hepatitis C virus

HIV	human immunodeficiency virus
IB	investigator's brochure
IC	immune-complex
IC_{50}	concentration necessary to achieve 50% inhibition of target
ICF	informed consent form
ICH	International Conference on Harmonisation
ID	identification
IEC	independent ethics committee
IFE	immunofixation electrophoresis
IND	Investigational New Drug (Application)
iNHL	indolent non-Hodgkin lymphoma
IRB	institutional review board
ITAM	immunoreceptor tyrosine-based activation motifs
IWCLL	International Workshop on Chronic Lymphocytic Leukemia
IxRS	Interactive Voice/Web Response System
IV	intravenous
IVD	intravenous drip
K_2-EDTA	potassium-ethylenediaminetetraacetic acid
kg	kilogram
L	liter
LD	longest diameter
LDH	lactate dehydrogenase
LPD	longest perpendicular diameter
LVD	longest vertical dimension
MAPK	mitogen-activated protein kinase
MCL	mantle cell lymphoma
mg	milligram
mL	milliliter
MLFS	morphologic leukemia free state
MLL	mixed lineage leukemia
mm	millimeter
MMRM	mixed model for repeated measures
Morphologic CR	morphologic complete remission
MRD	minimal residual disease
MRI	magnetic resonance imaging
mTOR	mammalian target of rapamycin
MTX	methotrexate
MZL	marginal zone lymphoma
NCI	National Cancer Institute
ND	no disease

NE	not evaluable
ng	nanogram
NHL	non-Hodgkin lymphoma
nM	nanomolar
NOAEL	no observable adverse effect level
OS	overall survival
ORR	objective response rate
PBMC	peripheral blood mononuclear cells
PD	progressive disease
PET	positron-emission tomography
PI	prescribing information
PI	principal investigator
PI3K	phosphatidylinositol 3-kinase
PK	pharmacokinetic(s)
PLT	platelets
PM	evening
PO	by mouth (orally)
PPD	product of the perpendicular diameters
PR	partial remission
pSYK	phospho-spleen tyrosine kinase
PTM	Placebo to match
QD	once-daily
RA	refractory anemia
RBC	red blood cell
REB	research ethics board
RFS	relapse - free survival
RNA	ribonucleic acid
RP2D	recommended Phase 2 dose
SCT	stem cell transplant
SD	stable disease
SD	standard deviation
SDD	spray dried dispersion
SADR	serious adverse drug reactions
SAE	serious adverse event
sMTD	subject maximum tolerated dose
SOP	standard operating procedure
SPD	sum of the products
SPEP	serum protein electrophoresis
SUSAR	Suspected Unexpected Serious Adverse Reaction
SYK	spleen tyrosine kinase

T_{max}	time (observed time point) of C_{max}
$T_{½}$	an estimate of the terminal elimination half-life of the drug, calculated by dividing the natural log of 2 by the terminal elimination rate constant (λ_z)
TK	tyrosine kinase
TNF	tumour necrosis factor
TNF-α	tumour necrosis factor-α
TTC	time to peripheral blast clearance
TTF	time to treatment failure
TTR	time to remission
ULN	upper limit of the normal range
µL	microliter
µM	micromolar
US	United States
WBC	white blood cell
WHO	World Health Organization
WM	Waldenström macroglobulinemia
yr	year
αIgM	anti-IgM
β	population mean slope
λ_z	terminal elimination rate constant, estimated by linear regression of the terminal elimination phase of the concentration of drug versus time curve

1. INTRODUCTION

1.1. Acute Myeloid Leukemia

Acute myeloid leukemia (AML) is a biologically heterogeneous disease of the hematopoietic system characterized by clonal accumulation and expansion of immature myeloid cells within the bone marrow {Lowenberg 1999} and is one of the most common forms of leukemia in adults. The median patient age at diagnosis is approximately 67 years {American Cancer Society 2007}. At presentation, symptoms may include fever, fatigue, easy bruising or bleeding, or signs of infection. A number of clinical factors including age, hyperleukocytosis, prior chemotherapy, and extramedullary or central nervous system disease have been found to be important in predicting prognosis, but the most important factor in predicting risk of relapse are chromosomal abnormalities detected at diagnosis{Steelman 2004}. Non-random chromosomal abnormalities, identified in approximately 50% to 70% of all adult primary acute leukemia patients, have long been recognized as one of the most important independent prognostic indicators for achievement of complete remission (CR), duration of first CR, and survival following intensive chemotherapy treatment {Steelman 2004}.The predictive value of chromosomal abnormalities is used to guide the direction of initial treatment strategies, including allogeneic transplantation in first CR. Unfortunately, with current treatment strategies, only approximately 40% of patients achieve long-term remission. Of those patients who relapse, only a fraction undergo successful salvage treatment followed by allogeneic stem cell transplant with curative intent{Mrozek 2008}. Outcomes for older patients are worse, as many elderly patients may not be candidates for standard therapy, such as stem cell transplantation, due to co-morbid illness, and other patients refuse standard therapy due to concerns of high toxicity and poor outcomes. Additionally, these patients are much less likely to have "favorable risk" cytogenetics and more likely to have "adverse risk" {Stone 2004}. Even with adaptation of cytogenetically risk stratified therapies, 20% to 30% of AML patients never achieve CR, and > 50% of patients who achieve CR subsequently experience very early disease relapse {Miller 2013}. The lack of significant advancements in the treatment of AML in adults highlights the need for development of novel therapeutic strategies.

1.1.1. SYK Biology in Stem Cells and AML

SYK is a nonreceptor protein tyrosine kinase that is expressed in cells of hematopoietic lineage. It is an important mediator of immune receptor signaling in mast cells, neutrophils, macrophages, and B cells. SYK contains 2 adjacent Src Homology 2 (SH2) domains that bind to immunoreceptor tyrosine-based activation motifs (ITAMs). Upon receptor activation, ITAMs are phosphorylated, resulting in SYK recruitment to the receptor complex and activation of the enzyme. Phosphorylated-SYK (pSYK) can then phosphorylate its specific substrates including other enzymes and adaptor proteins, orchestrating a complex series of cellular responses such as cell proliferation, differentiation, survival, and phagocytosis {Ruzza 2009}.

SYK activation has been associated with both Type 1 (proliferation) and Type 2 (differentiation) effects {Carnevale 2013, Oellerich 2013}. In AML patients, high expression of pSYK is associated with increased risk of death following chemotherapy, independent of other AML prognostic indicators such as age, cytogenetics, and white blood cell count {Boros 2015}. SYK is expressed in 90% of AML samples and is constitutively activated (pSYK-Y526/6) in AML blasts {Hahn 2009}. In AML, SYK has been shown to regulate leukemic cell survival and proliferation. Furthermore, inhibition of SYK with small molecule inhibitors results in differentiation of AML blasts and decreased AML progression in preclinical models {Hahn 2009}.

SYK signaling pathways in AML are activated through stimulation of several receptors including Fc-γ chain and the β integrins, Mac-1 and CD61/Integrin β3 (Figure 1-1) {Behnen 2014, Oellerich 2013}. Integrins are known to play a role in multiple cellular processes relevant to cancer, including homing, adhesion, motility, proliferation, and apoptosis. Genetic knockdown of Integrin β3 impaired homing of primary leukemia cells and induced myeloid differentiation in both murine models and in human leukemia cell lines resulting in decreased levels of pSYK in mixed lineage leukemia (MLL) mutated primary cells. Furthermore, activation of the downstream transcription factors, signal transducer and activator of transcription 3 and 5 (STAT3 and STAT5), which are responsible for the proliferation and survival of AML leukemic blasts, has also been demonstrated to be SYK-dependent {Oellerich 2013}. Ultimately, integrin signaling through SYK leads to SYK activation affecting transcription, differentiation, and leukemic stem cell survival {Oellerich 2013}.

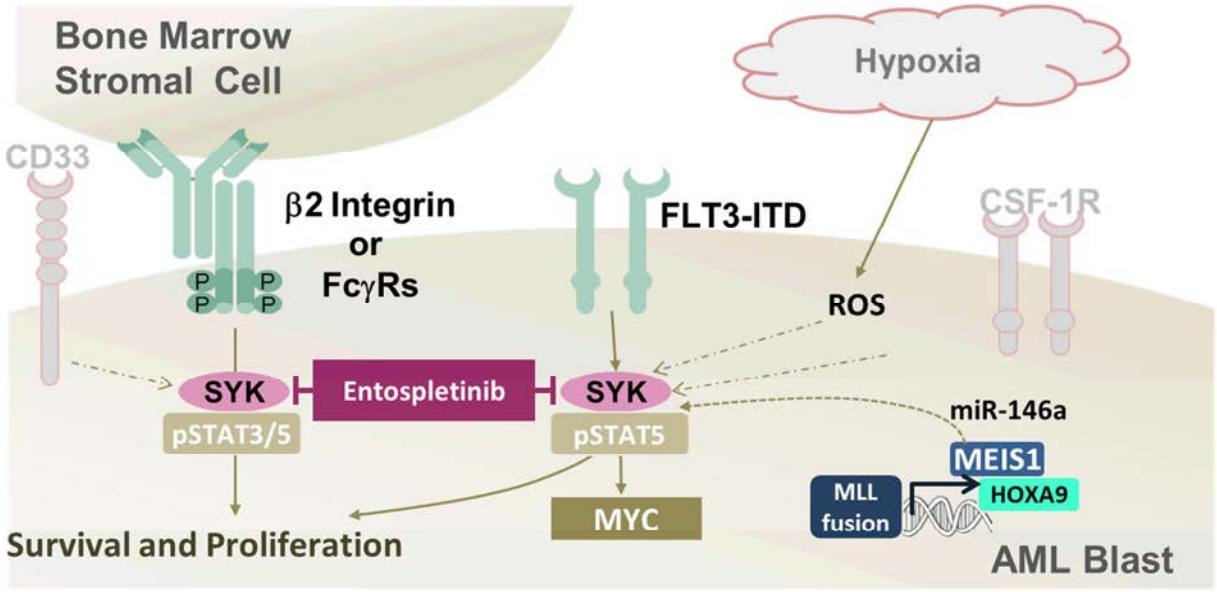
SYK has also been shown to directly phosphorylate the FLT3 receptor, modulate its activation, and possibly promote its role in leukemogenesis (Figure 1-1) {Puissant 2014}. Activating FLT3-ITD mutations have been found in 25% to 30% of patients with AML and are predictive of increased risk of AML relapse and reduced survival {Kottaridis 2003}. In FLT3 mutant AML, SYK is constitutively activated and has been shown to phosphorylate FLT3-ITD resulting in up-regulation of FLT3 signaling pathways, including downstream activation of STAT3, STAT5, and MYC transcriptional programs {Puissant 2014}. Notably in a FLT3-ITD mouse model, SYK was indispensable for myeloproliferative disease development, and SYK overexpression promoted overt transformation to AML and resistance to FLT3-ITD-targeted therapy {Puissant 2014}. SYK inhibition resulted in increased survival of mice developing AML, and showed a marked reduction of leukocytosis and a decrease in leukemic blasts {Puissant 2014}.

SYK signaling has also been implicated in HOXA9/MEIS1 high-risk form of AML. The homeodomain-containing transcription factors, HOXA9 and MEIS1, are overexpressed in approximately 30% to 40% of AML cases and expression is correlated with a poor AML prognosis {Drabkin 2002, Gao 2016, Heuser 2009, Zangenberg 2009}. Both HOXA9 and MEIS1 are critical to leukemic cell survival and high co-expression of HOXA9 and MEIS1 result in increased SYK protein levels in AML {Mohr 2017}. In a murine model of HOXA9/MEIS1-induced leukemia, genetic knockdown or pharmacologic inhibition of SYK with fostamatinib resulted in a dramatic survival benefit, suggesting a therapeutic role in AML for small molecule inhibitors of SYK {Mohr 2017}.

There is additional in vivo evidence to suggest that targeting SYK may be beneficial in treatment of AML. In multiple murine models of AML, treatment with a SYK inhibitor resulted in a significant decrease in the number of circulating AML cells after 6 days of dosing. In a human primary AML xenograft model, histopathological data from the bone marrow and spleen showed near resolution of AML cell infiltrates, including areas of necrosis and recovery, following treatment with a SYK inhibitor {Hahn 2009}.

These studies have shown that inhibition of SYK can induce AML differentiation and impair leukemia progression. Given the multiple important roles for SYK in AML proliferation and survival, SYK is an attractive therapeutic target for AML.

Figure 1-1. Positive and Negative Regulators of Antigen-dependent BCR Signaling

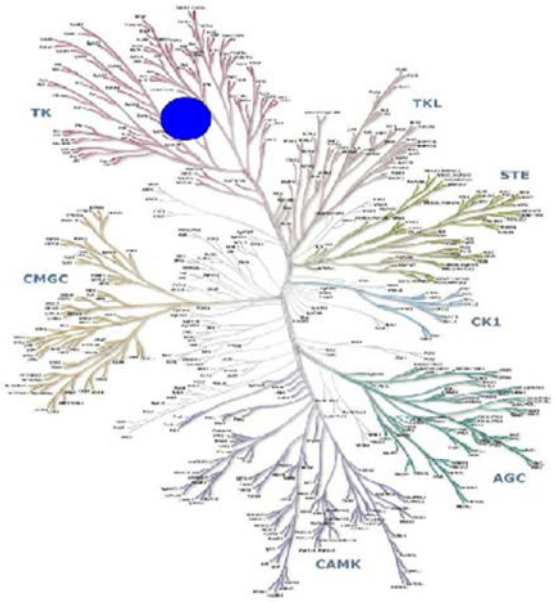


1.2. Entospletinib

1.2.1. Nonclinical Pharmacology

ENTO is an adenosine triphosphate (ATP) competitive inhibitor of SYK with an IC_{50} of 8.5 ± 3.6 nM. ENTO binds in the ATP pocket of the SYK active site and disrupts the kinase activity of the enzyme. Kinase selectivity profiling showed a > 14-fold selectivity of ENTO for SYK versus 359 nonmutant kinases. Furthermore, there was < 50% binding of ENTO at 1 uM to any of a panel of 67 ion channels, transporters, and receptors. Therefore, ENTO demonstrated at least 14-fold selectivity against a total of 426 biological targets tested (See Figure 1-2).

Figure 1-2. Entospletinib Kinome Scan



The cellular activity of ENTO was evaluated in 2 anti-IgM (αIgM)-stimulated CD86 expression assays in human peripheral and mouse splenic B-cells. ENTO potently inhibited αIgM-stimulated CD86 expression with a mean EC_{50} of 125.0 ± 78.2 nM and 94.5 ± 19.6 nM in human peripheral and murine splenic B-cells, respectively. Additionally, ENTO was evaluated in vitro in an FcεRI-triggered αIgE stimulated β-hexosaminidase release assay in mouse bone marrow derived mast cell (BMMC) cultures. ENTO inhibited the FcεRI-stimulated hexosaminidase release into the media with a mean EC_{50} of 159.3 ± 14.8 nM. ENTO was evaluated in vitro in an immune-complex (IC) stimulated TNFα release assay in primary human monocytes. ENTO inhibited the IC stimulated TNFα release with a mean EC_{50} of 147.0 ± 15.6 nM. These data support the concept that SYK inhibition blocks with similar potency, B-cell, αIgE, and Fcγ receptor signaling in vitro.

The potency of ENTO was evaluated in human whole blood by a αIgE-stimulated CD63 expression assay in human basophils. ENTO inhibited the αIgE-stimulated CD63 expression on CD123+/HLADR- human basophils with a mean EC_{50} ± SD of 0.387 ± 0.220 nM. Additionally, ENTO inhibited the pervanadate-induced autophosphorylation of SYK at phospho-SYK (Y525) in whole blood with a mean EC_{50} ± SD of 830 ± 560 nM. These data support the concept that SYK inhibition can block SYK activity in whole blood as determined by functional inhibition of CD63 expression and direct target inhibition of SYK autophosphorylation.

ENTO was evaluated in a battery of safety pharmacology studies. The $IC_{50}$for the inhibitory effect of ENTO on human ether-à-go-go-related gene (hERG) potassium current in vitro was estimated to be greater than 1 μM. Because ENTO is 97.3% protein bound in human plasma and the total plasma concentrations of ENTO are in the 1 to 3 μM range, with a corresponding range of free ENTO of 27 to 81 nM, it is unlikely that a clinically relevant effect on QT interval would

occur. No ENTO-related effects were noted on neurological or respiratory function in rats at doses up to 1000 mg/kg, the highest dose tested. In dogs, ENTO caused small increases in heart rates (during the night cycle) at doses ≥ 15 mg/kg but had no effects on electrocardiograms (ECGs) or blood pressure at up to 150 mg/kg, the highest dose evaluated.

ENTO is a potent and selective SYK inhibitor and disrupts the kinase activity of the enzyme. No significant off target or adverse pharmacological effects of clinical relevance were noted in preclinical evaluations.

Further information on the nonclinical pharmacology of ENTO is available in the Investigator's Brochure.

1.2.2. Nonclinical Drug Metabolism and Pharmacokinetics

Despite high plasma protein binding, ENTO had a moderate volume of distribution, close to that of total body water. The systemic clearance was low in rats, moderate in dogs, and moderate to high in monkeys.

Single-day dose escalation of ENTO administered orally to rats, dogs, and monkeys showed a less than dose proportional increase in ENTO systemic exposure in all species over the dose ranges tested.

Consistent with the moderate to high bioavailability seen in nonclinical species, ENTO showed high forward permeability across Caco-2 monolayers and low potential for efflux.

ENTO showed good metabolic stability with human hepatic material in vitro. In humans, clearance through metabolism is therefore expected to be low. The primary routes of metabolism of ENTO involved oxidative opening of the morpholine ring as well as further oxidation or conjugation. In humans, CYP2C9, CYP3A, and CYP1A2 were shown to oxidize ENTO.

Metabolism followed by biliary excretion is likely to be the major route of elimination of ENTO and its metabolites, as < 5% of the radiolabeled dose administered orally to rats was recovered in urine.

ENTO will be unlikely to cause clinical drug interactions through inhibition of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A. ENTO is an inhibitor of UGT1A1 and may transiently inhibit UGT1A1 activity in vivo at the expected clinical concentrations. The effect may be mitigated by the high plasma protein binding of ENTO (> 97%).

ENTO is an inhibitor of the uptake transporters OATP1B1 and OATP1B3 as well as the efflux transporters P-gp and BCRP with an IC_{50} value of approximately 2 μM for each of these transporters. ENTO may affect the activity of these transporters in vivo at the expected clinical concentrations and could transiently affect the disposition of other drugs. The high plasma protein binding of ENTO (> 97%) may mitigate some of the potential drug-drug interactions at clinically relevant doses.

ENTO is not expected to be a clinically relevant inducer of cytochrome P450 enzymes CYP1A2 or CYP3A4 and other drug metabolizing enzymes or transporters through activation of either the aryl hydrocarbon receptor (AhR) or pregnane-X-receptor (PXR).

Further information on the nonclinical drug metabolism and pharmacokinetics of ENTO is available in the Investigator's Brochure.

1.2.3. Nonclinical Toxicology

ENTO was well tolerated in single-dose studies at doses of 1000 mg/kg in dogs and cynomolgus monkeys. ENTO was well tolerated in rats for 14 days up to 1000 mg/kg/day and for 4 weeks at 50 mg/kg/day. In dogs, ENTO was well tolerated for 7 days at 50 mg/kg/day and at 10 mg/kg/day for 4 weeks. ENTO was well-tolerated in cynomolgus monkeys for 14 days or 13 weeks at 100 mg/kg/day, the highest dose tested. The highest feasible dose in cynomolgus monkeys was 100 mg/kg/day, as no increase in exposure was achieved by higher doses.

The target organ(s) of toxicity identified in rats was the duodenum, and in rabbits and dogs were predominantly the gastrointestinal tract and lymphoid organs. No target organs were identified in the cynomolgus monkey.

Because evidence of lymphoid tissue depletion was noted in rabbits and dogs at high doses, clinical assessments will also include monitoring for signs and symptoms of infection.

Increases in total and/or indirect bilirubin in rats, rabbits, and dogs at ≥ 30 mg/kg/day may have been due to the inhibition of the enzyme UGT1A1. ENTO inhibits this uridine glucuronyl transferase enzyme with an IC_{50} of 2 µM. This enzyme is involved in glucuronidation of bilirubin, and inhibitors of UGT1A1 have the potential to produce increased levels of total and indirect (unconjugated) bilirubin in the circulation. {Zhang 2005} As no histological evidence of hepatobiliary toxicity was noted concurrently with bilirubin increases in ENTO treated rats or dogs, and ENTO levels above the IC_{50} for UGT1A1 were achieved in serum, this seems a plausible mechanism for the noted increases in bilirubin.

No evidence of altered coagulation parameters were noted at any dose level in the ENTO nonclinical studies and no biologically relevant effects were noted in an in vitro study of platelet aggregation. Other inhibitors of SYK have been found to have no effect on platelet function at efficacious dose levels in patients with rheumatoid arthritis as determined by ex vivo assays, and similarly, SYK inhibition has not been found to affect bleeding time in rodents{Braselmann 2006}.

Adverse effects on lymphoid tissues including spleen, lymph nodes, and/or the thymus were noted in rabbits and dogs, but not in rats or cynomolgus monkeys, despite higher exposures achieved in both the rat and monkey. The relevance of the findings in rabbits and dogs to humans is unknown.

ENTO was negative in the bacterial mutation, in vitro chromosomal aberration, and rat micronucleus assays. ENTO can be considered non-genotoxic.

Further information on the nonclinical toxicology of ENTO is available in the Investigator's Brochure.

1.2.4. Clinical Trials of Entospletinib

To date, the ENTO clinical development programs consists of 18 clinical studies, which have been conducted in which 470 healthy subjects (including 16 subjects with hepatic impairment), 464 subjects with hematologic malignancies, 7 subjects with cGVHD, and 7 subjects with RA have participated. Of these subjects, 948 received ENTO and 26 received placebo.

Following administration under fasted conditions of 400 mg ENTO spray dried dispersion (SDD) tablets twice daily (CCI [redacted], ENTO exposures were similar to 900 mg twice daily of the previous formulation (Mono-MSA ENTO). Under fed conditions, ENTO exposures were lower compared with those under fasted conditions (~30%). Co-administration of ENTO SDD with the H2RA, famotidine, did not show a clinically meaningful interaction, whereas ENTO exposures were reduced (~60%) when co-administered with the PPI, omeprazole.

Based on results from Study GS-US-339-1627, cobicistat, a potent inhibitor of CYP3A had no clinically relevant effect on ENTO PK; the CYP2C9 inhibitor, fluconazole, caused an increase in ENTO exposure at steady state (~1.4-fold). Rifampin, a potent inducer of CYP3A, CYP2C9, and CYP1A2, significantly reduced ENTO exposure at steady state (~70%). Multiple dose administration of 400 mg ENTO SDD twice daily resulted in a significant increase in rosuvastatin (OATP/BCRP substrate) exposure (~3.8-fold); in contrast, a marginal increase, in digoxin (P-gp substrate) exposure was observed (~1.4-fold).

Entospletinib exposures were correlated with the PD responses observed with a surrogate CD63 assay. CCI [redacted]

To date in clinical studies, ENTO has been fairly well tolerated. Treatment emergent AEs commonly reported across the studies involving healthy volunteer subjects include headache, somnolence, and GI symptoms (nausea and abdominal pain), all of which were mild. When a development formulation of ENTO was administered for 26 days at a dose of 900 mg twice daily it was well tolerated by subjects with RA on stable doses of methotrexate. This dose and treatment schedule produced levels of drug exposure similar to what is expected in subjects with hematologic malignancies receiving doses of ENTO 400 mg twice daily.

Among healthy volunteers, increased transaminases were noted in some subjects approximately 2 weeks after completion of study drug. In the cohort of subjects with RA, 2 subjects had elevated transaminases while on study drug, which were also observed after completion of study drug. One subject with RA had elevated AST/ALT concurrent with bronchopneumonia while the other was diagnosed with acute hepatitis for which a specific etiology was not determined.

Entospletinib is expected to produce asymptomatic and transient elevations of unconjugated (indirect) bilirubin potentially due to inhibition of UGT1A1. Eight of 178 healthy subjects treated in studies developed asymptomatic indirect bilirubin elevations (6 Grade 1 cases, 1 Grade 2 case, and 1 Grade 3 case) that resolved following discontinuation of the drug. Three of 7 subjects with RA who received ENTO for 26 days developed asymptomatic indirect bilirubin elevations (2 Grade 1 cases and 1 Grade 3 case) that improved despite continued dosing. In preliminary data from Study GS-US-339-0102, 52 of 291 subjects developed indirect bilirubin elevations. Three subjects in Study GS-US-339-0103 developed indirect bilirubin elevations.

Most subjects in Studies GS-US-339-0102 and GS-US-339-0103 with elevations in indirect bilirubin were asymptomatic. The elevations in indirect bilirubin were generally self-limited and did not result in discontinuation of ENTO.

Currently, 8 active clinical studies are being conducted in adult subjects with hematologic malignancies and 1 study is being conducted in adult subjects with cGVHD. At this time preliminary results from Studies GS-US-339-0102 and GS-US-339-0103 are available and summarized herein.

Study GS-US-339-0102 is ongoing and has enrolled and treated 196 subjects with Mono-MSA ENTO (41 subjects with relapsed/refractory CLL, 41 subjects with FL, 43 subjects with DLBCL, 39 subjects with MCL, and 32 subjects with non-FL iNHL) and 95 subjects with ENTO SDD (35 subject with CLL with prior BCR therapy and 60 subjects with CLL in the dose-ranging cohort). Study GS-US-339-0103 is complete; the study has enrolled and treated 66 subjects with Mono-MSA ENTO and idelalisib: 35 subjects with CLL, 14 subjects with FL, 6 subjects with DLBCL, 3 subjects with MCL, and 8 subjects with non-FL iNHL (data cutoff date 05 February 2015).

The most common cause of death in both studies was disease progression. Thirty seven deaths have been reported in Study GS-US-339-0102 and 10 deaths have been reported in Study GS-US-339-0103.

Commonly reported AEs and SAEs reported for subjects in Studies GS-US-339-0102 and GS-US-339-0103 are summarized in Sections 4.2.1.3 and 4.2.2.4 of the Investigator's Brochure.

Study GS-US-339-0103 was closed to enrollment because an unacceptable number of subjects developed pneumonitis during the study. In this study subjects received combination treatment with Mono-MSA ENTO and idelalisib. Pneumonitis was reported for 12 subjects (18.2%). Eleven of the 12 pneumonitis cases (91.7%) were SAEs and were ≥ Grade 3 in severity: 7 cases were Grade 3, 2 cases were Grade 4, and 2 cases were Grade 5. Five subjects required treatment in the intensive care unit. Due to the unacceptable incidence of pneumonitis, dosing with a combination of Mono-MSA ENTO and idelalisib was discontinued. Subjects were given the option to continue on study for treatment with Mono-MSA ENTO monotherapy after a 14- to 28-day washout period. Of the 8 subjects (12.1%) who continued on with monotherapy, 6 (75.0%) discontinued treatment because of progressive disease.

1.2.5. Entospletinib Target Drug Concentrations

In healthy patients, SYK inhibition, as measured by the ability to inhibit CD63 basophil activation and pSYK activation was evaluated in peripheral blood mononuclear cells (PBMCs) at multiple doses and schedules of ENTO. Plasma ENTO exposures were correlated with the degree of SYK inhibition. ENTO inhibited SYK as measured by ex-vivo basophil activation (see Figure 1-3) and pSYK (see Figure 1-4) assays with EC_{70}s of 923 and 275 ng/mL, respectively.

Figure 1-3. Inhibition of Basophil Activation (Original Formulation)

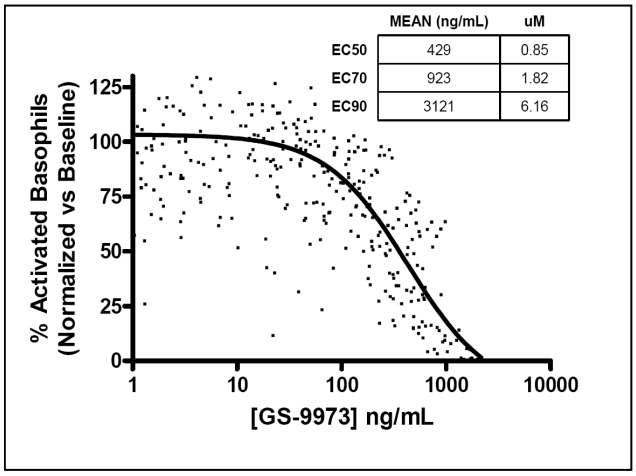
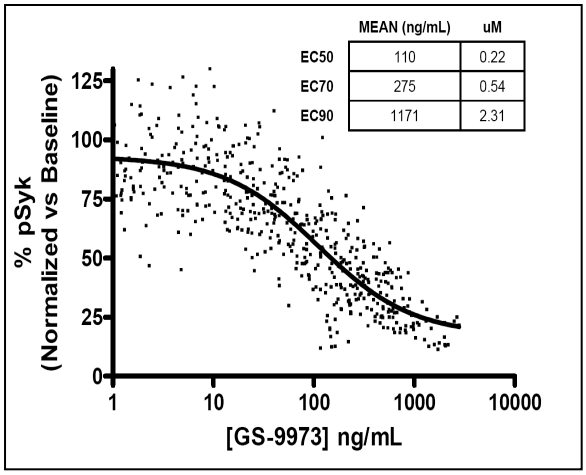


Figure 1-4. Inhibition of pSYK (Original Formulation)



1.2.6. Use of Concomitant Medications with Entospletinib

In vivo and in vitro data indicates that ENTO is a substrate of CYP2C9 and CYP3A. Co-administration of CYP2C9 inhibitors or inducers may increase or decrease ENTO exposure, respectively. As such, co-administration of strong CYP3A and CYP2C9 inducers and moderate CYP2C9 inducers are prohibited in this study. Caution should be exercised when co-administering drugs that are moderate/strong inhibitors of CYP2C9 (eg, fluconazole, voriconazole, or amiodarone) as they may increase ENTO exposure. Administration of strong CYP3A and CYP2C9 inducers and moderate CYP2C9 inducers should be avoided for 2 weeks prior to study drug administration.

Studies in healthy volunteers have demonstrated a significant reduction in ENTO exposure when proton pump inhibitors are co-administered. Therefore, **proton pump inhibitors are prohibited in combination with ENTO. Use of a proton pump inhibitor must be avoided for 1 week prior to study drug administration.** Examples of prohibited medicines in this study are provided in Section 5.2 (Table 5-1). The management of subjects who are benefiting from the protocol treatment and who subsequently require treatment with proton pump inhibitors should be discussed with the Medical Monitor.

In vitro data indicates that ENTO has the potential to inhibit several transporters and the metabolizing enzyme UGT1A1, which may affect the plasma concentrations of substrates of these transporters and/or enzyme. Caution should be exercised when co-administering medications that are transported by OATP1B1, OATP1B3, MATE1, P-gp, and BCRP, or metabolized by UGT1A1; dose adjustment or switching to an alternative medication may be necessary if clinically indicated.

In a study in healthy volunteers, ENTO 400 mg twice daily increased rosuvastatin exposure by approximately 4-fold, which may increase the risk of rhabdomyolysis. However, in a review of safety data from patients who received a statin with ENTO, there were no reports of rhabdomyolysis nor was there a difference in the adverse events profile for this subset of patients. But in the interest of caution, restrictions apply to the use of HMG-CoA reductase inhibitors with ENTO in this study. These restrictions are included in Section 5.2.

1.3. Rationale for the Current Study and Design

Despite progress made in understanding the biology and improvements in the treatment of AML, most patients unfortunately die of their disease, underscoring the need for novel therapeutic approaches. Increased activity of SYK in AML cells may play a role in leukemogenesis, and inhibition of SYK induces differentiation in myeloid effector cells both in vivo and in vitro. Therefore, we propose an early phase clinical trial of dose escalated ENTO in combination with intensive induction with 7+3 for fit subjects with previously untreated AML, with hypomethylating agents for subjects with previously untreated AML who are not fit for intensive induction therapy, and as a single agent in subjects with relapsed/refractory AML.

ENTO is an adenosine triphosphate (ATP) competitive inhibitor that disrupts the kinase activity of purified SYK protein with a concentration that results in 50% inhibition (IC_{50}) +/- standard deviation (SD) of 8.6 +/- 3.6 nM (Study PC-245-2006).

1.3.1. Rationale for the Entospletinib Dose Selection

An ENTO dose of 800 mg BID, original formulation, has been evaluated in a phase 2 program in subjects with CLL, indolent NHL, mantle cell lymphoma, and diffuse large B-cell lymphoma. This dosing regimen is supported by the safety and PK/PD data from single and multiple dose studies conducted with ENTO up to a 1200 mg dose in healthy volunteers and in subjects with rheumatoid arthritis.

A new SDD tablet formulation of ENTO demonstrated improved PK parameters and improved target coverage at trough. In a comparison of the new SDD vs. original ENTO formulation, 400 mg BID SDD tablet provides exposures comparable to 900 mg BID of the original formulation. In a comparison of various doses of the new SDD formulation, moderately higher exposures were achieved with the 800 mg BID SDD compared to 400 mg BID SDD dose. The doses of ENTO SDD proposed in the dose escalation phase of the current study, from 100 mg BID to 800 mg BID, CCI [redacted]. A top dose of 800 mg BID was selected to provide maximum exposures achievable with the SDD tablet in subjects with this rapidly progressing disease. A lower starting dose of ENTO 200 mg BID provides an adequate safety margin for evaluating interactions with the co-administered chemotherapeutic agents. Up to 2 dose escalations are permitted to the highest dose level of 400 mg BID for Groups A and B and 800 mg BID for Group C, which allows for a gradual dose increase and an adequate safety review of each dose level.

As of August 2017, the GS-US-339-1559 Group A dose escalation phase of the trial has treated 3 subjects in Group A at ENTO 200 mg BID and 9 subjects at ENTO 400 mg BID along with 7+3 induction chemotherapy, 6 subjects in Group B at ENTO 200 mg and 400 mg, and 9 subjects in Group C at ENTO 400 mg (n=3) and 800 mg (n=6) in evaluating DLT. No new safety signals have been identified with ENTO administration during the dose escalation phase. Three cases of Grade 3 transaminase elevations were observed in Group C in 2 subjects treated with ENTO monotherapy at the 800 mg dose level. Of these 3 cases, one Grade 3 ALT elevation met the protocol defined definition of DLT. Based on data from the dose escalation phase, the sponsor, in consultation with the coordinating center, has selected ENTO dose level 400 mg BID for all dose expansion cohorts.

Safety analyses obtained from 53 fit and untreated AML subjects treated with ENTO + 7+3 from the Phase 1b and Phase 2 portions of this study indicate that the most common adverse events related to ENTO are mild and include fatigue, gastrointestinal symptoms, and rash. Of note, 13.2% of subjects had persistent ≥ Grade 3 rash and 4 subjects stopped ENTO completely as a result of this. 7.5% of subjects were noted to have ≥ Grade 3 increase in total bilirubin. In addition, subjects were noted to have pancytopenia, including ≥ Grade 3 febrile neutropenia in 41 out of 53 subjects, which is consistent with the expected effects from a myelosuppressive chemotherapy regimen, like 7+3. Induction mortality at 30 days was 0% and no deaths were reported from adverse events, febrile neutropenia, or sepsis.

1.4. Cytarabine arabinoside

Cytarabine arabinoside (or ARA-C) is a nucleoside that differs from the endogeneous counterpart for the presence of an arabinoside rather than a ribose sugar. The compound is carried into the cells by a nucleoside transporter, which becomes saturated at concentrations greater than 20 μM, above which the transport is by passive diffusion. To become an active compound ARA-C is converted to ARA-C triphosphate (ARA-CPT) by 3 sequential enzymes, deoxycitidine kinase, deoxycitidine monophosphate kinase, and nucleotide-disphosphate kinase. Competing with these enzymes are 2 other enzymes, cytidine deaminize and dCMP deaminase, that convert ARA-C and ARA-CMP, respectively, to their corresponding inactive uridine compounds. The activated ARA-CTP competes with the natural deoxycytidine triphosphate for incorporation in DNA by DNA polymerase. Once incorporated in the DNA, ARA-CTP inhibits DNA polymerases resulting in termination of strand elongation important for DNA synthesis or repair. A relationship between intracellular levels of ARA-CTP and antileukemic effect has been identified, and strategies to increase these levels such as administration of high dose ARA-C or fludarabine prior to ARA-C are being studied. Side effects of this compound include myelosuppression, nausea, vomiting, mucositis, diarrhea, and neurotoxicity in particular with high doses. Cytarabine has served as the backbone of AML therapy for more than 50 years and is commonly used for AML consolidation treatment.

1.5. Daunorubicin

Daunorubicin hydrochloride is a hydrochloride salt of an anthracycline cytotoxic antibiotic produced by a strain of Streptomyces coeruleorubidus. Daunorubicin has both antimitotic and cytotoxic activity through a number of proposed mechanisms of action. Daunorubicin forms complexes with DNA by intercalating between base pairs. It inhibits topoisomerase II activity by stabilizing the DNA-topoisomerase II complex resulting insingle and double strand DNA breaks. Daunorubicin is rapidly and widely distributed in tissues where it binds to many cellular components, particularly nucleic acids. Daunorubicin is extensively metabolized in the liver and the primary metabolite, daunorubicinol, also has antineoplastic activity. Daunorubicin is a backbone of AML therapy, commonly delivered by IV bolus for three days during the cytarabine infusion. Side effects of daunorubicin include myelosuppression, cumulative cardiotoxicity, nausea, vomiting, and mucositis.

1.6. Azacitidine

Azacitidine for injection is a pyrimidine nucleoside analog of cytidine. Azacitidine for injection is believed to exert its antineoplastic effects by causing hypomethylation of DNA and direct cytotoxicity on abnormal hematopoietic cells in the bone marrow. The concentration of azacitidine required for maximum inhibition of DNA methylation in vitro does not cause major suppression of DNA synthesis. Hypomethylation may restore normal function to genes that are critical for differentiation and proliferation. The cytotoxic effects of azacitidine cause the death of rapidly dividing cells, including cancer cells that are no longer responsive to normal growth control mechanisms. Non-proliferating cells are relatively insensitive to azacitidine.

The PK of azacitidine were studied in 6 MDS subjects following a single 75 mg/m^2 subcutaneous (SC) dose and a single 75 mg/m^2 intravenous (IV) dose. Azacitidine is rapidly absorbed after SC administration; the peak plasma azacitidine concentration of 750 ± 403 ng/ml occurred in 0.5 hour. The bioavailability of SC azacitidine relative to IV azacitidine is approximately 89%, based on area under the curve. Mean volume of distribution following IV dosing is 76 ± 26 L. Mean apparent SC clearance is 167 ± 49 L/hour and mean half-life after SC administration is 41 ± 8 minutes. The AUC and C_{max} of SC administration of azacitidine in 21 subjects with cancer were approximately dose proportional within the 25 to 100 mg/m^2 dose range. Multiple dosing at the recommended dose-regimen does not result in drug accumulation.

Published studies indicate that urinary excretion is the primary route of elimination of azacitidine and its metabolites. Following IV administration of radioactive azacitidine to 5 cancer subjects, the cumulative urinary excretion was 85% of the radioactive dose. Fecal excretion accounted for <1% of administered radioactivity over 3 days. Mean excretion of radioactivity in urine following SC administration of 14C-azacitidine was 50%. The mean elimination half-lives of total radioactivity (azacitidine and its metabolites) were similar after IV and SC administrations, about 4 hours.

1.7. Decitabine

Decitabine, 5-aza-2'-deoxycytidine, was initially developed 40 years ago as a cytotoxic agent to overcome resistance to cytarabine, and appears to have 2 different mechanisms of action {Blum 2010, Pinto 1984}. At higher doses, the drug acts primarily as a cytotoxic agent. However, at a dose one log or more below that required for cytotoxic effects, decitabine induces demethylation of DNA and differentiation of hematopoietic cells {Blum 2010}. At these low doses, clinical activity with relatively low toxicity has been reported in subjects with myeloid malignancies such as AML and myelodysplastic syndromes (MDS) {Blum 2010, Blum 2007, Cashen 2010, Garcia-Manero 2006}. Blum, et al. have recently reported a phase II study with the azanucleoside decitabine in previously untreated AML subjects > 60 years of age who were not candidates for or refused standard induction treatment{Blum 2010}. All subjects received induction with an optimal biologic dose (OBD)/schedule of decitabine (20mg/m^2 IV on days 1-10 of a 28 day cycle) that was derived from a preceding phase I trial{Blum 2007}. A CR rate of 47% and an overall response rate of 64% was achieved in this high risk group of adult subjects with relatively low toxicity consisting mainly of cytopenias and infections typical of this disease.

1.8. Entospletinib

1.8.1. Formulation

ENTO tablets, 200 mg strength, are available as blue, capsule-shaped, film-coated tablets that are plain-faced. In addition to the active ingredient, ENTO tablets contain the following inactive ingredients: methanesulfonic acid, hydroxypropyl methylcellulose (hypromellose), mannitol, microcrystalline cellulose, crospovidone, poloxamer 188, silicon dioxide, magnesium stearate, polyethylene glycol, polyvinyl alcohol, talc, titanium dioxide, and FD&C blue #2 aluminum lake.

ENTO tablets, 200 mg strength, are also available as beige, capsule-shaped film-coated tablets debossed with "GSI" on one side and "9973" on the other side. In addition to the active ingredient, ENTO tablets contain the following inactive ingredients: methanesulfonic acid, hydroxypropyl methylcellulose (hypromellose), mannitol, microcrystalline cellulose, crospovidone, poloxamer 188, silicon dioxide, magnesium stearate, polyethylene glycol, polyvinyl alcohol, talc, titanium dioxide, ferrosoferric oxide/black iron oxide, iron oxide red, and iron oxide yellow.

1.8.2. Source

ENTO will be supplied free of charge by Gilead Sciences. Any questions or concerns regarding study treatment supply should be referred to your site monitor.

1.8.3. Packaging and Labeling

Study drug (Entospletinib [GS-9973] 200 mg tablets) is packaged in white, high -density polyethylene (HDPE) bottles. Each bottle contains 60 tablets, a silica gel desiccant and polyester packing material. Each bottle is enclosed with a white, continuous thread, child-resistant, polypropylene screw cap fitted with an induction-sealed, aluminum-faced liner.

Study drug to be distributed to centers in the US and other participating countries shall be labeled to meet applicable requirements of the United States Food and Drug Administration (FDA), EU Guideline to Good Manufacturing Practice - Annex 13 (Investigational Medicinal Products), and/or other local regulations

1.8.4. Storage and Handling

Study drug (Entospletinib [GS-9973]) should be stored at controlled room temperature of 25°C (77°F); excursions are permitted between 15°C and 30°C (59°F and 86°F). Storage conditions are specified on the label. Until dispensed to the subjects, all bottles of study drugs should be stored in a securely locked area, accessible only to authorized site personnel.

To ensure the stability and proper identification, study drug should not be stored in a container other than the container in which they were supplied. Keep the bottle tightly closed to protect from moisture. Consideration should be given to handling, preparation, and disposal through measures that minimize drug contact with the body. Appropriate precautions should be followed to avoid direct eye contact or exposure when handling.

1.8.5. Study Drug Accountability

The investigator or designee (eg, pharmacist) is responsible for ensuring adequate accountability of all used and unused study drug bottles during the study. This includes acknowledgement of receipt of each shipment of study drug (quantity and condition) and tracking of bottles assigned/utilized for subject dosing. All unused study drug bottles must be returned to the site by the subjects.

Investigational Drug Accountability records will be provided to each study site to:

- Record the date received and quantity of ENTO lot number
- Record the date, subject number, subject initials, and the ENTO lot number dispensed
- Record the date, quantity of used and unused ENTO returned, along with the initials of the person recording the information.

1.9. Compliance

This study will be conducted in compliance with this protocol, Good Clinical Practice (GCP), and all applicable regulatory requirements.

1.10. Risk/Benefit Assessment for the Study

1.10.1. Potential Risks Based on Nonclinical Safety Data with Entospletinib

Spleen tyrosine kinase (SYK) deficiency and SYK-deficient bone marrow in rodents have been associated with hemorrhage. In an ex vivo platelet function assay, ENTO showed no biologically relevant inhibition or activation of platelets at concentrations up to 12.3 μM. No evidence of altered coagulation parameters or effects on hemostasis were noted at any dose level in the ENTO nonclinical studies.

The target organ(s) of toxicity identified in rats was the duodenum, and in rabbits and dogs were predominantly the gastrointestinal (GI) tract and lymphoid organs. No target organs were identified in the cynomolgus monkey. Increases in total and/or indirect bilirubin in rats, rabbits and dogs administered ENTO may have been due to the inhibition of the enzyme UGT1A1 at ENTO exposure levels exceeding the IC_{50} for UGT1A1. No histological evidence of hepatobiliary toxicity was noted concurrent with bilirubin increases in any ENTO-treated species. Clinical assessments will monitor for signs and symptoms of infection, hemorrhage, GI distress, and changes in clinical pathology parameters (changes in hemoglobin, neutrophils, lymphocytes, liver enzymes, and total and indirect bilirubin) that could occur after ENTO administration.

Administration of ENTO to pregnant female rats and rabbits resulted in dose-dependent developmental findings (decreased fetal weights and delayed ossification) only at dose levels associated with maternal toxicity (reduced body weights and food consumption). No gross

external, soft tissue, or skeletal fetal alterations (malformations or variations) were observed. This clinical study will exclude females who are pregnant or breastfeeding, and only include female subjects of child bearing potential who are willing to use a protocol-recommended method of contraception from the screening visit throughout the study and for 1 month following the last dose of ENTO or as recommended in the prescribing information for other co-administered study drug (whichever is later). Male subjects having intercourse with females of childbearing potential must be willing to abstain from heterosexual intercourse or use a protocol-recommended method of contraception from the start of ENTO throughout the study treatment period and for 3 months following the last dose of ENTO or as recommended in the prescribing information for other co-administered study drug (whichever is later).

1.10.2. Potential Risks Based on Clinical Safety Data with Entospletinib

To date, 18 clinical studies have been conducted in which 470 healthy subjects (including 16 subjects with hepatic impairment), 464 subjects with hematologic malignancies, 7 subjects with cGVHD, and 7 subjects with rheumatoid arthritis have participated.

The following events from ENTO clinical studies have been reviewed and determined by the sponsor to have a causal association with ENTO (ie, adverse drug reactions). Noted events are transaminases increased, hyperbilirubinaemia and rash.

ENTO is an inhibitor of UGT1A1 and may transiently inhibit UGT1A1 activity in vivo at the expected clinical concentrations. Administration of drugs such as ENTO that inhibit UGT1A1 are expected to increase total bilirubin due to decreased conjugation rather than liver dysfunction. The elevations in indirect bilirubin observed in clinical trials with ENTO were generally self-limited and did not result in discontinuation of ENTO. In the absence of symptoms or other hepatic laboratory abnormalities, ENTO dose modification is not required for elevated indirect bilirubin levels.

The bis-MSA spray-dried dispersion (SDD) formulation will be used in this study and was chosen because it had less interaction with acid reducing agents compared to the original mono-MSA formulation. Administration of the bis-MSA SDD formulation in Studies GS-US-339-0111 and GS-US-245-1222 demonstrated that the change in ENTO exposure upon co-administration with omeprazole was less than the reduction in exposure observed in Study GS-US-245-0106 using the original formulation. The new formulation did not completely annul the DDI effect of a co-administered PPI agent, however the interaction of the bis-MSA SDD formulation with an H2 receptor antagonist (H2RA) (eg, famotidine) is not considered clinically meaningful.

Dose adjustments in line with the approved product information of the standard of care therapies are permitted within the protocol. Myelosuppression has been noted with the use of cytarabine, daunorubicin, decitabine, and azacitidine. To mitigate the risk of bone marrow suppression, hematology monitoring will be performed.

In addition, toxic myocardial damage has been associated with the use of daunorubicin; thus only subjects with Left Ventricular Ejection Fraction (LVEF) ≥ 45% (confirmed by ECHO) and no clinical evidence of congestive heart failure may be enrolled into the study.

Refer to the Investigator's Brochure (IB) for complete details of ENTO, including completed and ongoing nonclinical and clinical studies including summary safety and response data.

1.10.3. Potential Benefits with Entospletinib

The available nonclinical and clinical data support the evaluation of ENTO in eligible subjects with AML. Given the impact of myeloid cancers to the subject, and the aggregate potential benefits considered in the context of potential risk, further development of ENTO in this study is justified.

2. OBJECTIVES AND ENDPOINTS

2.1. Objectives

The primary objectives are:

- 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 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:

- 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:

- CCI [redacted]

2.2. Endpoints

Primary Endpoints:

Safety

- Occurrence of adverse events and laboratory abnormalities defined as DLTs for ENTO in combination with standard dose cytarabine and daunorubicin in subjects with previously untreated AML (Group A)
- Occurrence of adverse events and laboratory abnormalities defined as DLTs for ENTO in combination with decitabine or azacitidine in subjects with previously untreated AML who are unable to receive 7+3 chemotherapy (Group B)

- Occurrence of adverse events and laboratory abnormalities defined as DLTs for ENTO as a single agent in subjects with relapsed/refractory AML (Group C)

Efficacy

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

- Composite complete remission rate at induction completion: defined as the proportion of subjects who achieved 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 CR, CRi, or partial remission (PR) at induction completion.

Secondary Endpoints:

Exposure

- Drug administration and duration of exposure of study treatment

Safety

- Occurrence of AEs and laboratory abnormalities not defined as DLTs

Efficacy

- 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.

Exploratory Endpoints:

CCI

[redacted]

3. STUDY DESIGN

3.1. Overview

Approximately 190 subjects with previously untreated or relapsed/refractory AML will be dosed in 3 groups (Groups A, B, and C).

In Phase 1b (dose escalation), ENTO will be administered at 2 dose levels (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 2 dose levels (400 mg and 800 mg) every 12 hours as monotherapy for Group C. At the time of this amendment, Phase 1b had completed enrollment.

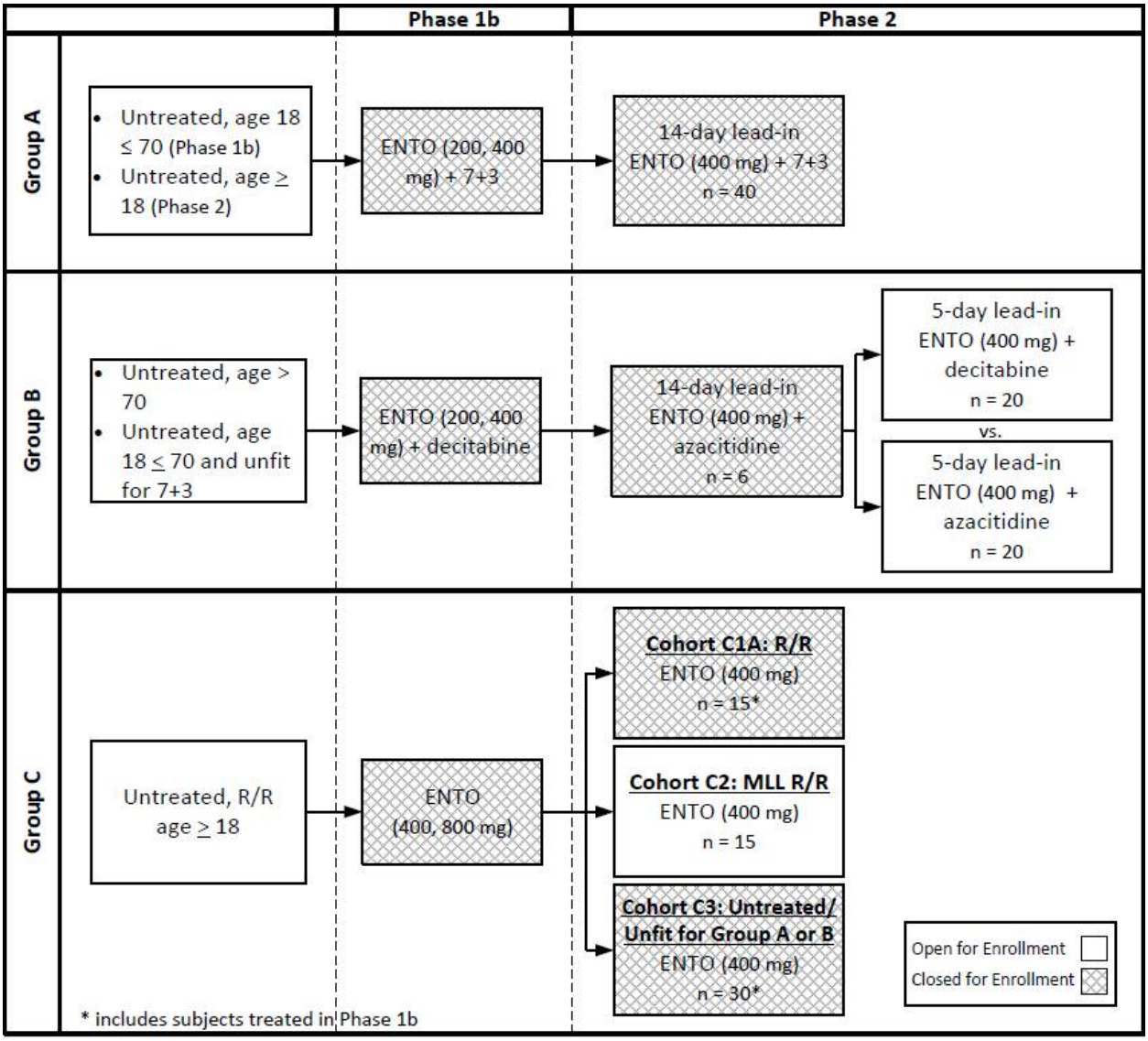
In Phase 2 (dose expansion), the recommended dose of 400 mg ENTO will be administered. At the time of this amendment, Group A had completed enrollment.

In Group B, the overall safety of ENTO in combination with a hypomethylating agent (decitabine or azacitidine) will be evaluated. Six evaluable subjects will initially be enrolled as part of the safety run-in to evaluate the safety of ENTO in combination with azacitidine. If 2 or more subjects experience DLTs, then this arm will be dropped from the study. If Phase 2 proceeds with an azacitidine arm, subjects will be randomized to receive ENTO in combination with either decitabine or azacitidine. At the time of this amendment, Group B safety run-in had completed enrollment and the Phase 2 portion of the trial is currently ongoing with plans to enroll 40 subjects in Group B, randomized equally to ENTO + decitabine vs. ENTO + azacitidine. Randomization will be stratified by the following 2 factors:

Stratification Factor	Stratification Levels
Age	$\leq$ 75 or > 75 years
White Blood Count	$\leq$ 5,000/μL or > 5,000/μL

In Group C, relapsed/refractory and previously untreated AML subjects will be evaluated in separate cohorts. At the time of this amendment, Cohort C1A had completed enrollment. This amendment identifies the closure of Cohort C3 to further enrollment.

Figure 3-1. Study Schema



No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the subject's leukemia.

3.1.1. Group A Phase 1b (Dose Escalation): Entospletinib + cytarabine + daunorubicin (7+3)

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

ENTO lead-in will be administered orally every 12 hours on Days 1-14 as a single agent (Cycle 0), and will continue to be given daily in combination with IV cytarabine (Days 1-7) and

IV daunorubicin (Days 1- 3) during induction chemotherapy of every 14-day cycle for up to 2 cycles. Subjects must be able to receive up to 2 cycles of induction chemotherapy.

Intra-subject dose escalation will not be allowed.

Table 3-1. Group A Entospletinib Cohort Dose Escalation Table

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

Although ENTO lead-in therapy (Cycle 0) is scheduled to end on Day 14, cytarabine and daunorubicin (7+3) treatment (Cycle 1) may be started after 5 days of exposure to ENTO if the Principal Investigator agrees with the treating physician that treatment should start sooner. Examples of such situations include but are not limited to:

- WBC count is increasing and greater than 20,000/μL
- Leukemic related complications that in the opinion of the treating physician require initiation of cytotoxic chemotherapy sooner

Hydroxyurea is allowed during the lead-in period per investigator discretion and after discussion with the medical monitor. Hydroxyurea should be discontinued prior to initiating 7+3 chemotherapy.

A bone marrow aspirate for disease assessment will be performed 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 initiating induction chemotherapy.

A bone marrow aspirate and biopsy will be performed on Cycle 1 Day 14. If the bone marrow cellularity at this time point is $\leq$20%, a repeat bone marrow examination will occur within 2 weeks or at count recovery, whichever comes first. Subjects with residual disease detected at the Cycle 1 Day 14 bone marrow evaluation will proceed with Cycle 2 of induction chemotherapy. The start of Cycle 2 will depend on the timing and result of the disease assessment. Subjects are to continue receiving ENTO while awaiting disease assessment results.

Subjects with cytogenetic and molecular mutations at screening must have cytogenetic and molecular mutation testing repeated at subsequent bone marrow examinations (Cycle 0 Day 14, Cycle 1 Day 14, count recovery, End of Study).

Subjects will undergo a daily complete blood count (CBC) from Cycle 1 Day 14 (ie, count nadir) until count recovery, at which time a bone marrow aspirate and biopsy is performed.

If a subject discontinues study treatment (eg, as a result of an AE), every attempt should be made to keep the subject in the study to perform the required study-related follow-up and procedures. If this is not possible or acceptable to the subject or investigator, the subject may be withdrawn from the study.

3.1.2. Group A Phase 2 (Dose Expansion): Entospletinib + cytarabine + daunorubicin (7+3)

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

Entospletinib lead-in (Cycle 0): ENTO 400 mg will be administered orally every 12 hours on Days 1-14 as a single agent during the lead-in (Cycle 0). However, cytarabine and daunorubicin (7+3) treatment (Cycle 1) may be started earlier, after 5 days of exposure to ENTO, if the Principal Investigator agreed with the treating physician that treatment should start sooner. Examples of such situations may include but are not limited to:

- White blood cell count is increasing and greater than 20,000/μL
- Leukemic related complications that in the opinion of the treating physician require the initiation of cytotoxic chemotherapy sooner

Hydroxyurea is allowed during the lead-in period per investigator discretion and after discussion with the medical monitor. Hydroxyurea should be discontinued prior to initiating cytarabine and daunorubicin (7+3) chemotherapy.

A bone marrow aspirate for disease assessment will be performed 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 initiating induction chemotherapy.

Subjects with cytogenetic and molecular mutations at screening must have cytogenetic and molecular mutation testing repeated at subsequent bone marrow examinations (Cycle 0 Day 14, Cycle 1 Day 14, count recovery, End of Study).

ENTO 400 mg will continue to be given every 12 hours from Cycle 0 Day 1 to the completion of induction therapy as determined by bone marrow response.

Entospletinib + 7+3 (Cycle 1-2): ENTO 400 mg will be administered every 12 hours in combination with IV cytarabine (Days 1-7) and IV daunorubicin (Days 1-3) for up to 2 induction cycles (Cycle 1 and 2). Subjects must be able to receive 2 cycles of induction chemotherapy.

A bone marrow aspirate and biopsy will be performed on Cycle 1 Day 14. If the bone marrow cellularity at this time point is ≤ 20%, a repeat bone marrow examination will occur within 2 weeks or at count recovery, whichever came first. Subjects with residual disease detected at the Cycle 1 Day 14 bone marrow evaluation will proceed with Cycle 2 of induction chemotherapy. The start of Cycle 2 will depend on the timing and result of the disease assessment. Subjects will continue receiving ENTO while awaiting disease assessment results.

The investigator must consult the medical monitor if subjects have not obtained a CR after Cycle 1 and prior to Cycle 2, and if there is any consideration to omit Cycle 2 of induction chemotherapy.

Subjects with cytogenetic and molecular mutations at screening must have cytogenetic and molecular mutation testing repeated at subsequent bone marrow examinations (Cycle 0 Day 14, Cycle 1 Day 14, count recovery, End of Study).

Subjects will undergo a daily CBC from Cycle 1 Day 14 (ie, count nadir) until count recovery at which time a bone marrow aspirate and biopsy will be performed.

Once a CR/CRi is confirmed on a recovery bone marrow examination (ie, the subject achieves < 5% blasts by morphology and flow cytometry), the subject will proceed to either allogeneic stem cell transplantation (SCT) or post-remission chemotherapy with cytarabine.

If CR/CRi is not achieved by the end of Cycle 2, the subject will be considered a treatment failure and will have met study efficacy endpoint criteria, but will remain on study for required study-related follow-up procedures.

Entospletinib + cytarabine post-remission (at least 3 cycles, and up to 4 cycles):
Post-remission chemotherapy will be offered to eligible subjects who have achieved CR/CRi and do not require or cannot proceed to allogeneic SCT. In addition, subjects who are awaiting a donor or transitioning to allogeneic SCT will be allowed to receive post-remission chemotherapy per investigator discretion. Therapy will consist of $3g/m^2$ high dose cytarabine administered IV every 12 hours on Days 1, 3, and 5 (< 60 years of age) or $1g/m^2$ cytarabine administered once daily on Days 1-5 (≥ 60 years of age) in combination with 400 mg ENTO every 12 hours on Days 1-28 of each 28-day cycle.

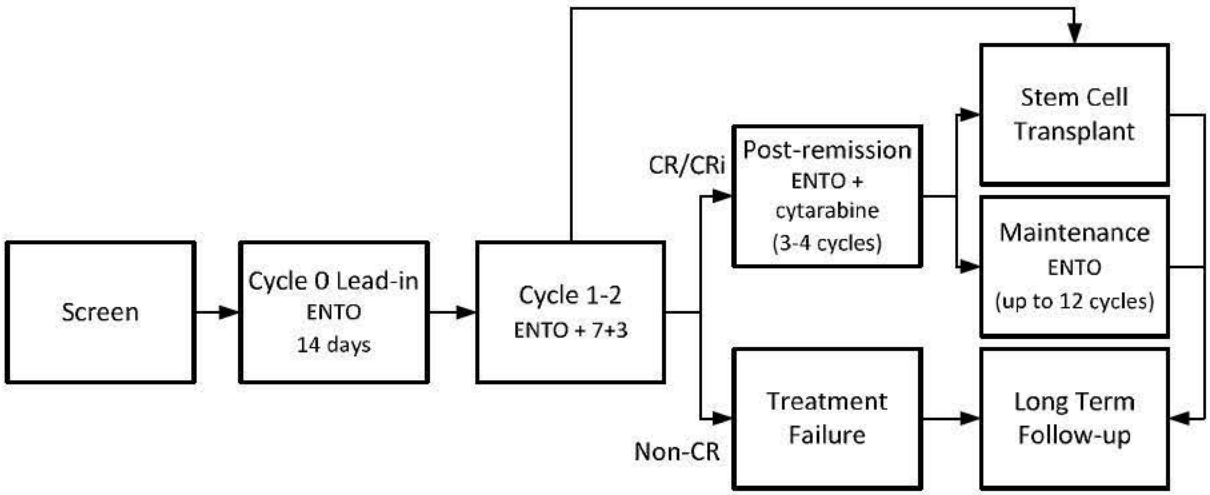
Subjects in whom definitive post-remission chemotherapy is planned will receive at least 3 and up to 4 cycles of cytarabine. Subjects who are awaiting a donor or transitioning to SCT may receive at least 1 and up to 4 cycles of cytarabine.

A bone marrow aspirate sample will be collected for disease assessment and biomarker research at the end of every 2 cycles (Cycle 2 Day 28 and Cycle 4 Day 28) and at suspected disease progression. Subjects who continue to maintain a CR/CRi after 3-4 cycles of post-remission chemotherapy will be offered maintenance with ENTO 400 mg every 12 hours for up to 12 cycles.

Entospletinib maintenance (up to 12 cycles): ENTO 400 mg will be administered orally every 12 hours on Days 1-28 of each 28-day cycle and will continue for up to maximum 12 cycles as long as the subject is experiencing benefit or until the subject becomes a candidate for SCT. A bone marrow aspirate sample will be collected for disease assessment and biomarker research at the end of every 4 cycles (eg, Cycle 4 Day 28, Cycle 8 Day 28, etc.) 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.

If a subject discontinues study treatment (eg, as a result of an AE), every attempt should be made to keep the subject in the study to perform the required study-related follow-up and procedures. If this is not possible or acceptable to the subject or investigator, the subject may be withdrawn from the study.

Figure 3-2. Group A Phase 2 Dosing Schema



3.1.3. Group B Phase 1b (Dose Escalation): Entospletinib + decitabine

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

During the dose escalation, the initial dosing level for the 1st cohort is defined as level 0 in table below. Intra-subject dose escalation will not be allowed.

Table 3-2. Group B Entospletinib Dose Escalation Table

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

Entospletinib lead-in (Cycle 0): ENTO will be administered orally every 12 hours on Days 1-14 as a single agent during the lead-in (Cycle 0). However, decitabine treatment may be started earlier, after 5 days of exposure to ENTO, if the Principal Investigator agrees with the treating physician that treatment should start sooner. Examples of such situations may include but are not limited to:

- White blood cell count is increasing and greater than 20,000/µL
- Leukemic related complications that in the opinion of the treating physician require the initiation of cytotoxic chemotherapy sooner

Hydroxyurea is allowed during the lead-in period per investigator discretion and after discussion with the medical monitor. Hydroxyurea should be discontinued prior to initiating decitabine induction.

A bone marrow aspirate for disease assessment will be performed 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 initiating decitabine induction.

Entospletinib + decitabine induction (Cycles 1-4): ENTO 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.

A bone marrow aspirate and biopsy sample will be collected for disease assessment and biomarker research at the end of every 2 cycles (Cycle 2 Day 28 and Cycle 4 Day 28) or as clinically indicated. Subjects with cytogenetic and molecular mutations at screening must have cytogenetic and molecular mutation testing repeated at subsequent bone marrow examinations (Cycle 0 Day 14, Cycle 1 Day 28, count recovery, End of Study).

If the subject achieves < 5% blasts by morphology and flow cytometry or has evidence of clinical benefit after completing 2-4 induction cycles but is not eligible for SCT, the subject will have the option to receive maintenance therapy with ENTO in combination with decitabine. Subjects with persistent evidence of disease (ie, blasts ≥ 5%) after Cycle 2 may receive up to 2 more induction cycles until subject achieves < 5% blasts.

If < 5% blasts by morphology and flow cytometry is not achieved or the subject does not show evidence of clinical benefit after 4 induction cycles, the subject is considered a treatment failure and will have met study efficacy endpoint criteria, but will remain on study for required study-related follow-up procedures.

Entospletinib + decitabine maintenance (at least 2 cycles): ENTO will be administered orally every 12 hours on Days 1-28 in combination with decitabine on Days 1-5 of every 28-day cycle. A bone marrow aspirate sample will be collected at the end of every 4 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. After completing at least 2 cycles, the subject may proceed to SCT. If not eligible for SCT, subjects will have the option to continue on maintenance therapy with ENTO in combination with decitabine. Subjects who are intolerant of decitabine may switch to ENTO monotherapy maintenance at any time after completing the first 2 cycles. Maintenance may continue as long as the subject is experiencing benefit and does not meet the criteria for study treatment discontinuation.

Entospletinib maintenance (up to 12 cycles): ENTO will be administered orally every 12 hours as monotherapy on Days 1-28 of each 28-day cycle and continued for up to 12 cycles as long as the subject is experiencing benefit and does not meet the criteria for study treatment discontinuation. A bone marrow aspirate sample will be collected for disease assessment and biomarker research at the end of every 4 cycles (eg, Cycle 4 Day 28, Cycle 8 Day 28) 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. Extension of maintenance may occur on an individual basis if approved by the Principal Investigator.

If a subject discontinues study treatment (eg, as a result of an AE), every attempt should be made to keep the subject in the study to perform the required study-related follow-up and procedures. If this is not possible or acceptable to the subject or investigator, the subject may be withdrawn from the study.

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

3.1.4. Group B Phase 2 (Dose Expansion): Entospletinib + Hypomethylating agent

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 400 mg in combination with azacitidine 75mg/m^2 will be administered to 6 evaluable subjects.

Following completion of the safety run-in (DLT window, Section 3.2), the safety of the azacitidine arm will be reviewed to determine if enrollment of the expansion cohort may proceed with azacitidine. If 2 or more subjects experience DLT, all ongoing subjects in the safety run-in will be discontinued and the azacitidine arm will be dropped from the study. If Phase 2 proceeds with an azacitidine arm, subjects will be randomized to receive ENTO in combination with either decitabine or azacitidine.

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

Entospletinib Safety lead-in (Cycle 0): ENTO 400 mg will be administered orally every 12 hours on Days 1-14 as a single agent during the lead-in (Cycle 0). However, chemotherapy with the assigned hypomethylating agent (Cycle 1) may be started earlier, after 5 days of exposure to ENTO, if the Principal Investigator agrees with the treating physician that treatment should start sooner. Examples of such situations may include but are not limited to:

- White blood cell count is increasing and greater than 20,000/μL
- Leukemic related complications that in the opinion of the treating physician require the initiation of cytotoxic chemotherapy sooner

Hydroxyurea is allowed during the lead-in period per investigator discretion and after discussion with the medical monitor. Hydroxyurea should be discontinued prior to initiating hypomethylating agent.

A bone marrow aspirate for disease assessment will be performed 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 initiating therapy with hypomethylating agent.

Subjects with cytogenetic and molecular mutations at screening must have cytogenetic and molecular mutation testing repeated at subsequent bone marrow examinations (Cycle 0 Day 14, Cycle 1 Day 28, count recovery, End of Study).

Entospletinib Randomization lead-in (Cycle 0): ENTO 400 mg will be administered orally every 12 hours on Days 1-5 as a single agent during the lead-in.

Hydroxyurea is allowed during the lead-in period per investigator discretion and after discussion with the medical monitor. Hydroxyurea should be discontinued prior to initiating hypomethylating agent.

If circulating blasts have cleared at the end of monotherapy lead-in (Cycle 0 Day 5), then a bone marrow aspirate will be performed for disease assessment.

Subjects with cytogenetic and molecular mutations at screening must have cytogenetic and molecular mutation testing repeated at subsequent bone marrow examinations (Cycle 0 Day 5, Cycle 1 Day 28, count recovery, End of Study).

Entospletinib + Hypomethylating agent induction (Cycles 1-4): In subsequent induction cycles (Cycles 1-4), ENTO 400 mg will be administered orally every 12 hours on Days 1-28 in combination with the assigned hypomethylating agent dose and schedule. All subjects will receive at least 2 but no more than 4 cycles of induction chemotherapy.

Table 3-3. Hypomethylating Agent Dose and Schedule Table (Induction)

Agent	Dose	Days	Cycle Duration
decitabine	20mg/m^2	1-10	28 days
azacitidine	75mg/m^2	1-7	

A bone marrow aspirate and biopsy sample will be collected for disease assessment and biomarker research at the end of every 2 cycles (Cycle 2 Day 28 and Cycle 4 Day 28) or as clinically indicated. Subjects with cytogenetic and molecular mutations at screening must have cytogenetic and molecular mutation testing repeated at subsequent bone marrow examinations (Cycle 0 Day 14, Cycle 1 Day 28, count recovery, End of Study).

If the subject achieves < 5% blasts by morphology and flow cytometry or has evidence of clinical benefit after completing 2-4 induction cycles but is not eligible for SCT, the subject will have the option to receive maintenance therapy with ENTO in combination with decitabine or azacitidine. Subjects with persistent evidence of disease (ie, blasts ≥ 5%) after Cycle 2 may receive up to 2 more induction cycles until subject achieves < 5% blasts.

If < 5% blasts by morphology and flow cytometry is not achieved or the subject does not show evidence of clinical benefit after 4 induction cycles, the subject is considered a treatment failure and will have met study efficacy endpoint criteria, but will remain on study for required study-related follow-up procedures.

Entospletinib + Hypomethylating agent maintenance (at least 2 cycles): ENTO will be administered orally every 12 hours on Days 1-28 in combination with assigned hypomethylating agent dose and schedule.

Table 3-4. Hypomethylating Agent Dose and Schedule Table (Maintenance)

Agent	Dose	Days	Cycle Duration
decitabine	20mg/m^2	1-5	28 days
azacitidine	75mg/m^2	1-7	

A bone marrow aspirate sample will be collected at the end of every 4 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.

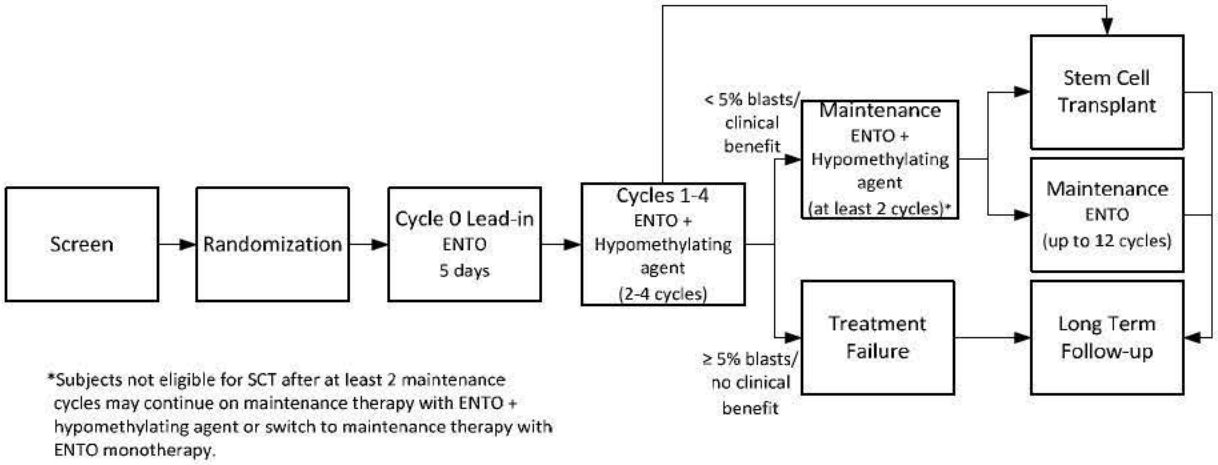
After completing at least 2 cycles, the subject may proceed to SCT. If not eligible for SCT, subjects will have the option to continue on maintenance therapy with ENTO in combination with the assigned hypomethylating agent. Subjects who are intolerant of the hypomethylating agent after completing 2 cycles 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.

Entospletinib maintenance (maximum up to 12 cycles): ENTO 400 mg will be administered every 12 hours as a single agent on Days 1-28 of each 28-day cycle and will continue for up to 12 cycles as long as the subject is experiencing benefit and does not meet the criteria for study treatment discontinuation.

A bone marrow aspirate sample will be collected for disease assessment and biomarker research at the end of every 4 cycles (eg, Cycle 4 Day 28, Cycle 8 Day 28) 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.

If a subject discontinues study treatment (eg, as a result of an AE), every attempt should be made to keep the subject in the study to perform the required study-related follow-up and procedures. If this is not possible or acceptable to the subject or investigator, the subject may be withdrawn from the study.

Figure 3-3. Group B Phase 2 Randomization Dosing Schema



3.1.5. Group C Phase 1b (Dose Escalation): Entospletinib Monotherapy

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

ENTO monotherapy will be administered orally every 12 hours at the dose level indicated in the table below for every 28-day cycle until the subject meets criteria for study treatment discontinuation. The initial dosing level for the 1st cohort is defined as level 0 in table below.

Intra-subject dose escalation will not be allowed.

Table 3-5. Group C Entospletinib Cohort Dose Escalation Table

Dose Level	Entospletinib
0	400 mg
1	800 mg

Subjects will receive ENTO continuously on Days 1-28 of a 28-day cycle until the subject meets criteria for study treatment discontinuation (see Section 6.4.1). A bone marrow biopsy and aspirate sample will be collected for disease assessment and biomarker research on Cycle 1 Day 28 and Cycle 2 Day 28.

A bone marrow aspirate sample will be collected for disease assessment and biomarker research every 4 cycles starting on Cycle 4 Day 28 of subsequent cycles (ie, Cycle 4 Day 28, Cycle 8 Day 28) unless the subject achieved CR/CRi, in which case further marrow aspirations are not required, unless clinically indicated (exception: if the subject clearly has circulating leukemia cells in the peripheral blood, bone marrow aspiration after Cycle 2 or beyond is not mandated).

If a subject discontinues study treatment (eg, as a result of an AE), every attempt should be made to keep the subject in the study to perform the required study-related follow-up and procedures. If this is not possible or acceptable to the subject or investigator, the subject may be withdrawn from the study.

3.1.6. Group C Phase 2 (Dose Expansion): Entospletinib Monotherapy

Note: At the time of this amendment, Cohort C1A had completed enrollment (n=15). This amendment identifies the closure of Cohort C3 to further enrollment (n=12).

Relapsed/refractory and previously untreated subjects will be evaluated in separate cohorts during phase 2 as 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 biopsy and aspirate sample will be collected for disease assessment and biomarker research at the end of Cycles 1 and 2 on Day 28. A bone marrow aspirate sample will also be collected for disease assessment and biomarker research on Day 28 of every 4 cycles beginning on Cycle 4 Day 28 (eg, Cycle 4 Day 28, Cycle 8 Day 28) and at suspected disease progression. 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 15 relapsed/refractory AML subjects. If 5 or more of the initial 15 subjects achieve CR/CRi after 1-2 cycles, an additional 15 subjects would then 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 this time, futility has been met and, thus, Cohort C1A will not move forward (ie, will not enroll any subjects).

Cohort C2: 15 relapsed/refractory AML subjects with MLL.

Cohort C3: 30 previously untreated AML subjects who are unfit (eg, very elderly, have multiple comorbidities, and a poor ECOG/performance status) for chemotherapy or hypomethylating agent, or refuse either of these 2 treatment options.

If a subject discontinues study treatment (eg, as a result of an AE), every attempt should be made to keep the subject in the study to perform the required study-related follow-up and procedures. If this is not possible or acceptable to the subject or investigator, the subject may be withdrawn from the study.

3.2. Dose Limiting Toxicities

It is recognized that drug-related toxicity in this population may be difficult to ascertain given the aggressive hematologic disease. Investigators will attempt to assign attribution of toxicities to each drug when possible. The CTEP Active Version of the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 will be utilized for AE reporting.

The assessment of DLTs for dose escalation decisions will occur during the DLT assessment window. DLTs will also be assessed in Phase 2 during the Group B safety run-in to evaluate the safety of ENTO in combination with azacitidine. The DLT assessment window for each group is as follows:

Group A: begins on Cycle 0 Day 1 and ends 28 days after Cycle 1 Day 1 or 28 days after 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 below

Group B (including Phase 2 safety run-in): begins on Cycle 0 Day 1 and ends 28 days after Cycle 1 Day 1

Group C: 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 below

During the DLT assessment window, subjects who fail to complete 21 days of ENTO, or miss any doses of cytarabine and daunorubicin in Group A, or decitabine (or azacitidine during the Phase 2 safety run-in) in Group B for reasons other than DLT, will not be evaluable for the ENTO DLT assessment. Additional subjects will be enrolled to the appropriate dose level to replace unevaluable DLT subjects in order to provide adequate safety data on which to base dose escalation decisions as well as expansion decisions. Non-hematologic toxicity of Grade 4 attributable to ENTO with the exception of alopecia, nausea and vomiting controllable with anti-emetic therapy, line associated venous thrombosis, infection (infection-related toxicities such as fever/sepsis), and fatigue will be considered DLT.

Subjects with transient Grade 4 electrolyte abnormalities that are not clinically significant and are correctable within 24 hours will not be considered DLT.

Subjects with transient liver function test abnormalities (AST, ALT, bilirubin, or alkaline phosphatase) that resolve to ≤ Grade 2 within 10 days will not be considered DLT.

In general, infection will not constitute a DLT unless it is felt that the infection resulted from unexpectedly complicated prolonged myelosuppression.

Toxicities that require temporary interruption of treatment with ENTO (but not permanent discontinuation) will not be considered DLT unless the toxicity does not resolve to ≤ Grade 2 in 10 days.

In subjects with < 5% blasts in the bone marrow, absence of myelodysplastic changes, and/or absence of AML by flow cytometry in the bone marrow, hematologic toxicity will be defined as: failure to recover neutrophil count (ANC > 500/µL) or platelet count (> 25000/µL) within 4 weeks after achieving < 5% blasts in Group A and Group C. Hematologic toxicities will not be used to assess DLTs in Group B.

3.2.1. Guidelines for Phase 1b Dose Escalation and Phase 2 Group B Dose Expansion

In Phase 1b, the trial employs the standard NCI definition of MTD (starting dose associated with DLT in < 33.3% of subjects during the DLT assessment window). After considering the available safety and efficacy data and in consultation with the study PI, a dose at or below MTD will be chosen by the sponsor for further evaluation.

Dose escalation for Groups A, B, and C will proceed independently and in parallel per Table 3-6.

Table 3-6. Dose Escalation/ DLT Guidelines

Number of Subjects with DLT at a given level	Escalation Decision Rule
0 out of 3	Enroll 3 subjects at the next dose level. An additional 3 subjects can be enrolled at the current dose level without a DLT if additional evaluation is warranted after discussion with the study PI and medical monitor.
≥ 2	Dose escalation will be stopped. This dose level will be declared maximally administered dose (highest dose administered). Three (3) additional Pts. will be entered at next lower dose level if only 3 subjects were treated previously at that dose.
1 out of 3	Enroll at least 3 more subjects at this dose level. If 0 of these 3 subjects experience DLT, proceed to the next dose level. If 1 or more of this group suffer DLT, then dose escalation is stopped, and this dose is declared the maximally administered dose. Three (3) additional subjects will be entered at the next lower dose level if only 3 subjects were treated previously at that dose.
≤ 1 out of 6 at highest dose level below the maximally administered dose	This is the maximum tolerated dose (MTD) and generally the effective dose. At least 6 subjects must be entered at the effective dose. The recommended expansion dose may be a dose lower than the MTD.

In Phase 2 Group B (ENTO + azacitidine) safety run-in cohort, if 2 or more subjects experience DLT, all ongoing subjects in the cohort will be discontinued and the cohort will be closed.

3.3. Dosing Delays/Dose Modifications Attributed to Entospletinib (Beyond Cycle 1)

If the following signs or symptoms are medically manageable, they are not to be a consideration with respect to the subject's dosing or continuation on study: nausea/mild vomiting/diarrhea, drug-related fever or chills, transient and correctable laboratory test abnormalities, line associated thrombosis, or alopecia (see Appendix 3). Subjects who are intolerant of dose beyond Cycle 1, may either stop study drug (permanent discontinuation) or have a dose hold in consultation with the Medical Monitor if the AE or lab has resolved to Grade 1 or less which may not be re-escalated. If there is loss of disease control during drug interruption which has resolved to Grade 1 or less, subjects may re-start ENTO per the dose modification guidelines below.

Group A:

Subjects experiencing toxicity attributed to any of the study medication during Cycle 1 requiring permanent discontinuation of either drug shall be removed from study. There will be no dose modifications for ENTO for hematologic toxicity during Cycle 1.

Dose modification of ENTO in subsequent cycles is permitted following guidelines provided below. Subjects who experience a non-hematologic toxicity assessed as ENTO related that is Grade 3 or higher will hold dosing of ENTO until the toxicity resolves to Grade 1, and then restart at the next lower dose and continue through the end of the cycle. Missed doses are not to be made up.

Adverse events and laboratory abnormalities will be graded using the CTCAE, Version 4.03.

Dose Modifications for Non-Hematologic Toxicity for Entospletinib and Daunorubicin and Cytarabine and High Dose Cytarabine Maintenance

In subjects who experience florid heart failure (EF < 45%) or cerebellar toxicity, protocol treatment will be held and no further anthracyclines or cytarabine will be permitted while on the trial. To re-administer and continue with protocol treatment, EF will need to recover to ≥ 45%.

If a subject experiences any non-hematologic clinically significant Grade 3 or greater toxicity felt to be related to the combination agents, or high dose cytarabine maintenance, hold the protocol therapy until it resolves to less than Grade 2. Then, if determined related to ENTO, restart ENTO with one dose level reduction. If a subject experiences pneumonitis at Grade 4, study treatment must be discontinued.

Dose Modifications for Hematologic Toxicity for Entospletinib and Daunorubicin and Cytarabine and High Dose Cytarabine Maintenance

No dose modifications are planned for hematological toxicity for cytarabine and daunorubicin during induction chemotherapy. In subjects who require Cycle 2 induction, an ECHO/MUGA is recommended prior to starting Cycle 2 and daunorubicin will be administered if EF is ≥ 45% per investigator discretion.

No renal dose reductions are necessary when standard dose cytarabine is used (100-200mg/m^2/24hrs). Reduced doses should be considered when using high dose cytarabine as indicated below:

Glomerular Filtration Rate (mL/min)	Dose Administered
> 60	100%
46-60	60%
31-45	50%
< 30	Contraindicated

For cerebellar neurotoxicity ≥ Grade 2 due to high dose cytarabine, discontinue high dose cytarabine for the remainder of the induction cycle.

If prolonged hematologic clinically significant Grade 3 or greater toxicity felt to be related to ENTO occur after Cycle 1, hold ENTO until it resolves to less than Grade 2. Then, restart ENTO with one dose level reduction.

Group B:

Cycle 0 will be defined as Days 1-14. Cycles 1-4 and maintenance therapy will be defined as Days 1-28. Subsequent cycles of therapy are to begin as soon as possible after Day 28. Delays of up to 14 days will not constitute a protocol violation.

Delays of longer than 14 days must be discussed with the PI and Medical Monitor; repeat BM aspiration and biopsy is required if treatment is delayed more than 4 weeks. Delays longer than 14 days are only permitted (but not required) under special circumstances after discussion with PI and Medical Monitor and permissible reasons for these extended delays include:

- Drug related myelosuppression (defined here as ANC < 500/µL or platelet count < 25,000/µL, with no evidence of AML in blood or marrow – including flow cytometry or cytogenetics). A repeat BM aspiration and biopsy is required if treatment is delayed more than 4 weeks.
- Ongoing febrile neutropenia or active infection in subjects with no evidence of AML. Note - this does not apply to subjects with febrile neutropenia/infection in the setting of active AML.
- Serious hemorrhagic complication in a subject who is refractory to platelet transfusions.

For subjects entering the maintenance phase of treatment, drug related myelosuppression is a greater concern. However, it should again be noted that subjects with continued evidence of AML such as by flow or cytogenetics (even if morphologic blasts are < 5%) should proceed with therapy in a timely way as described above.

For subjects with no evidence of AML, the first cycle of maintenance should proceed on Day 29 as long as marrow cellularity is ≥ 10%. However, the second (or subsequent) cycles of maintenance therapy may be held until ANC is greater than or equal to 1000. If there is no evidence of ANC recovery after 14 days, repeat marrow evaluation is needed. If negative for disease and cellularity is ≥ 10%, proceed with decitabine and ENTO at decreased doses. Bone marrow evaluation may be done sooner than 14 days at the discretion of the treating physician.

Dose Modifications for Non-Hematologic Toxicity for Entospletinib, Decitabine or Azacitidine

If the subject experiences any non-hematologic clinically significant Grade 3 or greater toxicity felt to be related to either agent during the induction phase beyond DLT assessment, hold the protocol therapy until it resolves to less than Grade 2. Then, if related to ENTO, restart ENTO

with one dose level reduction. If related to decitabine or azacitidine, the respective package insert should be followed for any dose reductions. If institutional guidelines are to be followed, contact the study team for additional guidance. If the toxicity recurs, subject will be removed from study. If protocol therapy is withheld for more than 2 weeks for toxicity related to protocol-based therapy or up to 4 weeks for any other reason, subjects will be removed from protocol. If a subject experiences pneumonitis at Grade 4, study treatment must be discontinued. For additional safety information, reference the package insert for decitabine and azacitidine.

Subjects who have been dose-reduced cannot be returned to a higher dose level.

Toxicities in an individual subject must resolve to less than Grade 2 or to baseline levels before proceeding with the next cycle of treatment.

Dose Modifications for Hematologic Toxicity for Entospletinib, Decitabine or Azacitidine

It is recognized that drug-related hematologic toxicity in this population may be difficult to ascertain given the aggressive hematologic disease and the fact that multiple cycles of therapy may need to be administered for maximal clinical response. Therefore, there will be no dose modifications for hematologic toxicity due to ENTO, decitabine or azacitidine during the first 3 cycles for subjects with active AML. However, after the third cycle of ENTO and decitabine is administered, subjects suspected to have study treatment related ANC and/or platelet count toxicity (ie, fail to recover to at least 50% of the prior cycle's baseline value) will have the dose of decitabine reduced to 20 mg/m^2/d on Days 1-9 and the dose of ENTO reduced one dose level. Similarly, after the third cycle of ENTO and azacitidine administration, subjects suspected to have study treatment related ANC and/or platelet count toxicity (ie, fail to recover to at least 50% of the prior cycle's baseline value) will have the dose of azacitidine reduced according to Table 3-7 and the dose of ENTO reduced one dose level. Dose modifications because of concern for drug induced cytopenias prior to Cycle 4 will be discussed with the medical monitor. Dose modifications for hematologic toxicity for subjects who have achieved a CR or CRi are detailed below. For additional safety information, reference the package insert for decitabine and azacitidine.

Table 3-7. Azacitidine Dose Modifications

Nadir Counts		% Dose in the Next Course
ANC (x10^9/L)	Platelets (x10^9/L)	
< 0.5	< 25.0	50%
0.5 –1.5	25.0-50.0	67%
> 1.5	> 50.0	100%

Dose Modifications for Hematologic Toxicity for Subjects Who HAVE Achieved < 5% Blasts and Receive Maintenance Therapy With Decitabine or Azacitidine

Subjects who have had a previous dose reduction of decitabine and ENTO and then subsequently have a decrease in blasts to < 5% by morphology, the number of days of decitabine will be reduced to Days 1-4 of each cycle, but the daily dose will remain the same. For example, a subject receiving 20 mg/m^2/day on Days 1-9 will move on to receive 20 mg/m^2/day on Days 1-4. Subjects will receive the same dose reduction of ENTO. For azacitidine, no dose reduction regimen is necessary.

Neutropenia

In the event of Grade 4 neutropenia (ANC < 500/μL) that occurs with the second or subsequent cycles of maintenance and persists for 14 days or more or is associated with febrile neutropenia, further cycles of ENTO/decitabine shall be administered once ANC recovers to ≥ 1000/μL with a decrease in the number of days of decitabine and the dose of ENTO will be decreased by 1 dose level (ie, for the first occurrence omit the final day 5 dose of decitabine; for the second occurrence omit the final day 4 dose of decitabine). If there is no evidence of ANC recovery after 14 days, repeat marrow evaluation should be considered. Subjects who require a dose reduction below dose level -1 will not receive ENTO and instead will continue maintenance treatment with decitabine alone. If Grade 4 neutropenia that persists for 14 days or more (or grade 4 neutropenia associated with fever) recurs for the third time, discontinue the ENTO/decitabine. Similarly, in the event of neutropenia that occurs with the second or subsequent cycles of maintenance with azacitidine, and persists for 14 days or more or is associated with febrile neutropenia, the dose of azacitidine will be reduced according to Table 3-8.

Thrombocytopenia

In the event of Grade 4 thrombocytopenia (platelets < 25,000/μL) that occurs with the second or subsequent cycles of maintenance and persists for more than 14 days (or >25,000/μL but requiring prophylactic platelet transfusions to maintain this over the 14 day period), further cycles of ENTO/decitabine shall be administered with a decrease in the number of days of decitabine and the dose of ENTO will be decreased by 1 dose level (ie, for the first occurrence omit the final day 5 dose of decitabine; for the second occurrence omit the final day 4 dose of decitabine). Subjects who require a dose reduction below dose level -1 will not receive ENTO and instead will continue maintenance with decitabine alone. If Grade 4 thrombocytopenia persisting for more than 14 days (or subject requires prophylactic platelet transfusions to maintain >25,000/μL over the 14 day period) recurs for the third time, discontinue the ENTO/decitabine. Similarly, in the event of thrombocytopenia that occurs with the second or subsequent cycles of maintenance with azacitidine, and persists for 14 days or more or is associated with prophylactic platelet transfusions, the dose of azacitidine will be reduced according to Table 3-8.

Table 3-8. Azacitidine Dose Reductions

WBC or Platelet Nadir % decrease in counts from baseline	Bone Marrow Biopsy Cellularity at Time of Nadir (%)		
	30-60	15-30	<15
	% Dose in the Next Course		
50 - 75	100	50	33
>75	75	50	33

Dose Modifications for Non-hematologic Toxicity for Subjects Who HAVE Achieved CR or CRi and Receive Maintenance Therapy With Decitabine or Azacitidine

Subjects who experience any significant Grade 3 or greater toxicity attributed to decitabine, azacitidine, or ENTO will hold the protocol therapy until it resolves to ≤ Grade 2. Then restart ENTO with one dose level reduction and reduce the dose of decitabine to 20 mg/m^2/d on Days 1-4 for the first occurrence and decrease the dose of decitabine to 20 mg/m^2/d on Days 1-3 for the second occurrence and restart ENTO at the next lower dose. For azacitidine specifically, 50% dose reduction will be applied in combination with ENTO at the next lower dose. Subjects who require a dose reduction below dose level -1 will not receive ENTO and instead will continue maintenance with decitabine or azacitidine alone. If the toxicity recurs for a third time during treatment period, therapy should be discontinued. Decitabine/ENTO or azacitidine/ENTO should not be restarted until the toxicity has resolved to Grade 2 or better. Subjects with controlled Grade 3 infection or febrile neutropenia may continue decitabine or azacitidine in combination with ENTO. If a subject experiences pneumonitis at Grade 4, study treatment must be discontinued but may continue with decitabine or azacitidine alone.

Dose reductions (for either hematologic or non-hematologic toxicity) for subjects with < 5% blasts by morphology may be done twice during the course of maintenance therapy, if necessary.

Group C:

Dose modifications and delays attributed to ENTO for hematologic and non-hematologic toxicities will follow the guidelines in Appendix 3.

3.3.1. Management of Low Grade Chronic Toxicities

Since subjects will be receiving the study treatments daily, low grade chronic side effects, such as nausea, fatigue and diarrhea, while not meeting the above definition for dose limiting toxicities, may not be tolerable when experienced for long periods of time. Following discussion with the Gilead Sciences Medical Monitor, dose reduction may be permitted if low grade chronic side effects cannot be managed effectively with supportive care.

3.3.2. Specific Considerations for Managing Hyperbilirubinemia

3.3.2.1. Unconjugated (Indirect) Bilirubin Elevations

ENTO is an inhibitor of UGT1A1 and reversible increases in unconjugated (indirect) bilirubin values occurred in healthy subjects receiving ENTO. In the absence of symptoms or other hepatic laboratory abnormalities, ENTO dose modification is not required for elevated indirect bilirubin levels.

3.4. Duration of Treatment

For subjects enrolled to Group A Phase 1b (Dose Escalation):

ENTO lead-in will be administered daily on Days 1-14 as a single agent (Cycle 0) and will continue to be given daily in combination with IV daunorubicin (Days 1-3 for Cycle 1 and 2) and cytarabine (Days 1-7 for Cycle 1 and 2) during induction chemotherapy of every 14-day cycle for up to 2 cycles (Cycle 1 and 2). Subjects must be able to receive up to 2 cycles of induction chemotherapy. Cytarabine and daunorubicin (7+3) treatment (Cycle 1) may be started after 5 days of exposure to ENTO if the Principal Investigator agrees with the treating physician that treatment should start sooner. Subjects that experience a DLT may continue on protocol at a de-escalated dose.

Subjects with residual disease detected at the Cycle 1 Day 14 bone marrow evaluation will proceed with Cycle 2 of induction chemotherapy. The start of Cycle 2 will depend on the timing and result of the disease assessment. Subjects are to continue receiving ENTO while awaiting disease assessment results.

The investigator must consult the medical monitor if subjects have not obtained a CR after Cycle 1 and prior to Cycle 2, and if there is any consideration to omit Cycle 2 of induction chemotherapy.

If a subject discontinues study treatment (eg, as a result of an AE), every attempt should be made to keep the subject in the study to perform the required study-related follow-up and procedures. If this is not possible or acceptable to the subject or investigator, the subject may be withdrawn from the study.

For subjects enrolled to Group A Phase 2 (Dose Expansion):

ENTO 400 mg lead-in will be administered daily every 12 hours on Days 1-14 as a single agent (Cycle 0) to the completion of induction therapy as determined by bone marrow response. However, 7+3 treatment (Cycle 1) may be started earlier, after at least 5 days of exposure to ENTO, if the Principal Investigator agrees with the treating physician that treatment should start sooner.

ENTO 400 mg will be administered daily every 12 hours in combination with IV daunorubicin (Days 1-3) and cytarabine (Days 1-7) for up to 2 induction cycles (Cycle 1 and 2). Subjects must be able to receive 2 cycles of induction chemotherapy. Subjects with residual disease detected at the Cycle 1 Day 14 bone marrow evaluation proceed with Cycle 2 of induction chemotherapy. The start of Cycle 2 will depend on the timing and result of the disease assessment. Subjects are to continue receiving ENTO while awaiting disease assessment results.

The investigator must consult the medical monitor if subjects have not obtained a CR after Cycle 1 and prior to Cycle 2, and if there is any consideration to omit Cycle 2 of induction chemotherapy.

If CR/CRi is achieved at the end of Cycle 1 or 2, the subject may proceed to SCT or will receive post-remission chemotherapy. If CR/CRi is not achieved by the end of Cycle 2, the subject is considered a treatment failure and will have met study efficacy endpoint criteria, but will remain on study for required study-related follow-up procedures.

Post-remission chemotherapy will consist of $3g/m^2$ cytarabine every 12 hours on Days 1, 3, and 5 (< 60 years of age) or $1g/m^2$ high dose cytarabine once daily on Days 1-5 (≥ 60 years of age) in combination with ENTO every 12 hours on Days 1-28 of each 28-day cycle for at least 3 cycles and up to 4 cycles. Subjects who are awaiting a donor or transitioning to allogeneic SCT may receive at least 1 cycle and up to 4 cycles of cytarabine.

Maintenance therapy will consist of ENTO 400 mg as a single agent every 12 hours on Days 1-28 of each 28-day cycle and will continue for up to 12 cycles as long as the subject is experiencing benefit or until the subject becomes a candidate for SCT. Extension of maintenance may occur on an individual basis if approved by the Principal Investigator.

If a subject discontinues study treatment (eg, as a result of an AE), every attempt should be made to keep the subject in the study to perform the required study-related follow-up and procedures. If this is not possible or acceptable to the subject or investigator, the subject may be withdrawn from the study.

For subjects enrolled to Group B Phase 1b/2 (Dose Escalation and Expansion):

ENTO lead-in will be administered every 12 hours on Days 1-14 as a single agent (Cycle 0) for subjects enrolled to Group B Phase 1b and Group B Phase 2 safety run-in. However, chemotherapy with the assigned hypomethylating agent (Cycle 1) may be started earlier, after 5 days of exposure to ENTO, if the Principal Investigator agrees with the treating physician that treatment should start sooner.

For subjects enrolled to Group B Phase 2 randomization, ENTO lead-in will be administered every 12 hours on Days 1-5 as a single agent (Cycle 0).

In subsequent induction cycles (Cycles 1-4), ENTO will be administered every 12 hours on Days 1-28 in combination with assigned hypomethylating agent dose and schedule. Only azacitidine will be given during the Phase 2 safety run-in. Subjects will receive at least 2 cycles

of induction therapy but no more than 4 cycles. If the subject achieves < 5% blasts by morphology and flow cytometry or has evidence of clinical benefit after completing 2-4 induction cycles but is not eligible for SCT, the subject will have the option to receive maintenance therapy with ENTO in combination with decitabine or azacitidine. Subjects with persistent evidence of disease (ie, blasts ≥ 5%) after Cycle 2 may receive up to 2 more induction cycles until subject achieves < 5% blasts. If < 5% blasts by morphology and flow cytometry is not achieved or the subject does not show evidence of clinical benefit after 4 induction cycles, the subject is considered a treatment failure and will be discontinued from the study.

During ENTO + hypomethylating agent maintenance therapy, ENTO will be administered every 12 hours on Days 1-28 in combination with assigned hypomethylating agent dose and schedule. ENTO will be administered every12 hours on Days 1-28 in combination with decitabine on Days 1-5 or in combination with azacitidine on Days 1-7 of every 28-day cycle for at least 2 cycles. 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.

During ENTO maintenance therapy, ENTO will be administered as monotherapy every 12 hours on Days 1-28. Treatment may continue until the subject meets the criteria for study treatment discontinuation or up to 12 cycles. Extension of maintenance may occur on an individual basis if approved by the Principal Investigator.

If a subject discontinues study treatment (eg, as a result of an AE), every attempt should be made to keep the subject in the study to perform the required study-related follow-up and procedures. If this is not possible or acceptable to the subject or investigator, the subject may be withdrawn from the study.

For subjects enrolled to Group C Phase 1b (Dose Escalation):

ENTO monotherapy will be administered every 12 hours on Days 1-28 of every 28-day cycle until the subject meets the criteria for study treatment discontinuation (see Section 6.4.1). Subjects who experience a DLT may continue on protocol at a de-escalated dose.

If a subject discontinues study treatment (eg, as a result of an AE), every attempt should be made to keep the subject in the study to perform the required study-related follow-up and procedures. If this is not possible or acceptable to the subject or investigator, the subject may be withdrawn from the study.

For subjects enrolled to Group C Phase 2 (Dose Expansion):

ENTO monotherapy will be administered every 12 hours on Days 1-28 of every 28-day cycle and may continue as long as the subject is experiencing benefit and does not meet criteria for study treatment discontinuation.

If a subject discontinues study treatment (eg, as a result of an AE), every attempt should be made to keep the subject in the study to perform the required study-related follow-up and procedures. If this is not possible or acceptable to the subject or investigator, the subject may be withdrawn from the study.

4. SUBJECT POPULATION

4.1. Number of Subjects and Subject Selection

Subjects with AML and who meet the eligibility criteria will be studied. Approximately 190 subjects with newly diagnosed, relapsed/refractory AML will be dosed in 3 groups, using a 3 + 3 design for the dose escalation phase.

Screening laboratory data is required within 2 weeks prior to administration of study treatment as shown in Table 4-1. Note: Confirmation should be considered for out of range values to determine if the abnormality is real or artifactual. Values should be obtained within the screening period and should be the most recent measurement obtained. Subjects with any degree of neutropenia, thrombocytopenia, or anemia due to malignancy may enroll.

Table 4-1. Required Screening Laboratory Values Organ System Parameter Required Value

Organ System	Parameter	Required Value
Hepatic	Serum total bilirubin	≤ 1.5 x ULN (unless elevated due to Gilbert's syndrome or hemolysis)
	Serum ALT	≤ 2.5 x ULN
	Serum AST	
Renal	Serum creatinine	< 1.5 x ULN
Coagulation	INR[a]	< 1.7
Pregnancy	β-HCG[b]	Negative
Infection	HIV	Negative HIV antibody
	HBV	Negative HBsAg and negative HBc antibody
	HCV	Negative viral RNA (if HCV antibody is positive)

a For subjects on warfarin, the required value is < 3.0
b A negative serum pregnancy test is required for female subjects (unless surgically sterile or menopausal). Female subjects with medically documented ovarian failure must also have serum FSH levels within the institutional postmenopausal range.

4.2. Inclusion Criteria

Group A

- Subjects age ≥ 18 with previously untreated AML by WHO criteria, excluding acute promyelocytic leukemia (M3), who are able and should receive up to 2 cycles of induction chemotherapy with 7+3 as determined by the treating physician

Group B

- Subjects age > 70 years with previously untreated AML by WHO criteria, excluding acute promyelocytic leukemia (M3)
- Subjects age ≤ 70 years with previously untreated AML by WHO criteria, excluding acute promyelocytic leukemia (M3), who refuse or are unable to receive 7+3 as determined by the treating physician

Group C Phase 1b (Dose Escalation)

- Subjects age ≥ 18 years with relapsed/refractory AML by WHO criteria, excluding acute promyelocytic leukemia (M3)
- Subjects with previously untreated AML by WHO criteria, excluding acute promyelocytic leukemia (M3), and who would have met disease eligibility criteria for Group A or B but refuse or are unable to receive 7+3 or decitabine chemotherapy as determined by the treating physician

Group C Phase 2 (Dose Expansion)

- Cohort C1A: Subjects age ≥ 18 years with relapsed/refractory AML by WHO criteria, excluding acute promyelocytic leukemia (M3)
- Cohort C2: Subjects age ≥ 18 years with relapsed/refractory AML with MLL
- Cohort C3: Subjects with previously untreated AML by WHO criteria, excluding acute promyelocytic leukemia (M3), and who would have met disease eligibility criteria for Group A or B but refuse or are unable to receive chemotherapy and hypomethylating agent as determined by the treating physician

ALL subjects must meet all of the following inclusion criteria to be eligible for participation in this study:

1) Male or female ≥ 18 years of age with a diagnosis AML (M0-M7, except M3)
2) All acute toxic effects of any prior anti-leukemia therapy resolved to Grade ≤ 1 before the start of study treatment (with the exception of alopecia [any grade permitted], or bone marrow parameters [any grade permitted] due to leukemia in the investigators opinion)
3) ECOG performance status less than or equal to 2
4) Life expectancy of at least 3 months
5) Meet required screening laboratory criteria unless leukemia related, as shown in Table 4-1.
6) Left Ventricular Ejection Fraction (LVEF) ≥ 45% confirmed by ECHO or MUGA (only ECHO for Germany) and no clinical evidence of congestive heart failure
7) For female subjects of childbearing potential, willingness to abstain from heterosexual intercourse or use a protocol-recommended method of contraception from the screening visit throughout the study treatment period and for 30 days following the last dose of ENTO or as recommended in the prescribing information for other co-administered study drugs (whichever is later).

   Note: See Appendix 4 for definition of childbearing potential and information regarding recommendations for contraception.

For male subjects of childbearing potential having intercourse with females of childbearing potential, willingness to abstain from heterosexual intercourse or use a protocol recommended method of contraception from the start of study treatment throughout the study treatment period and for 90 days following the last dose of ENTO or as recommended in the prescribing information for other co-administered study drugs (whichever is later), and to refrain from sperm donation from the start of study treatment throughout the study treatment period and for 90 days following the last dose of ENTO or as recommended in the prescribing information for other co-administered study drugs (whichever is later).

Note: See Appendix 4 for definition of childbearing potential and information regarding recommendations for contraception.

8) Willingness to comply with scheduled visits, drug administration plan, imaging studies, laboratory tests, other study procedures, and study restrictions

9) Have the ability to understand and sign a written informed consent form, which must be obtained prior to initiation of study procedures

4.3. Exclusion Criteria

Subjects who meet any of the following exclusion criteria are not eligible for study participation:

1) Subjects with acute promyelocytic leukemia (M3)

2) Known active central nervous system or leptomeningeal leukemic involvement.
Note: Central nervous system testing (CSF analysis) is only required in subjects with suspected involvement based on symptoms or signs.

3) Treatment with proton pump inhibitors (PPIs) within 7 days prior to enrollment. Note: PPIs are likely to interfere with ENTO absorption, thus requiring a 7-day washout period. H2 blockers and antacids will be allowed for use during the protocol.

4) History of active non-myeloid malignancy except for the following: adequately treated local basal cell or squamous cell carcinoma of the skin, cervical carcinoma in situ, superficial bladder cancer, asymptomatic prostate cancer without known metastatic disease and with no requirement for therapy or requiring only hormonal therapy and with normal prostate specific antigen for > 1 year prior to start of study therapy, or any other cancer that has been in complete remission without treatment for ≥ 5 years prior to enrollment. Subjects who are on prophylaxis with long-term adjuvant hormonal therapy and are ≥ 5 years from therapy for their primary tumor are eligible for enrollment.

5) Evidence of ongoing uncontrolled systemic bacterial, fungal, or viral infection at the time of start of study treatment. Note: Subjects with localized fungal infections of skin or nails are eligible.

6) Ongoing, drug-induced liver injury, known chronic active hepatitis C Virus (HCV), chronic active hepatitis B Virus (HBV), alcoholic liver disease, non-alcoholic steatohepatitis, primary biliary cirrhosis, ongoing extrahepatic obstruction caused by cholelithiasis, cirrhosis of the liver, or portal hypertension

7) Ongoing (within the past 6 weeks) hepatic encephalopathy

8) Ongoing drug-induced pneumonitis

9) Ongoing inflammatory bowel disease

10) Ongoing alcohol or drug addiction as determined by investigator

11) Pregnancy or breastfeeding

12) History of prior allogeneic bone marrow progenitor cell or solid organ transplantation. Note: prior allogeneic bone marrow progenitor cell or solid organ transplantation is NOT an exclusion criteria for Cohort C2 ie, MLL cohort.

13) Ongoing immunosuppressive therapy, including systemic chemotherapy for treatment of leukemia. Subjects may not have received AML-directed therapy prior to enrollment other than Hydroxyurea or apheresis, if de-novo or for current relapse, except for subjects defined as refractory disease at study enrollment. Concurrent use of methotrexate for rheumatologic conditions is permitted.

    Note: Subjects may use topical, enteric, or inhaled corticosteroids as therapy for comorbid conditions and systemic steroids for autoimmune anemia and/or thrombocytopenia. Ongoing use of low-dose systemic corticosteroids (< 5 mg/day of methylprednisolone or equivalent) for rheumatologic conditions is permitted. During study participation, subjects may receive systemic or other corticosteroids needed for treatment-emergent comorbid conditions

14) Concurrent participation in an investigational drug trial with therapeutic intent defined as prior study therapy within 14 days prior to study treatment

15) Any other prior or ongoing condition that, in the opinion of the investigator, could adversely affect the safety of the subject or impair the assessment of study results

16) Inability to tolerate oral medications, symptomatic disease significantly affecting gastrointestinal function manifested from resection of the stomach or small bowel or active ulcerative colitis, symptomatic inflammatory bowel disease, or partial or complete bowel obstruction

17) Uncontrolled intercurrent illness including, but not limited to:

    a) unstable angina pectoris

    b) psychiatric illness/social situations that would limit compliance with study requirements

    c) subjects with active infection are permitted to enroll provided that the infection is documented to be under control

18) Known hypersensitivity to ENTO, decitabine, azacitidine, cytarabine and daunorubicin, the metabolites, or formulation excipient

5. TREATMENT PLAN

5.1. Treatment Plan

5.1.1. Premedication

No specific premedications or supporting medications are required in conjunction with ENTO administration.

For cytarabine, daunorubicin, decitabine, and azacitidine please follow the currently approved version of the package insert and institutional guidelines when administering.

5.1.2. Administration Instructions

ENTO should be taken under fasted conditions. Fasting is defined as no food or liquids other than water for 2 hours pre- and 1 hour post-dose. Subjects should be instructed not to bite or chew the tablets. In case of breakage of the tablets in the oral cavity, additional water should be taken as a rinse.

If a subject is unable to take the whole pill, contact the Sponsor and Medical Monitor for further instructions.

5.1.3. Dosing Schedule

ENTO will be administered orally every 12 hours. ENTO should be taken at approximately the same time each day. Doses should be taken at approximately 12-hour intervals, while in a fasted state. While it is realized that variations in the dosing schedule may occur, the prescribed regimen should be followed as closely as possible. Compliance with the protocol dosing schedule will be documented in the subject's chart and the electronic data capture (EDC) at each scheduled visit. Counseling regarding subject compliance may be required.

5.1.4. Dose Schedule Interruptions and Vomited Doses

Subjects who have a delay in administration of a dose of ENTO of < 6 hours should take the planned dose as soon as possible after the intended time of administration. For subjects who have a delay in administration of ENTO of ≥ 6 hours, the dose should not be taken. ENTO administration may continue but the missed dose should not be made up and the planned timing of subsequent ENTO dosing should not be altered.

Vomited doses should be retaken, but only if the tablets are visible in the vomitus.

5.1.5. Concomitant and Supportive Therapy

Subjects should receive full supportive care including transfusions of blood and blood products, antibiotics, antiemetics, antifungals, allopurinol, etc., when appropriate.

No other direct anti-leukemia therapy is permitted.

Growth Factor use in Cycle 1 is discouraged and may not be used without PI approval as it may impact the determination of DLT. Beyond Cycle 1, the use of myeloid growth factors is permitted according to guidelines for use in AML but is generally discouraged.

rEPO is not permitted at any time on the study.

Palliative radiation therapy may not be administered while the subject is on study.

5.2. Restricted/Prohibited Medication

During the course of the clinical trial, study subjects are anticipated to continue the use of prescribed medications identified during the screening procedures, consistent with study inclusion and exclusion criteria.

The following therapies are not permitted at any point during the trial beginning with the first dose of study treatment (if administered, the subject may be discontinued from the trial).

- Any non-study leukemia directed therapy or non-study leukemia directed immunotherapy (approved or investigational), except steroids used as anti-emetics. Prophylaxis with intrathecal chemotherapy will not be considered as leukemia directed therapy.

The following restricted medications are only permitted under the circumstances given. Each concomitant medication must be individually assessed against all exclusion criteria. If in doubt, the investigator should contact the GSI Medical Monitor before enrolling the subject or allowing a new medication to be started.

- Proton Pump Inhibitors (PPIs) have been shown by PK drug-drug interaction studies to decrease absorption and exposure of ENTO by ~60%. Thus, use of a proton pump inhibitor must be avoided for 7 days prior to and along with study drug administration. Examples include but are not limited to: esomeprazole, omeprazole, lansoprazole, etc.

  Note: H2 blockers and antacids will be allowed for use during the protocol. In addition, if a subject experiences a gastrointestinal bleed and must be placed on PPIs eg, IV pantoprazole, please contact the Medical Monitor and hold ENTO for the duration of use of the PPI until the subject is clinically stable.

- Co-administration of moderate CYP2C9 and strong CYP3A and CYP2C9 inducers are prohibited in this study. Administration of these medications should be avoided for 2 weeks prior to study drug administration. Examples of these medicines are provided in Table 5-1.

Caution should be exercised when co-administering drugs that are moderate or strong inhibitors of CYP2C9 (eg, fluconazole, voriconazole or amiodarone) as they may increase ENTO exposure.

Caution should be exercised when co-administering medications that are transported by UGT1A1, OATP1B1, OATP1B3, MATE1, P-gp and BCRP; dose adjustment or switching to an alternative medication may be necessary if clinically indicated.

Table 5-1. Restricted Medications in this Study that Require Prior MM Discussion and Approval

	Strong	Moderate
CYP3A Inducer	carbamazepine, phenytoin, rifampin, St. John's Wort, enzalutamide, rifabutin, phenobarbital, mitotane, avasimibe	Not prohibited
CYP2C9 Inducer		carbamazepine, rifampin, ritonavir, enzalutamide
Proton Pump Inhibitors	omeprazole, esomeprazole, pantoprazole, lansoprazole, rabeprazole, dexlansoprazole	

In a study in healthy volunteers, ENTO 400 mg every 12 hours increased rosuvastatin exposure by approximately 4-fold, which may increase the risk of rhabdomyolysis. In reviewing the safety of subjects who have received a statin with ENTO, there have been no reports of rhabdomyolysis or a different adverse events profile, but in the interest of caution, the following restrictions apply to the use of HMG-CoA reductase inhibitors with ENTO:

Concomitant Medication	Restriction
Atorvastatin	Maximum dose 20 mg QD
Rosuvastatin	Maximum dose 10 mg QD
Pravastatin	Maximum dose 40 mg QD
Simvastatin	Maximum dose 20 mg QD
Lovastatin	Maximum dose 20 mg QD
Fluvastatin	Maximum dose 20 mg BID or 40 mg QD
Pitavastatin	Maximum dose 1 mg QD

The management of subjects who are benefiting from the protocol treatment and who subsequently require treatment with the above medications should be discussed with the Medical Monitor.

5.3. Study Drug Disposal

At the start of the study, the study monitor will evaluate each study center's study drug disposal procedures and provide appropriate instruction for return or destruction of unused study drug supplies. If the site has a process instruction (eg, Standard Operating Procedures [SOPs]) for on-site drug destruction which is reviewed by the study monitor, then the site should destroy used (empty bottles) and unused study drug supplies performed in accordance with the site's (hospital/pharmacy) procedure. The destruction process should include records noting the identification and quantity of each unit destroyed the method of destruction, and person who disposed of the drug. A copy of the site's SOP/process document will be obtained for central files at the pre-study or otherwise applicable monitoring visit. Upon study completion, a copy of the relevant Investigational Drug Accountability records must be filed at the site and provided for the sponsor files. If the site does not have acceptable procedures in place for drug destruction, arrangements will be made between the site and Gilead Sciences (or Gilead Sciences' representative) for return of unused study drug supplies.

6. STUDY PROCEDURES

The study procedures to be conducted for each subject enrolled in the study are presented in tabular form in Appendix 2: Study Procedure Tables and described in the text that follows.

The investigator must document any deviation from protocol procedures and notify the sponsor or contract research organization (CRO).

6.1. Subject Enrollment and Treatment Assignment

The screening number and/or subject ID will be assigned for the individual subject by the designed IxRS. This is an open-label study.

It is the responsibility of the Investigator to ensure that subjects are eligible to participate in the study prior to enrollment and throughout the study. Once consent is obtained, all screening tests and procedures are assessed, and study eligibility is confirmed, subjects will be enrolled to receive ENTO.

In Phase 2 Group B, subjects will be randomized in a 1:1 manner in IxRS to treatment arm ENTO in combination with decitabine or ENTO in combination with azacitidine.

6.2. Pretreatment Assessments

6.2.1. Screening Visits

Subjects will be screened within 14 days before the first administration of study treatment to determine eligibility for participation in the study. Bone marrow biopsy and aspirate may be performed within 21 days before the first administration of study treatment. The following will be performed and documented at screening:

- Obtain written informed consent
- Obtain medical history
- Obtain current smoking status
- Review prior/concomitant medication
- Complete physical examination including body weight, and height
- Vital signs; including blood pressure, respiratory rate, pulse, temperature, oxygen saturation level
- 12-lead ECG
- ECHO or MUGA (Note: For German sites, only ECHO to be performed)

- Obtain blood samples for:
  - Chemistry
  - Hematology
  - Coagulation
  - Serum pregnancy test (for all female subjects unless surgically sterile or menopausal) and serum FSH (for female subjects with medically documented ovarian failure)
  - HIV/HBV/HCV
- Urinalysis
- X-ray (Note: For German sites, X-ray not to be performed)
- Bone marrow aspirate (FISH will be performed) and biopsy (mutational testing for FLT3, NPM1, and CEBPA will be performed) for disease assessment and biomarker testing. If the bone marrow aspirate and biopsy could not be obtained, diagnostic samples should be used.
- ECOG performance status
- Record any serious adverse events and all adverse events related to protocol mandated procedures occurring after signing of the consent form
- CCI [redacted]

Subjects meeting all of the inclusion criteria and none of the exclusion criteria will return to the clinic for their first administration of study treatment within 14 days after screening into the study.

From the time of obtaining informed consent through the first administration of investigational medicinal product, record all serious adverse events (SAEs), as well as any adverse events related to protocol-mandated procedures on the adverse events case report form (CRF/eCRF). All other untoward medical occurrences observed during the screening period, including exacerbation or changes in medical history are to be captured on the medical history CRF/eCRF. See Section 7 Adverse Events and Toxicity Management for additional details.

6.3. Treatment Assessments

Subjects who have met all eligibility criteria will come to the clinic on Cycle 0 Day 1 (Cycle 1 Day 1 for Group C) to perform study required procedures prior to dosing, review prior/concomitant medications, and record adverse events at each clinic visit.

For study purposes, the ENTO lead-in (Cycle 0) is 14 days for Groups A, B, and C. One cycle of induction therapy is 14 days (or up to 28 days depending on count recovery) for Group A, and 28 days for Groups B and C.

6.3.1. Group A

The following procedures will be conducted during the Lead-in (Cycle 0) on Days 1, 8, and 14 (unless otherwise specified).

- ENTO will be administered orally every 12 hours on Days 1-14 as a single agent
- Review prior/concomitant medication
- Record any adverse events
- Vital signs; including blood pressure, respiratory rate, pulse, temperature, oxygen saturation level
- Complete physical examination (Day 1)
- Obtain current smoking status (Day 1)
- ECOG performance status (Day 1)
- CCI [redacted]
- Urine pregnancy test (negative pregnancy test required for all female subjects unless surgically sterile or menopausal prior to dose on Day 1)
- Obtain blood samples:
  - Chemistry (Days 1, 8, and 14)
  - Hematology (Days 1, 8, and 14)
  - Coagulation (Day 14)
  - PK (Days 1, 8, and 14 at pre-dose and 2 hours post-dose of ENTO)
  - Biomarkers (Days 1, 8, and 14 at pre-dose of ENTO)

  Note: ENTO should be held until the pre-dose blood samples have been drawn. Record the approximate time of the last 2 doses of ENTO on PK collection days and the time the PK blood samples are obtained.

- A bone marrow aspirate for disease assessment will be performed 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 initiating 7+3 chemotherapy. Biopsy will be used in the event the aspirate cannot be collected or analyzed (eg, dry-tap, hemodiluted specimen, or lack of spicules).

  — Subjects with cytogenetic and molecular mutations at screening must have cytogenetic and molecular mutation testing repeated at subsequent bone marrow examinations (Cycle 0 Day 14, Cycle 1 Day 14, count recovery, End of Study).

The following procedures will be conducted during Cycle 1 (and Cycle 2, if needed) on Days 1, 3, 7, and 14 (unless otherwise specified).

- ENTO will continue to be administered orally every 12 hours for 14 days in combination with IV cytarabine (Days 1-7) and IV daunorubicin (Days 1-3). Subjects are to continue receiving ENTO while awaiting disease assessment results. Subjects must be able to receive 2 cycles of induction chemotherapy.

- Review prior/concomitant medication

- Record any adverse events

- Vital signs; including blood pressure, respiratory rate, pulse, temperature, oxygen saturation level (daily during hospitalization and at the Investigator's discretion after discharge)

- Weight (Day 1)

- ECOG performance status (Day 14)

- Physical exam (Day 1 and at the Investigator's discretion after hospital discharge)

- Obtain smoking status for past 28 days (Day 1 of each cycle)

- 12-lead ECG (at the investigator's discretion)

- ECHO or MUGA prior to re-induction, if applicable (Note: For German sites, only ECHO to be performed)

- Urine pregnancy test (for all female subjects unless surgically sterile or menopausal prior to dose on Day 1)

- Obtain blood samples for:

  — Chemistry (Days 7 and 14)

  — Hematology (Days 7, 14, and up to blood count recovery)

— Coagulation (Days 7 and 14)

— PK

- Phase 1b (Dose Escalation): Cycle 1 Day 3 and Cycle 1 Day 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 (Dose Expansion): Cycle 1 Day 3 (and Cycle 2, if needed) 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

— Biomarkers (Cycle 1 Day 7 and Cycle 1 Day 14 or at the end of Cycle 1 at the time of blood count recovery at pre-dose)

Note: ENTO should be held until the pre-dose blood samples have been drawn. Record the approximate time of the last 2 doses of ENTO on PK collection days and the time the PK blood samples are obtained.

- Obtain bone marrow aspirate and biopsy samples on Cycle 1 Day 14 for disease assessment and biomarker testing. If the bone marrow is consistent with Morphologic CR or CRi status per Appendix 5, evaluate MRD as per institutional practice and Appendix 7. Biopsy will be used in the event the aspirate cannot be collected or analyzed (eg, dry-tap, hemodiluted specimen, or lack of spicules).

  — If the bone marrow cellularity is ≤ 20% at Cycle 1 Day 14, a repeat bone marrow examination will occur within 2 weeks or at count recovery. Subjects with residual disease detected at the Cycle 1 Day 14 bone marrow evaluation will proceed with Cycle 2 of induction chemotherapy. The start of Cycle 2 will depend on the timing and result of the disease assessment. Subjects are to continue receiving ENTO while awaiting disease assessment results.

  — The investigator must consult the medical monitor if subjects have not obtained a CR after Cycle 1 and prior to Cycle 2, and if there is any consideration to omit Cycle 2 of induction chemotherapy.

  — Subjects with cytogenetic and molecular mutations at screening must have cytogenetic and molecular mutation testing repeated at subsequent bone marrow examinations (Cycle 0 Day 14, Cycle 1 Day 14, count recovery, End of Study).

If CR/CRi is not achieved by the end of Cycle 2, the subject will be considered a treatment failure and will have met study efficacy endpoint criteria, but will remain on study for required study-related follow-up procedures.

<u>Phase 2 only:</u> The following procedures will be conducted during each 28-day Post-Remission cycle on Days 1 and 28 (unless otherwise specified) for 3-4 cycles.

- ENTO will be administered orally every 12 hours for 28 days in combination with $3g/m^2$ high dose cytarabine administered every 12 hours on Days 1, 3, and 5 (< 60 years of age) or $1g/m^2$ cytarabine administered once daily on Days 1-5 (≥ 60 years of age)
- Review prior/concomitant medication
- Record any adverse events
- Vital signs; including blood pressure, respiratory rate, pulse, temperature, oxygen saturation level (Day 1 of Cycle 2 and Cycle 4)
- Complete physical examination (Day 1 of Cycle 2 and Cycle 4)
- Obtain smoking status for past 28 days (Day 1 of each cycle)
- ECOG performance status (Day 28 of Cycle 2 and Cycle 4)
- Urine pregnancy test (for all female subjects unless surgically sterile or menopausal prior to dose on Day 1)
- Obtain blood samples for:
  - Chemistry (Day 28 of Cycle 2 and Cycle 4)
  - Hematology (Day 28 of Cycle 2 and Cycle 4)
  - Coagulation (Day 28 of Cycle 2 and Cycle 4)
  - PK at pre-dose and 2 hours post-dose of ENTO (Day 5 and Day 28 of each cycle)
- Obtain bone marrow aspirate samples for disease assessment and biomarker testing on Cycle 2 Day 28 and Cycle 4 Day 28 or as clinically indicated. Biopsy will be used in the event the aspirate cannot be collected or analyzed (eg, dry-tap, hemodiluted specimen, or lack of spicules).

<u>Phase 2 only:</u> The following procedures will be conducted during each 28-day Maintenance cycle on Days 1 and 28 (unless otherwise specified).

- ENTO will be administered orally every 12 hours for 28 days and may continue up to 12 cycles as long as the subject is experiencing benefit or becomes a candidate for SCT. Extension of maintenance may occur on an individual basis if approved by the Principal Investigator.

- Review prior/concomitant medication
- Record any adverse events
- Vital signs; including blood pressure, respiratory rate, pulse, temperature, oxygen saturation level every 2 cycles (eg, Cycle 1 Day 1, Cycle 3 Day 1)
- Complete physical examination every 2 cycles (eg, Cycle 1 Day 1, Cycle 3 Day 1)
- Obtain smoking status for past 28 days (Day 1 of each cycle)
- ECOG performance status every 2 cycles on Day 28 (eg, Cycle 2 Day 28, Cycle 4 Day 28)
- Urine pregnancy test (for all female subjects unless surgically sterile or menopausal prior to dose on Day 1)
- Obtain blood samples for:
  - Chemistry (every 2 cycles from Cycle 1 Day 28)
  - Hematology (every 2 cycles from Cycle 1 Day 28)
  - Coagulation (every 2 cycles from Cycle 1 Day 28)
  - PK at pre-dose and 2 hours post-dose of ENTO (Day 28 of each cycle)
- Obtain bone marrow aspirate samples for disease assessment and biomarker testing at the end of every 4 cycles on Day 28 (eg, Cycle 4 Day 28, Cycle 8 Day 28, etc.) or as clinically indicated. Biopsy will be used in the event the aspirate cannot be collected or analyzed (eg, dry-tap, hemodiluted specimen, or lack of spicules). 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.

The following procedures will be conducted at Blood Count Recovery/Remission/Relapse.

- Obtain blood samples for:
  - Chemistry
  - Hematology
  - Biomarkers
- Obtain bone marrow aspirate samples for disease assessment and biomarker testing. Biopsy will be used in the event the aspirate cannot be collected or analyzed (eg, dry-tap, hemodiluted specimen, or lack of spicules). 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.

6.3.2. Group B

The following procedures will be conducted during the Phase 1b and Phase 2 Safety run-in Lead-in (Cycle 0) on Days 1, 8, and 14 (unless otherwise specified).

- ENTO will be administered orally every 12 hours on Days 1-14 as a single agent
- Review prior/concomitant medication
- Record any adverse events
- Vital signs; including blood pressure, respiratory rate, pulse, temperature, oxygen saturation level
- Complete physical examination (Day 1)
- Obtain current smoking status (Day 1)
- CCI
- ECOG performance status (Day 1)
- Urine pregnancy test (negative pregnancy test required for all female subjects unless surgically sterile or menopausal prior to dose on Day 1)
- Obtain blood samples for:
  - Chemistry (Days 1, 8, and 14)
  - Hematology (Days 1, 8, and 14)
  - Coagulation (Day 14 only)
  - PK (Days 1, 8, and 14 at pre-dose and 2 hours post-dose of ENTO)
  - Biomarkers (Days 1, 8, and 14 at pre-dose)

  Note: ENTO should be held until the pre-dose blood samples have been drawn. Record approximate times of the last 2 doses of ENTO on PK collection days and the time the PK blood samples are obtained.
- A bone marrow aspirate sample for disease assessment and biomarker research will be collected 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 initiating therapy with hypomethylating agent. Biopsy will be used in the event the aspirate cannot be collected or analyzed (eg, dry-tap, hemodiluted specimen, or lack of spicules).
  - Subjects with cytogenetic and molecular mutations at screening must have cytogenetic and molecular mutation testing repeated at subsequent bone marrow examinations (Cycle 0 Day 14, Cycle 1 Day 28, count recovery, End of Study).

The following procedures will be conducted during the Phase 2 Randomization Lead-in (Cycle 0) on Days 1 and 5 (unless otherwise specified).

- ENTO will be administered orally every 12 hours on Days 1-5 as a single agent
- Review prior/concomitant medication
- Record any adverse events
- Vital signs; including blood pressure, respiratory rate, pulse, temperature, oxygen saturation level
- Complete physical examination (Day 1)
- Obtain current smoking status (Day 1)
- CCI
- ECOG performance status (Day 1)
- Urine pregnancy test (negative pregnancy test required for all female subjects unless surgically sterile or menopausal prior to dose on Day 1)
- Obtain blood samples for:
  - Chemistry (Days 1 and 5)
  - Hematology (Days 1 and 5)
  - Coagulation (Day 5 only)
  - PK (Days 1 and 5 at pre-dose and 2 hours post-dose of ENTO)
  - Biomarkers (Days 1 and 5 at pre-dose)

  Note: ENTO should be held until the pre-dose blood samples have been drawn. Record approximate times of the last 2 doses of ENTO on PK collection days and the time the PK blood samples are obtained.
- If circulating blasts have cleared at the end of monotherapy lead-in (Cycle 0 Day 5), then a bone marrow aspirate sample will be performed for disease assessment. Biopsy will be used in the event the aspirate cannot be collected or analyzed (eg, dry-tap, hemodiluted specimen, or lack of spicules).
  - Subjects with cytogenetic and molecular mutations at screening must have cytogenetic and molecular mutation testing repeated at subsequent bone marrow examinations (Cycle 0 Day 5, Cycle 1 Day 28, count recovery, End of Study).

The following procedures will be conducted on Days 1, 8, and 28 of induction Cycles 1-4 (unless otherwise specified).

- ENTO will continue to be administered orally every 12 hours on Days 1-28 in combination with IV decitabine 20 mg/m^2 daily on Days 1-10 or IV/SC azacitidine 75mg/m^2 daily on Days 1-7 of each 28-day cycle. Subjects enrolled in the Phase 2 safety run-in will only receive ENTO in combination with azacitidine. Subjects enrolled in Phase 2 randomization will receive ENTO in combination with decitabine or azacitidine. Subjects will receive at least 2 cycles of induction therapy but no more than 4 cycles.
- Review prior/concomitant medication
- Record any adverse events
- Vital signs; including blood pressure, respiratory rate, pulse, temperature, oxygen saturation level (Days 1 and 8 of each cycle)
- Weight (Day 1 of each cycle)
- ECOG performance status (Day 1 of each cycle)
- Physical exam (Day 1 of each cycle)
- Obtain smoking status for past 28 days (Day 1 of each cycle)
- Urine pregnancy test (for all female subjects unless surgically sterile or menopausal prior to dose on Day 1)
- Obtain blood samples for:
  - Chemistry (Days 8 and 28 of each cycle)
  - Hematology (Days 8 and 28 of each cycle)
  - Coagulation (Day 8 of each cycle)
  - PK (Cycle 1 Day 8 at pre-dose, 2 hours, and 4 hours post-dose of ENTO; Day 8 of subsequent cycles at pre-dose and 2 hours post-dose of ENTO; Day 28 of every cycle at pre-dose and 2 hours post-dose of ENTO)
  - Biomarkers (Cycle 1 Days 8 and 28 at pre-dose)

Note: ENTO should be held until the pre-dose blood samples have been drawn. Record approximate times of the last 2 doses of ENTO on PK collection days and the time the PK blood samples are obtained.

- Obtain bone marrow aspirate and biopsy samples at the end of every 2 cycles (Cycle 2 Day 28 and Cycle 4 Day 28) or as clinically indicated for disease assessment and biomarker research. If the bone marrow is consistent with Morphologic CR or CRi status per Appendix 5, then evaluate MRD as per institutional practice and Appendix 7. Biopsy will be used in the event the aspirate cannot be collected or analyzed (eg, dry-tap, hemodiluted specimen, or lack of spicules).

  — If the subject achieves < 5% blasts by morphology and flow cytometry or has evidence of clinical benefit after completing 2-4 induction cycles but is not eligible for SCT, the subject will have the option to receive maintenance therapy with ENTO in combination with decitabine or azacitidine. Subjects with persistent evidence of disease (ie, blasts ≥ 5%) after Cycle 2 may receive up to 2 more induction cycles until subject achieves < 5% blasts.

If < 5% blasts by morphology and flow cytometry is not achieved or the subject does not show evidence of clinical benefit after 2-4 induction cycles, the subject is considered a treatment failure and will have met study efficacy endpoint criteria, but will remain on study for required study-related follow-up procedures.

The following procedures will be conducted on Days 1 and 28 of each 28-day cycle of Entospletinib + Hypomethylating agent Maintenance Therapy.

- ENTO will be administered orally every 12 hours on Days 1-28 in combination with IV decitabine 20 mg/m^2 daily on Days 1-5 or IV/SC azacitidine 75mg/m^2 daily on Days 1-7 of each cycle for at least 2 cycles. Subjects enrolled in the safety run-in will only receive ENTO in combination with azacitidine.

  — After completing at least 2 cycles, the subject may proceed to SCT. If not eligible for SCT, subjects will have the option to continue on maintenance therapy with ENTO in combination with the assigned hypomethylating agent. Subjects who are intolerant of the hypomethylating agent may switch to ENTO monotherapy maintenance at any time after completing the first 2 cycles. Maintenance may continue as long as the subject is experiencing benefit and does not meet the criteria for study treatment discontinuation.

- Review prior/concomitant medication
- Record any adverse events
- Vital signs; including blood pressure, respiratory rate, pulse, temperature, oxygen saturation level (Day 1 of each cycle)
- Physical exam (Day 1 of each cycle)
- Obtain smoking status for past 28 days (Day 1 of each cycle)
- Urine pregnancy test (for all female subjects unless surgically sterile or menopausal prior to dose on Day 1)

- Obtain blood samples on Day 28 of each cycle:
  - Chemistry
  - Hematology
  - PK (pre-dose and 2 hours post-dose of ENTO)

Note: ENTO should be held until the pre-dose blood samples have been drawn. Record approximate times of the last 2 doses of ENTO on PK collection days and the time the PK blood samples are obtained.

- Obtain a bone marrow aspirate for disease assessment and biomarker research at the end of every 4 cycles on Day 28 (eg, Cycle 4 Day 28, Cycle 8 Day 28) 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. Biopsy will be used in the event the aspirate cannot be collected or analyzed (eg, dry-tap, hemodiluted specimen, or lack of spicules).

The following procedures will be conducted on Days 1 and 28 of each 28-day cycle of Entospletinib Maintenance Therapy.

- ENTO will be administered orally every 12 hours as a single agent on Days 1-28 and may continue up to 12 cycles 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.
- Review prior/concomitant medication
- Record any adverse events
- Vital signs; including blood pressure, respiratory rate, pulse, temperature, oxygen saturation level (Day 1 of each cycle)
- Physical exam (Day 1 of each cycle)
- Obtain smoking status for past 28 days (Day 1 of each cycle)
- Urine pregnancy test (for all female subjects unless surgically sterile or menopausal prior to dose on Day 1)
- Obtain blood samples on Day 28 of each cycle:
  - Chemistry
  - Hematology
  - PK (pre-dose and 2 hours post-dose of ENTO)

Note: ENTO should be held until the pre-dose blood samples have been drawn. Record approximate times of the last 2 doses of ENTO on PK collection days and the time the PK blood samples are obtained.

- Obtain a bone marrow aspirate for disease assessment and biomarker research at the end of every 4 cycles on Day 28 (eg, Cycle 4 Day 28, Cycle 8 Day 28) 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. Biopsy will be used in the event the aspirate cannot be collected or analyzed (eg, dry-tap, hemodiluted specimen, or lack of spicules).

The following procedures will be conducted at Remission/Relapse.

- Obtain blood samples for:
  - Chemistry
  - Hematology
  - Biomarkers
- Obtain bone marrow aspirate samples for disease assessment and biomarker testing. Biopsy will be used in the event the aspirate cannot be collected or analyzed (eg, dry-tap, hemodiluted specimen, or lack of spicules). 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.

6.3.3. Group C

The following procedures will be conducted on Days 1, 8, 14, and 28 of each 28-day cycle (unless otherwise specified).

- ENTO will be administered orally every 12 hours on Days 1-28 as a single agent as long as the subject is experiencing benefit and does not meet criteria for study treatment discontinuation.
- Review prior/concomitant medication
- Record any adverse events
- Vital signs; including blood pressure, respiratory rate, pulse, temperature, oxygen saturation level (Day 1 of each cycle and Cycle 1 Days 8, 14, and 28)
- Weight (Day 1 of each cycle)
- ECOG performance status (Day 1 of each cycle and Cycle 1 Day 14)
- Physical exam (Day 1 of each cycle and Cycle 1 Day 14)

- Obtain smoking status for past 28 days (Day 1 of each cycle)
- CCI [redacted]
- Urine pregnancy test (negative pregnancy test required for all female subjects unless surgically sterile or menopausal prior to dose on Day 1)
- Obtain blood samples for:
  - Chemistry (Cycle 1 Days 1, 8, 14, and 28; Days 1 and 28 of each subsequent cycle)
  - Hematology (Cycle 1 Days 1, 8, 14, and 28; Days 1 and 28 of each subsequent cycle)
  - Coagulation (Day 1 of each cycle)
  - PK (Cycle 1 Days 1, 8, 14, and 28; Day 28 of each subsequent cycle at pre-dose and 2 hours post-dose of ENTO)
  - Biomarkers (Cycle 1 Days 1, 8, 14, and 28 at pre-dose)
  - **Phase 1b only:** For subjects dosed with 400 mg and 800 mg ENTO, pharmacodynamic (BAT assay) samples will be collected (Cycle 1 Days 1, 8, 14, and 28 at pre-dose and 2 hours post-dose of ENTO). BAT assay samples may also be collected at pre-dose on Day 28 of subsequent cycles during the escalation phase.

  Note: ENTO should be held until the pre-dose blood samples have been drawn. Record approximate times of the last 2 doses of ENTO on PK collection days and the time the PK blood samples are obtained.
- Obtain a bone marrow aspirate and biopsy on Day 28 of Cycles 1 and 2 for disease assessment and biomarker testing. If the bone marrow is consistent with Morphologic CR or CRi status per Appendix 5, then evaluate MRD as per institutional practice and Appendix 7.
- Obtain a bone marrow aspirate sample for disease assessment and biomarker testing every 4 cycles beginning on Cycle 4 Day 28 of subsequent cycles (eg, Cycle 4 Day 28, Cycle 8 Day 28) 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. Biopsy will be used in the event the aspirate cannot be collected or analyzed (eg, dry-tap, hemodiluted specimen, or lack of spicules).

The following procedures will be conducted at Remission/Relapse.

- Obtain blood samples for:
  - Chemistry
  - Hematology
  - Biomarkers

- Obtain bone marrow aspirate samples for disease assessment and biomarker testing. Biopsy will be used in the event the aspirate cannot be collected or analyzed (eg, dry-tap, hemodiluted specimen, or lack of spicules). 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.

6.4. Assessments for Premature Discontinuation from Study

If a subject discontinues study treatment (eg, as a result of an AE), every attempt should be made to keep the subject in the study to perform the required study-related follow-up and procedures. If this is not possible or acceptable to the subject or investigator, the subject may be withdrawn from the study.

6.4.1. Criteria for Discontinuation of Study Treatment

Study treatment may be discontinued in the following instances:

- Intercurrent illness that would, in the judgment of the investigator, affect assessments of clinical status to a significant degree. Following resolution of intercurrent illness, the subject may resume study dosing at the discretion of the investigator.

- Unacceptable toxicity, or toxicity that, in the judgment of the investigator, compromises the ability to continue study-specific procedures or is considered to not be in the subject's best interest

- Group C subjects with the following increases in pre-treatment baseline blast percentage in the bone marrow:

  — < 5% blasts at baseline with an increase to ≥ 10% blasts

  — 5 to 10% blasts at baseline with an increase to ≥ 20% blasts

  — 11 to 20% blasts at baseline with an increase to ≥ 30% blasts

  — **Exception:** Subjects will be allowed to continue therapy for up to 2 cycles. If at the time of the post Cycle 2 disease assessment there has not been an improvement in cytopenias or blast count, peripheral blood or marrow, that would suggest clinical benefit, the subject is to be removed from study. Decisions regarding continuation of therapy in subjects on Group C past Cycle 2 will be reviewed with the PI and Medical Monitor.

- Subjects may be removed in the case of new CNS disease or other new sites of extramedullary involvement

- Groups B and C: requires continued treatment with hydroxyurea after Cycle 1

- Subject request to discontinue for any reason. Subjects who withdraw from the study treatment phase of the study should still be followed for survival until 3 years from study start (see Section 6.5, Long term follow up)

- Subject noncompliance with study treatment administration, study procedures, or study requirements should be withdrawn from study treatment in circumstances that increase risk or substantially compromise the interpretation of study results

- Pregnancy during the study (refer to Appendix 4)

- The investigator, in consultation with the Gilead Sciences Medical Monitor or designee, may withdraw any subject from the study treatment, if, in the investigator's opinion, it is not in the subject's best interest to continue.

- Discontinuation of the study at the request of Gilead, a regulatory agency or an institutional review board or independent ethics committee (IRB/IEC)

- If allowed by local regulations, Gilead Sciences may transition subjects from study treatment to commercial drug supply when ENTO becomes commercially available in the country where the subject is living.

6.4.2. End of Study Treatment

Subjects will be removed from study treatment when any of the criteria listed in Section 6.4.1 apply. The following procedures will be conducted when a subject discontinues study treatment and prior to initiating a new therapy.

- Review prior/concomitant medication

- Record any adverse events

- ECOG performance status

- Physical exam

- Vital signs; including blood pressure, respiratory rate, pulse, temperature, oxygen saturation level

- Weight

- Obtain blood samples for:

  — Chemistry

  — Hematology

  — Coagulation

— Biomarker testing

— **Phase 1b only:** For Group C subjects dosed with 400 mg and 800mg ENTO, a BAT assay sample may be collected

- Obtain bone marrow aspirate and biopsy samples for disease assessment and biomarker testing (if not performed within the last 2 weeks). If the bone marrow is consistent with Morphologic CR or CRi status per Appendix 5, then evaluate MRD as per institutional practice and Appendix 7.
- CCI [redacted]

6.4.3. 30-day Follow-up

After the last dose of study drug, subjects should be followed for any drug-related AEs and/or ongoing serious adverse events (SAEs) until those events have resolved or become stable, whichever occurs later. The site will contact the study subject regardless of AE/SAE status approximately 30 days after the subject's last dose of study drug to assess adverse events since the last study visit and review concomitant medications. Contact the subject by phone (or in person, if necessary) to assess the subject's condition and record any adverse events reported during the follow-up contact. Document the phone call or visit.

6.5. Long Term Follow-up

Long term follow-up for survival will be conducted every 6 months (± 4 weeks) after the End of Study Treatment visit for up to 3 years (since the start of study therapy). Information to be gathered includes leukemia treatments, other malignancies, and survival. This follow-up can be done during a routine clinic visit, other contact with the subject, or via telephone. Gilead reserves the right to discontinue or shorten the duration of participation in the long term follow-up period at any time. See section 9.3.4 for details regarding study discontinuation.

6.6. Description of Study Procedures

6.6.1. Prior/Concomitant Medications

At screening all medication taken up to 30 days prior to the screening visit will be recorded on the eCRF. At each study visit, the site will capture any and all medications taken by the subject since the last visit or during the visit (as applicable). Concomitant medications include prescription, non-prescription medications, vitamins, and minerals.

6.6.2. Performance Assessment

Performance assessments should be completed using the ECOG scale. If performance is assessed using the Karnofsky scale, scores should be converted to ECOG as outlined in Appendix 6.

6.6.3. Laboratory Safety Tests

Blood will be collected for laboratory safety tests according to the Study Procedures Table in Appendix 2 and may be collected as clinically indicated. The date and time of blood collection will be recorded in the subject's source documentation. The tests will be analyzed using standard procedures. All laboratory tests must be reviewed by the Investigator or qualified designee. See Table 6-1 for tests to be conducted.

6.6.4. CCI

CCI

CCI [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

6.6.5. CCI [redacted]

CCI [redacted]

[redacted]

[redacted]

CCI [redacted]

6.6.6. CCI [redacted]

CCI [redacted]

[redacted]

Blood Collection

Table 6-1. Blood Samples Collected During the Course of the Study

Serum Chemistry	Hematology	Other
Sodium Potassium Chloride Lipase Amylase Bicarbonate Creatinine BUN Phosphorus LDH[a] Uric acid[a] Magnesium[a] Total bilirubin Direct bilirubin Indirect bilirubin ALT AST Alkaline phosphatase Total CPK [b] Beta-2 microglobulin[c]	Hemoglobin Hematocrit Red Blood Cell (RBC) count White Blood Cell (WBC) Count Neutrophils Lymphocytes Monocytes Eosinophils Basophils Platelets	Basophil Activation Assay (400 mg and 800 mg ENTO dose levels in Group C during Phase 1b only) Pharmacokinetic Sampling Biomarker Sampling • Blood • Bone marrow aspirate • Bone marrow biopsy
	Coagulation	
	Prothrombin time APTT INR	
Pregnancy Testing	**Virology**	
Serum Qualitative β-HCG and FSH[a]	Hep B (antigen, antibody) Hep C (antibody) HIV	

a Screening only. Serum FSH also required for female subjects with medically documented ovarian failure.
b At screening, end of every cycle (ie, Day 14 of every cycle for Group A, Cycle 0 Day 14 and Day 28 of every cycle thereafter for Group B, and Day 28 of every cycle for Group C), and End of Study Treatment.
c For all groups at screening, end of Cycle 0 (Group A Cycle 0 Day 14), Cycle 1 Day 28, and Cycle 2 Day 28.

6.6.7. Biological Sample Storage

Biological samples at the conclusion of this study may be retained in storage by the Sponsor for a period up to 15 years for purposes of this study.

6.6.8. Efficacy Assessments

Assessment of clinical response will be made according to the revised International Working Group criteria {Cheson 2003} (See Appendix 5). The major criteria for judging response will include physical examination and examination of blood and bone marrow.

7. ADVERSE EVENTS AND TOXICITY MANAGEMENT

7.1. Definitions of Adverse Events, Adverse Reactions, and Serious Adverse Events

7.1.1. Adverse Events

An adverse event (AE) is any untoward medical occurrence in a clinical study subject administered a medicinal product, which does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and/or unintended sign, symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. AEs may also include pre- or post-treatment complications that occur as a result of protocol specified procedures, lack of efficacy, overdose, drug abuse/misuse reports, or occupational exposure. Preexisting events that increase in severity or change in nature during or as a consequence of participation in the clinical study will also be considered AEs.

An AE does not include the following:

- Medical or surgical procedures such as surgery, endoscopy, tooth extraction, and transfusion. The condition that led to the procedure may be an adverse event and must be reported.
- Pre-existing diseases, conditions, or laboratory abnormalities present or detected before the screening visit that do not worsen
- Situations where an untoward medical occurrence has not occurred (eg, hospitalization for elective surgery, social and/or convenience admissions)
- Overdose without clinical sequelae (see Section 7.6.1)
- Any medical condition or clinically significant laboratory abnormality with an onset date before the consent form is signed and not related to a protocol-associated procedure is not an AE. It is considered to be pre-existing and should be documented on the medical history CRF.

7.1.2. Serious Adverse Events

A **serious adverse event** (SAE) or serious adverse drug reaction (SADR) is defined as an event that, at any dose, results in the following:

- Death
- Life-threatening (Note: The term “life-threatening” in the definition of “serious” refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.)

- In-patient hospitalization or prolongation of existing hospitalization
- Persistent or significant disability/incapacity
- A congenital anomaly/birth defect
- A medically important event or reaction: such events may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes constituting SAEs. Medical and scientific judgment must be exercised to determine whether such an event is a reportable under expedited reporting rules. Examples of medically important events include intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; and development of drug dependency or drug abuse. For the avoidance of doubt, infections resulting from contaminated medicinal product will be considered a medically important event and subject to expedited reporting requirements.

7.1.2.1. Protocol-Specific Serious Adverse Event Instructions

Disease Progression and Death Related to Disease Progression: Given the endpoints of the study, in order to maintain the integrity of the study, the following events that are assessed as unrelated to study drugs will not be considered SAEs:

- Progression of malignancy being studied
- Death due to malignancy being studied

Disease progression and death from disease progression should be reported as SAEs by the investigator only if it is assessed that the study drugs caused or contributed to the disease progression (ie, by a means other than lack of effect). Unrelated disease progression should be captured on the eCRF.

These events will be reported, as appropriate, in the final clinical study report and in any relevant aggregate safety reports.

Protocol-specific SAE reporting exemptions: subjects with AML at initial diagnosis or relapse will require transfusional support with red cells and platelets and these will be considered exemptions to reporting.

7.1.3. Clinical Laboratory Abnormalities and Other Abnormal Assessments as Adverse Events or Serious Adverse Events

Laboratory abnormalities without clinical significance are not recorded as AEs or SAEs. However, laboratory abnormalities (eg, clinical chemistry, hematology, and urinalysis) that require medical or surgical intervention or lead to ENTO interruption, modification, or discontinuation must be recorded as an AE, as well as an SAE, if applicable. In addition,

laboratory or other abnormal assessments (eg, electrocardiogram, x-rays, vital signs) that are associated with signs and/or symptoms must be recorded as an AE or SAE if they meet the definition of an AE or SAE as described in Sections 7.1.1 and 7.1.2. If the laboratory abnormality is part of a syndrome, record the syndrome or diagnosis (eg, anemia), not the laboratory result (ie, decreased hemoglobin).

7.2. Assessment of Adverse Events and Serious Adverse Events

The investigator or qualified sub-investigator is responsible for assessing AEs and SAEs for causality and severity, and for final review and confirmation of accuracy of event information and assessments.

7.2.1. Assessment of Causality for Study treatments and Procedures

The investigator or qualified sub-investigator is responsible for assessing the relationship to ENTO therapy using clinical judgment and the following considerations:

- **No**: Evidence exists that the adverse event has an etiology other than the IMP. For SAEs, an alternative causality must be provided (eg, pre-existing condition, underlying disease, intercurrent illness, or concomitant medication).

- **Yes**: There is reasonable possibility that the event may have been caused by the investigational medicinal product.

It should be emphasized that ineffective treatment should not be considered as causally related in the context of adverse event reporting.

The relationship to study procedures (eg, invasive procedures such as venipuncture or biopsy) should be assessed using the following considerations:

- **No:** Evidence exists that the adverse event has an etiology other than the study procedure.

- **Yes:** The adverse event occurred as a result of protocol procedures, (eg, venipuncture)

7.2.2. Assessment of Severity

The severity of AEs will be graded using the CTCAE, Version 4.03. For each episode, increasing grade changes should be reported.

If a CTCAE criterion does not exist, the investigator should use the grade or adjectives: Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), Grade 4 (life-threatening), or Grade 5 (fatal) to describe the maximum intensity of the AE. For purposes of consistency with the CTCAE, these intensity grades are defined below.

Grading of Adverse Event Severity

Grade	Adjective Description
Grade 1	Mild Sign or symptom is present, but it is easily tolerated, is not expected to have a clinically significant effect on the subject's overall health and well-being, does not interfere with the subject's usual function, and is not likely to require medical attention.
Grade 2	Moderate Sign or symptom causes interference with usual activity or affect clinical status, and may require medical intervention.
Grade 3	Severe Sign or symptom is incapacitating or significantly affects clinical status and likely requires medical intervention and/or close follow-up.
Grade 4	Life-threatening Sign or symptom results in a potential threat to life.
Grade 5	Fatal Sign or symptom results in death.

The distinction between the seriousness and the severity of an AE should be noted. Severe is a measure of intensity; thus, a severe reaction is not necessarily a serious reaction.

7.3. Investigator Requirements and Instructions for Reporting Adverse Events and Serious Adverse Events to Gilead

Requirements for collection prior to study treatment initiation:

After informed consent, but prior to initiation of study medication, the following types of events should be reported on the case report form (CRF/eCRF): all SAEs and adverse events related to protocol-mandated procedures.

Adverse Events

Following initiation of study medication, collect all AEs, regardless of cause or relationship, until 30 days after last administration of study treatment must be reported to the CRF/eCRF database as instructed.

All AEs should be followed up until resolution or until the adverse event is stable, if possible. Gilead Sciences may request that certain AEs be followed beyond the protocol defined follow up period.

Serious Adverse Events

All SAEs, regardless of cause or relationship, that occurs after the subject first consents to participate in the study (ie, signing the informed consent) and throughout the duration of the study, including the protocol-required post treatment follow-up period, must be reported to the CRF/eCRF database and Gilead Pharmacovigilance and Epidemiology (PVE) as instructed. This also includes any SAEs resulting from protocol-associated procedures performed after informed consent is signed.

Any SAEs and deaths that occur after the post treatment follow-up visit and throughout the duration of the study, regardless of causality, should also be reported.

Investigators are not obligated to actively seek SAEs after the protocol defined follow up period; however, if the investigator learns of any SAEs that occur after study participation has concluded and the event is deemed relevant to the use of IMP, he/she should promptly document and report the event to Gilead PVE.

- All AEs and SAEs will be recorded in the CRF/eCRF database within the timelines outlined in the CRF/eCRF completion guideline.

Electronic Serious Adverse Event (eSAE) Reporting Process

- Site personnel record all SAE data in the eCRF database and from there transmit the SAE information to Gilead PVE within 24 hours of the investigator's knowledge of the event. Detailed instructions can be found in the eCRF completion guidelines.

- If for any reason it is not possible to record the SAE information electronically, ie, the eCRF database is not functioning, record the SAE on the paper serious adverse event reporting form and submit within 24 hours to:
  Gilead PVE Email: PPD and Fax: PPD

- As soon as it is possible to do so, any SAE reported via paper must be transcribed into the eCRF Database according to instructions in the eCRF completion guidelines.

- If an SAE has been reported via a paper form because the eCRF database has been locked, no further action is necessary.

- For fatal or life-threatening events, copies of hospital case reports, autopsy reports, and other documents are also to be submitted by e-mail or fax when requested and applicable. Transmission of such documents should occur without personal subject identification, maintaining the traceability of a document to the subject identifiers.

- Additional information may be requested to ensure the timely completion of accurate safety reports.

- Any medications necessary for treatment of the SAE must be recorded onto the concomitant medication section of the subject's CRF/eCRF and the event description section of the SAE form.

7.4. Gilead Reporting Requirements

Depending on relevant local legislation or regulations, including the applicable US FDA Code of Federal Regulations, the EU Clinical Trials Directive (2001/20/EC) and relevant updates, and other country-specific legislation or regulations, Gilead may be required to expedite to worldwide regulatory agencies reports of SAEs, serious adverse drug reactions (SADRs), or

suspected unexpected serious adverse reactions (SUSARs). In accordance with the EU Clinical Trials Directive (2001/20/EC), Gilead or a specified designee will notify worldwide regulatory agencies and the relevant IEC in concerned Member States of applicable SUSARs as outlined in current regulations.

Assessment of expectedness for SAEs will be determined by Gilead using reference safety information specified in the investigator's brochure or relevant local label as applicable.

All investigators will receive a safety letter notifying them of relevant SUSAR reports associated with any study IMP. The investigator should notify the IRB or IEC of SUSAR reports as soon as is practical, where this is required by local regulatory agencies, and in accordance with the local institutional policy.

7.5. Toxicity Management

It is recognized that drug-related toxicity in this population may be difficult to ascertain given the aggressive hematologic disease. Investigators will attempt to assign attribution of toxicities to each drug if possible. The CTEP Active Version of the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 will be utilized for AE reporting.

7.6. Special Situations Reports

7.6.1. Definitions of Special Situations

Special situation reports include all reports of medication error, abuse, misuse, overdose, reports of adverse events associated with product complaints, and pregnancy reports regardless of an associated AE.

Medication error is any unintentional error in the prescribing, dispensing, or administration of a medicinal product while in the control of the health care provider, subject, or consumer.

Abuse is defined as persistent or sporadic intentional excessive use of a medicinal product by a subject.

Misuse is defined as any intentional and inappropriate use of a medicinal product that is not in accordance with the protocol instructions or the local prescribing information.

An overdose is defined as an accidental or intentional administration of a quantity of a medicinal product given per administration or cumulatively which is above the maximum recommended dose as per protocol or in the product labelling (as it applies to the daily dose of the subject in question). In cases of a discrepancy in drug accountability, overdose will be established only when it is clear that the subject has taken the excess dose(s). Overdose cannot be established when the subject cannot account for the discrepancy except in cases in which the investigator has reason to suspect that the subject has taken the additional dose(s).

Product complaint is defined as complaints arising from potential deviations in the manufacture, packaging, or distribution of the medicinal product.

7.6.2. Instructions for Reporting Special Situations

7.6.2.1. Instructions for Reporting Pregnancies

The investigator should report pregnancies in female study subjects that are identified after initiation of study medication and throughout the study, including the post study treatment follow-up period, to the Gilead PVE using the pregnancy report form within 24 hours of becoming aware of the pregnancy.

The pregnancy itself is not considered an AE nor is an induced elective abortion to terminate a pregnancy without medical reasons.

Any premature termination of pregnancy (eg, a spontaneous abortion, an induced therapeutic abortion due to complications or other medical reasons) must be reported within 24 hours as an SAE. The underlying medical reason for this procedure should be recorded as the AE term.

A spontaneous abortion is always considered to be an SAE and will be reported as described in Sections 7.1.1 and 7.1.2. Furthermore, any SAE occurring as an adverse pregnancy outcome post study must be reported to Gilead PVE.

The subject should receive appropriate monitoring and care until the conclusion of the pregnancy. The outcome should be reported to Gilead PVE using the pregnancy outcome report form. If the end of the pregnancy occurs after the study has been completed, the outcome should be reported directly to Gilead PVE. Gilead PVE contact information is as follows:
Email: PPD and Fax: PPD

Pregnancies of female partners of male study subjects exposed to Gilead or other study treatments must also be reported and relevant information should be submitted to Gilead PVE using the pregnancy and pregnancy outcome forms within 24 hours. Monitoring of the subject should continue until the conclusion of the pregnancy. If the end of the pregnancy occurs after the study has been completed, the outcome should be reported directly to Gilead PVE, fax number PPD or email PPD

Refer to Appendix 4 for Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Requirements.

7.6.2.2. Reporting Other Special Situations

All other special situation reports must be reported on the special situations report form and forwarded to Gilead PVE within 24 hours of the investigator becoming aware of the situation. These reports must consist of situations that involve study IMP and/or Gilead concomitant medications, but do not apply to non-Gilead concomitant medications.

Special situations involving non-Gilead concomitant medications does not need to be reported on the special situations report form; however, for special situations that result in AEs due to a non-Gilead concomitant medication, the AE should be reported on the AE form.

Any inappropriate use of concomitant medications prohibited by this protocol should not be reported as "misuse," but may be more appropriately documented as a protocol deviation.

All clinical sequelae in relation to these special situation reports will be reported as AEs or SAEs at the same time using the AE CRF/eCRF and/or the SAE report form. Details of the symptoms and signs, clinical management, and outcome will be reported, when available.

8. STATISTICAL CONSIDERATIONS

8.1. Analysis Objectives and Endpoints

8.1.1. Analysis Objectives

The primary objectives are:

- To demonstrate the overall safety of ENTO in combination with 7+3 in subjects with previously untreated AML who are candidates for chemotherapy (fit subjects) and to assess the efficacy of ENTO at the 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 AML with or without MLL and to assess the efficacy of ENTO at the RP2D (Group C)

The secondary objectives of this study are:

- 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:

- CCI [redacted]

8.1.2. Endpoints

Primary Endpoints:

Safety

- Occurrence of adverse events and laboratory abnormalities defined as DLTs for ENTO in combination with standard dose cytarabine and daunorubicin (7+3) in subjects with previously untreated AML (Group A)
- Occurrence of adverse events and laboratory abnormalities defined as DLTs for ENTO in combination with decitabine or azacitidine in subjects with previously untreated AML who are unable to receive 7+3 chemotherapy (Group B)

- Occurrence of adverse events and laboratory abnormalities defined as DLTs for ENTO as a single agent in subjects with relapsed/refractory AML with or without MLL or previously untreated AML (Group C)

Efficacy

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

Secondary Endpoints:

Exposure

- Drug administration and duration of exposure of study treatment

Safety

- Occurrence of AEs and laboratory abnormalities not defined as DLTs

Efficacy

- 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 death from any cause

Exploratory Endpoints:

CCI

[redacted]

8.2. Analysis Sets

8.2.1. Full Analysis Set

The full-analysis set (FAS) includes all subjects who receive at least 1 dose of study treatment ENTO. This analysis set will be used in the analyses of subject characteristics, exposure, safety, and efficacy. Summary and listing will be presented by study group, dose level, treatment arm, cohort, and overall if applicable.

For analysis by dose levels, subjects from phase 1b and phase 2 will be pooled and analyzed by the dose level first received, unless otherwise specified.

8.2.2. DLT Analysis Set

DLT analysis set includes subjects in FAS with sufficient drug exposure or experience a DLT during the DLT assessment window (see Section 3.2).

8.2.3. Pharmacokinetic Analysis Sets

The pharmacokinetic analysis sets include data from subjects in the full analysis set who have the necessary baseline and on-study measurements to provide interpretable results for the specific parameters of interest.

These analysis sets will be used in the analyses of ENTO plasma pharmacokinetics.

8.3. Data Handling Conventions

8.3.1. General Methods

By-subject listings will be created for important variables from each eCRF module. Summary tables for continuous variables will contain the following statistics: N (number in population), n (number with data), mean, standard deviation, 95% confidence intervals (CIs) on the mean, median, minimum, and maximum. Summary tables for categorical variables will include: N, n, percentage, and 95% CIs on the percentage. Unless otherwise indicated, 95% CIs for binary variables will be calculated using the binomial distribution (exact method) and will be 2 sided. Data will be described and summarized by dose level, analysis set, and timepoint. As appropriate, changes from baseline to each subsequent timepoint will be described and summarized. Similarly, as appropriate, the best change from baseline during the study will also be described and summarized. Graphical techniques (eg, waterfall plots, Kaplan-Meier curves, line plots) may be used when such methods are appropriate and informative.

The baseline value used in each analysis will be the last (most recent) pre-treatment value. Data from all sites will be pooled for all analyses. Analyses will be based upon the observed data unless methods for handling missing data are specified. If there is a significant degree of non-normality, analyses may be performed on log-transformed data or nonparametric tests may be applied, as appropriate.

Unless otherwise specified, all analyses will be 2-sided at the 0.05 level of significance.

8.4. Demographic Data and Baseline Characteristics

A listing of all full-analysis subjects will be generated to describe site, subject number, first screening date, first treatment date, stage (escalation and expansion), dose level, duration of study treatment, and the reason for discontinuing study treatment. Available information on subjects who were screened or registered but not treated may be listed separately. A table will be created summarizing these categories in terms of number and percent for the full analysis set.

Subject baseline characteristics will be listed and summarized by stage and dose level for the full analysis set.

8.5. Efficacy Analysis

The efficacy of ENTO when used as monotherapy or in combination with chemotherapy will be evaluated using the International Working Group criteria {Cheson 2003}, which is documented in Appendix 5.

8.5.1. Categorical Endpoints

Categorical endpoints, such as complete remission rate, composite complete remission (CR/CRi) rate, and overall response (CR/CRi/PR) rate at initial induction, will be summarized. For all analyses, the corresponding 95% exact CIs will be presented.

8.5.2. Time-to-Event Endpoints

For a subject who is not known to have relapsed or died by the end of the study follow-up or data cutoff, RFS is censored on the date of the last available assessment of the subject.

For subjects with none of the events defined in EFS before the end of the study follow-up or data cutoff, EFS is censored at the date of the last available assessment of the subject.

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

RFS, 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.

For subjects who die without report of relapse, remission duration is censored on the date of death, regardless of cause. For a subject with no report of relapse by the end of the study follow-up or data cutoff date, observation is censored on the date of the last available assessment of the subject.

Analysis of remission duration will be analyzed using cumulative incidence by considering competing risks. The estimate of the cumulative incidence of relapse (CIR) will be reported with the associated 95% CI.

8.5.3. Continuous Endpoints

Continuous endpoints (eg, TTR and TTC) will be summarized using descriptive statistics.

8.6. Safety Analysis

All safety data collected on or after the date that ENTO was first dispensed up to 30 days after the date of last dose of ENTO will be summarized by dose level. For Group A and Group B, safety data will be presented by the lead-in ENTO therapy phase and the induction chemotherapy phase separately, and overall.

8.6.1. Extent of Exposure

Descriptive information will be provided by dose level regarding the number of doses of study therapy prescribed, the total number of doses taken, the percent of expected doses taken, duration of treatment, and the number and timing of prescribed dose reductions and interruptions.

ENTO compliance will be described in terms of the proportion of study treatment actually taken based on returned pill count relative to the amount that was dispensed (taking into account physician-prescribed reductions and interruptions).

8.6.2. Adverse Events

All adverse events will be listed. The focus of adverse event summarization will be on treatment emergent adverse events. A treatment-emergent adverse event is defined as an adverse event that onset in the period from the first dose of study treatment to 30 days after the permanent discontinuation of study treatment or that leads to permanent discontinuation of study treatment. Adverse events that occur before the first dose of study treatment or >30 days after the subject has been discontinued from study treatment will be included in data listings.

Adverse events will be classified using MedDRA (http://www.meddramsso.com) with descriptions by System Organ Class, High-Level Group Term, High Level Term, Preferred Term, and Lower-Level Term. The severity of adverse events will be graded by the investigator according to the CTCAE, Version 4.03 (http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010 06-14_QuickReference_8.5x11.pdf), whenever possible. If a CTCAE criterion does not exist for a specific type of adverse event, the grade corresponding to the appropriate adjective will be used by the investigator to describe the maximum intensity of the adverse event: Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), Grade 4 (life threatening), or Grade 5 (fatal). The relationship of the adverse event to the study treatment will be categorized as related or unrelated.

Treatment-emergent adverse events will be summarized. Summary tables will be presented to show the number of subjects reporting treatment-emergent adverse events by severity grade and corresponding percentages. A subject who reports multiple treatment-emergent adverse events within the same Preferred Term (or System Organ Class) is counted only once for that Preferred Term (or System Organ Class) using the worst severity grade. Adverse event descriptions will be presented in alphabetical order of System Organ Class, then by decreasing frequency in the "overall" column for a given Preferred Term.

Separate listings and summaries will be prepared for the following types of treatment emergent adverse events:

- Study-drug-related adverse events
- Adverse events that are Grade ≥3 in severity
- Adverse events leading to study treatment interruption and/or dose modification

- Adverse events leading to study treatment discontinuation
- Serious adverse events (with categorization of the primary reason that the adverse event is considered serious, eg, death, hospitalization, etc.)
- DLT will be listed and summarized and the DLT rate will be presented by study group and dose cohort and the corresponding 90% CIs will be presented

8.6.3. Laboratory Evaluations

All laboratory data will be listed. Summaries of laboratory data will be based on observed data and will be reported using conventional units. The focus of laboratory data summarization will be on treatment-emergent laboratory abnormalities. A treatment emergent laboratory abnormality is defined as an abnormality that, compared to baseline, worsens by ≥ 1 grade in the period from the first dose of study treatment to 30 days after the last dose of study treatment. If baseline data are missing, then any graded abnormality (ie, an abnormality that is Grade ≥ 1 in severity) will be considered treatment emergent. Laboratory abnormalities that occur before the first dose of study treatment or > 30 days after the subject has been discontinued from study treatment will be included in data listings.

Hematological, serum biochemistry, and urine data will be programmatically graded according to CTCAE severity grade, when applicable. For parameters for which a CTCAE scale does not exist, reference ranges from the central laboratory will be used to determine programmatically if a laboratory parameter is below, within, or above the normal range for the subject's age, sex, etc.

Hematological and serum biochemistry and their changes from baseline will be summarized. Summary tables will be presented for each relevant assay to show the number of subjects by CTCAE severity grade with corresponding percentages. 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. Subjects will be characterized only once for a given assay, based on their worst severity grade observed during a period of interest (eg, during the study or from baseline to a particular visit).

Shift tables for hematology and serum biochemistry will also be presented by showing change in CTCAE severity grade from baseline to each visit. For parameters for which a CTCAE scale does not exist, shift tables will be presented showing change in results from baseline (normal, low and high [or abnormal]) to each visit (normal, low and high [or abnormal]). Tables will be prepared to show frequencies adjusted for baseline values; for this frequency, subjects with the same or worse toxicity grade at baseline are not considered.

Separate listings and summaries will be prepared for laboratory abnormalities that are Grade ≥ 3 in severity.

8.7. Pharmacokinetic Analysis

Concentrations of ENTO in plasma will be determined using a validated bioanalytical assay. Plasma concentrations will be displayed as individual concentration vs. time using scheduled sampling times. Concentrations of ENTO will be listed by subject and summarized using descriptive statistics (eg, n, arithmetic mean, geometric mean, % coefficient of variation [CV], StD, median, Q1, Q3, min, and max). Mean (± StD) plasma concentration-time curves will be plotted in both semi-logarithmic and linear formats.

8.8. CCI

CCI

8.9. Sample Size

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 Phase 2, approximately 40 additional subjects will be enrolled in Group A. Table 8-1 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 composite complete remission rate of standard chemotherapy (7+3) has been reported as 52% in the CALGB study of over 1000 subjects.

Table 8-1. Exact 90% CIs of Composite Complete Remission Rate for a Cohort Size of 40 in Group A

Expected 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 or > 75 years) and WBC (≤ 5,000/µL or > 5,000/µL). Assuming an 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% – 30%. Evaluation between the treatment arms will be based on the totality of clinical data.

Approximately 60 additional subjects will be enrolled in the Group C dose expansion.

A total of 15 initial subjects in Cohort C1A will be evaluated for futility. 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%). At this time, futility has been met, and thus, Cohort C1A will not move forward.

The sample size is 15 for Cohort C2. This sample size is based on practical considerations. The sample size is 30 for Cohort C3, which will provide adequate precision of efficacy estimates. Table 8-2 provides the 90% confidence interval (CI) of 30 subjects for the assumed composite complete remission rate.

Table 8-2. Exact 90% CIs of Composite Complete Remission Rate for a Cohort Size of 30 in Cohort C3

Expected Composite Complete Remission Rate of Entospletinib Monotherapy in Cohort C3	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 74 subjects (including 14 in Phase 1b and 60 in Phase 2) in Group C will be enrolled for the duration of the study.

8.9.1. Statistical Basis for Dose Escalation

A total of 3 to 6 subjects will be treated at each of the proposed ENTO dose levels. Based on the 3+3 dose-escalation scheme, Table 8-3 shows the probability of escalating to the next dose level or proceeding to the next stage, based on the true rate of DLT at the current dose level.

Table 8-3. Probability of Dose Escalation (N=3+3)

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

Thus, if the true underlying proportion 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.

The trial employs the standard NCI definition of MTD (starting dose associated with DLT in < 33.3% of subjects during the DLT assessment window).

8.10. Timing of Analyses

8.10.1. Interim Analyses

No formal interim analyses are planned in this Phase 2 trial with lead-in. The Gilead Sciences study team and the investigators will collectively discuss study conduct and accumulating safety and other data through teleconferences. In phase 1b, it is expected that these discussions will be scheduled to occur immediately following DLT window for the third subject of each cohort unless accrual to the study and the need for decisions regarding dose escalation or stage progression indicate the need for more frequent reviews. In Phase 2, it is expected that these discussions will occur immediately following completion of the DLT window for the Group B safety run-in cohort unless accrual to the study and the need for decisions regarding dose expansion indicate the need for more frequent reviews.

8.10.2. Final Analysis

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

9. RESPONSIBILITIES

9.1. Investigator Responsibilities

9.1.1. Good Clinical Practice

The investigator will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki (as amended in Edinburgh, Tokyo, Venice, Hong Kong, and South Africa), International Conference on Harmonisation (ICH) guidelines, or with the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the study subject. These standards are consistent with the European Union Clinical Trials Directive 2001/20/EC and Good Clinical Practice Directive 2005/28/EC.

The investigator will ensure adherence to the basic principles of Good Clinical Practice, as outlined in 21 CFR 312, subpart D, "Responsibilities of Sponsors and Investigators," 21 CFR, part 50, 1998, and 21 CFR, part 56, 1998.

The investigator and all applicable sub-investigators will comply with 21 CFR, Part 54, 1998, providing documentation of their financial interest or arrangements with Gilead, or proprietary interests in the investigational drug under study. This documentation must be provided prior to the investigator's (and any sub-investigator's) participation in the study. The investigator and sub-investigator agree to notify Gilead of any change in reportable interests during the study and for 1 year following completion of the study. Study completion is defined as the date when the last subject completes the protocol-defined activities.

9.1.2. Institutional Review Board (IRB Review and Approval)

The investigator (or sponsor as appropriate according to local regulations) will submit this protocol, informed consent form, and any accompanying material to be provided to the subject (such as advertisements, subject information sheets, or descriptions of the study used to obtain informed consent) to an IRB. The investigator will not begin any study subject activities until approval from the IRB and/or appropriate committees has been documented and provided as a letter to the investigator.

Before implementation, the investigator will submit to and receive documented approval from the IRB any modifications made to the protocol or any accompanying material to be provided to the subject after initial IRB approval, with the exception of those necessary to reduce immediate risk to study subjects.

9.1.3. Informed Consent

The investigator is responsible for obtaining written informed consent from each individual participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study and before undertaking any study-related procedures. The investigator must use the most current IRB-approved consent form for documenting written

informed consent. Each informed consent (or assent as applicable) will be appropriately signed and dated by the subject or the subject's legally authorized representative and the person conducting the consent discussion, and also by an impartial witness if required by IRB or local requirements. The consent form will inform subjects about genomic testing and sample retention, and their right to receive clinically relevant genomic analysis results.

9.1.4. Confidentiality

The investigator must assure that subjects' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. Only subject initials, date of birth, another unique identifier (as allowed by local law) and an identification code will be recorded on any form or biological sample submitted to the Sponsor, IRB, or laboratory. Laboratory specimens must be labeled in such a way as to protect subject identity while allowing the results to be recorded to the proper subject. Refer to specific laboratory instructions. NOTE: The investigator must keep a screening log showing codes, names, and addresses for all subjects screened and for all subjects enrolled in the trial. Subject data will be processed in accordance with all applicable regulations.

The investigator agrees that all information received from Gilead, including but not limited to the investigator brochure, this protocol, CRF/eCRF, the IMP, and any other study information, remain the sole and exclusive property of Gilead during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from Gilead. The investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the study site to any third party or otherwise into the public domain.

9.1.5. Study Files and Retention of Records

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into at least the following 2 categories: (1) investigator's study file, and (2) subject clinical source documents.

The investigator's study file will contain the protocol/amendments, CRF and query forms, IRB and governmental approval with correspondence, informed consent, drug records, staff curriculum vitae and authorization forms, and other appropriate documents and correspondence.

The required source data should include sequential notes containing at least the following information for each subject:

- Subject identification (name, date of birth, gender);
- Documentation that subject meets eligibility criteria, (ie, history, physical examination, and confirmation of diagnosis) to support inclusion and exclusion criteria;

- Documentation of the reason(s) a consented subject is not enrolled
- Participation in study (including study number);
- Study discussed and date of informed consent;
- Dates of all visits;
- Documentation that protocol specific procedures were performed;
- Results of efficacy parameters, as required by the protocol;
- Start and end date (including dose regimen) of IMP, including dates of dispensing and return;
- Record of all adverse events and other safety parameters (start and end date, and including causality and severity);
- Concomitant medication (including start and end date, dose if relevant; dose changes);
- Date of study completion and reason for early discontinuation, if it occurs.

All clinical study documents must be retained by the investigator until at least 2 years or according to local laws, whichever is longer, after the last approval of a marketing application in an ICH region (ie, United States, Europe, or Japan) and until there are no pending or planned marketing applications in an ICH region; or, if no application is filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and regulatory authorities have been notified. Investigators may be required to retain documents longer if specified by regulatory requirements, by local regulations, or by an agreement with Gilead. The investigator must notify Gilead before destroying any clinical study records.

Should the investigator wish to assign the study records to another party or move them to another location, Gilead must be notified in advance.

If the investigator cannot provide for this archiving requirement at the study site for any or all of the documents, special arrangements must be made between the investigator and Gilead to store these records securely away from the site so that they can be returned sealed to the investigator in case of an inspection. When source documents are required for the continued care of the subject, appropriate copies should be made for storage away from the site.

9.1.6. Case Report Forms

For each subject consented, an eCRF will be completed by an authorized study staff member whose training for this function is documented according to study procedures. eCRF should be completed on the day of the subject visit to enable the sponsor to perform central monitoring of safety data. Subsequent to data entry, a study monitor will perform source data verification within the EDC system. Original entries as well as any changes to data fields will be stored in the

audit trail of the system. Prior to database lock (or any interim time points as described in the clinical data management plan), the investigator will use his/her log in credentials to confirm that the forms have been reviewed, and that the entries accurately reflect the information in the source documents. The eCRF capture the data required per the protocol schedule of events and procedures. System-generated or manual queries will be issued to the investigative site staff as data discrepancies are identified by the monitor or internal Gilead staff, who routinely review the data for completeness, correctness, and consistency. The site coordinator is responsible for responding to the queries in a timely manner, within the system, either by confirming the data as correct or updating the original entry, and providing the reason for the update (eg, data entry error). At the conclusion of the trial, Gilead will provide the site with a read-only archive copy of the data entered by that site. This archive must be stored in accordance with the records retention requirements outlined in Section 9.1.5.

9.1.7. Investigational Medicinal Product Accountability and Return

Gilead recommends that used and unused IMP supplies be returned to the shipping facility from which it came for eventual destruction. The study monitor will provide instructions for return. If return is not possible, the study monitor will evaluate each study center's IMP disposal procedures and provide appropriate instruction for destruction of unused IMP supplies. If the site has an appropriate standard operating procedure (SOP) for drug destruction as determined by Gilead QA, the site may destroy used (empty or partially empty) and unused IMP supplies in accordance with that site's approved SOP. A copy of the site's approved SOP will be obtained for central files.

If IMP is destroyed on site, the investigator must maintain accurate records for all IMP destroyed. Records must show the identification and quantity of each unit destroyed, the method of destruction, and the person who disposed of the IMP. Upon study completion, copies of the IMP accountability records must be filed at the site. Another copy will be returned to Gilead.

The study monitor will review IMP supplies and associated records at periodic intervals.

9.1.8. Inspections

The investigator will make available all source documents and other records for this trial to Gilead's appointed study monitors, to IRB, or to regulatory authority or health authority inspectors.

9.1.9. Protocol Compliance

The investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol.

9.2. Sponsor Responsibilities

9.2.1. Protocol Modifications

Protocol modifications, except those intended to reduce immediate risk to study subjects, may be made only by Gilead. The investigator must submit all protocol modifications to the IRB in accordance with local requirements and receive documented IRB approval before modifications can be implemented.

9.2.2. Study Report and Publications

A clinical study report (CSR) will be prepared and provided to the regulatory agency. Gilead will ensure that the report meets the standards set out in the ICH Guideline for Structure and Content of Clinical Study Reports (ICH E3). Note that an abbreviated report may be prepared in certain cases.

Investigators in this study may communicate, orally present, or publish in scientific journals or other scholarly media only after the following conditions have been met:

The results of the study in their entirety have been publicly disclosed by or with the consent of Gilead in an abstract, manuscript, or presentation form or the study has been completed at all study sites for at least 2 years.

The investigator will submit to Gilead any proposed publication or presentation along with the respective scientific journal or presentation forum at least 30 days before submission of the publication or presentation.

No such communication, presentation, or publication will include Gilead's confidential information (see Section 9.1.4).

The investigator will comply with Gilead's request to delete references to its confidential information (other than the study results) in any paper or presentation and agrees to withhold publication or presentation for an additional 60 days in order to obtain patent protection if deemed necessary.

9.3. Joint Investigator/Sponsor Responsibilities

9.3.1. Payment Reporting

Investigators and their study staff may be asked to provide services performed under this protocol, eg, attendance at Investigator's Meetings. If required under the applicable statutory and regulatory requirements, Gilead will capture and disclose to Federal and State agencies any expenses paid or reimbursed for such services, including any clinical trial payments, meal, travel expenses or reimbursements, consulting fees, and any other transfer of value.

9.3.2. Access to Information for Monitoring

In accordance with regulations and guidelines, the study monitor must have direct access to the investigator's source documentation in order to verify the accuracy of the data recorded in the CRF/eCRF.

The monitor is responsible for routine review of the CRF/eCRF at regular intervals throughout the study to verify adherence to the protocol and the completeness, consistency, and accuracy of the data being entered on them. The monitor should have access to any subject records needed to verify the entries on the CRF/eCRF. The investigator agrees to cooperate with the monitor to ensure that any problems detected through any type of monitoring (central, on site) are resolved.

9.3.3. Access to Information for Auditing or Inspections

Representatives of regulatory authorities or of Gilead may conduct inspections or audits of the clinical study. If the investigator is notified of an inspection by a regulatory authority the investigator agrees to notify the Gilead medical monitor immediately. The investigator agrees to provide to representatives of a regulatory agency or Gilead access to records, facilities, and personnel for the effective conduct of any inspection or audit.

9.3.4. Study Discontinuation

The sponsor reserves the right to terminate the study at any time due to safety concerns, concerns regarding efficacy of the treatment, serious non-compliance at an investigator site that could affect subject safety, or new or emerging scientific or clinical developments in the field. Should this be necessary, both Gilead and the investigator will arrange discontinuation procedures and notify the appropriate regulatory authority(ies), IRBs, and IECs. In terminating the study, Gilead and the investigator will assure that adequate consideration is given to the protection of the subjects' interests. Should the primary objective of the trial not be met after primary analysis, Gilead will assess if further development of ENTO in AML is warranted and may determine to discontinue the trial. Subjects that remain on study may be considered for continued treatment with Gilead investigational product until disease progression, unacceptable toxicity, withdrawal of consent, or the Investigator or Sponsor deems treatment is no longer appropriate. Subjects will be reviewed for evidence of individual benefit by the investigator, and in consultation with the sponsor will ensure that the appropriate risk to benefit ratio is maintained for each subject. However, Gilead reserves the right, at its sole discretion, to determine whether to supply Gilead investigational product, and by what mechanism, after termination of the trial.

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11. APPENDICES

Appendix 1. Investigator Signature Page

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STUDY ACKNOWLEDGEMENT

GS-US-339-1559: A Phase 1b/2 Study of Entospletinib (GS-9973) Monotherapy and in Combination with Chemotherapy in Patients with Acute Myeloid Leukemia (AML)

Protocol GS-US-339-1559, Amendment 7, 15 February 2018

This protocol has been approved by Gilead Sciences, Inc. The following signature documents this approval.

PPD

Name (Printed)
Medical Monitor

PPD

Signature

20 FEB 2018

Date

INVESTIGATOR STATEMENT

I have read the protocol, including all appendices, and I agree that it contains all necessary details for me and my staff to conduct this study as described. I will conduct this study as outlined herein and will make a reasonable effort to complete the study within the time designated.

I will provide all study personnel under my supervision copies of the protocol and access to all information provided by Gilead Sciences, Inc. I will discuss this material with them to ensure that they are fully informed about the drugs and the study.

Principal Investigator Name (Printed)

Signature

Date

Site Number

Appendix 2. Study Procedures Tables

Group A: Phase 1b Dose Escalation (Entospletinib + cytarabine + daunorubicin)

Study Phase	Screening	Cycle 0 Entospletinib Lead-in			Cycle 1 (and Cycle 2, if needed) Entospletinib + 7+3				At Blood Count Recovery/ Remission/ Relapse	End of Study Treatment	30-day Follow-up	3-year Long Term Follow-up
Study Day	**Screening**	**1**	**8**	**14**	**1**	**3**	**7**	**14**				
Window (day)	**-14**	**±2**	**±2**	**±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	X	
Physical Exam[a]	X	X			X					X		
Vital Signs[b]	X	X	X	X	X	X	X			X		
Height and Weight[c]	X				X		X			X		
ECG[d]	X											
ECHO/MUGA[e]	X							X				
ECOG Performance Status	X	X						X		X		
Overall survival, leukemia treatments, and other malignancies												X (every 6 months)
X-ray[m] (Investigator's discretion)	X											
Study Treatment												
Entospletinib Administration[f]		X	X	X	X	X	X	X				
IV daunorubicin[f]					X	X						
IV cytarabine[f]					X	X	X					

Study Phase	Screening	Cycle 0 Entospletinib Lead-in			Cycle 1 (and Cycle 2, if needed) Entospletinib + 7+3				At Blood Count Recovery/ Remission/ Relapse	End of Study Treatment	30-day Follow-up	3-year Long Term Follow-up
Study Day	**Screening**	**1**	**8**	**14**	**1**	**3**	**7**	**14**				
Window (day)	**-14**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±7**	**±7**	**± 4 weeks**
Laboratory Assessments												
Chemistry[g]	X	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[h]	X											
HIV/HBV/HCV	X											
Bone Marrow Assessments												
Biopsy[l]	X							X	X	X		
Aspirate[j]	X			X				X	X	X		
PK[k]		X	X	X		X	X	X				
Biomarkers[l]		X	X	X			X	X	X	X		
CCI												

a After discharge from the hospital, a focused physical exam may be completed at the Investigator's discretion.
b Vital signs include measurement of blood pressure, respiratory rate, pulse, temperature, and oxygen saturation level. Vitals signs may be measured daily during hospitalization and at the Investigator's discretion after discharge from the hospital.
c Height and weight will be measured at Screening. Only weight will be measured on Days 1 and 7 of Cycles 1 and 2 and at End of Study Treatment.
d ECG is required at Screening and may be performed at the Investigator's discretion following enrollment.
e An ECHO or MUGA must be performed at Screening and prior to re-induction on Cycle 1 Day 14. For German sites only ECHO to be performed.
f ENTO will be administered orally every 12 hours on Days 1-14 as a single agent in Cycle 0 then in combination with IV daunorubicin (Days 1-3) and IV cytarabine (Days 1-7) during induction chemotherapy of every 14-day cycle (Cycle 1 and up to Cycle 2). Subjects are to continue receiving ENTO while awaiting disease assessment results.
g Include Total CPK at Screening, Day 14 of every cycle, and End of Study Treatment (see Table 6-1).
h A negative serum pregnancy test is required for female subjects (unless surgically sterile or menopausal) at Screening. Female subjects with medically documented ovarian failure must also have serum FSH levels within the institutional postmenopausal range.

i A bone marrow biopsy will be performed at Screening (within 21 days before the first administration of study treatment), Cycle 1 Day 14 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. If the bone marrow biopsy could not be obtained at Screening, diagnostic samples should be used. At all bone marrow biopsy time points, slides for biomarker research and disease assessment will be requested from the bone marrow biopsy core. Refer to the most current Covance Lab Manual for collection instructions. If the bone marrow is consistent with Morphologic CR or CRi status per Appendix 5, perform cytogenetics, flow cytometry and FISH or PCR for MRD evaluation as per institutional practice and Appendix 7.

j A bone marrow aspirate will be collected at Screening (within 21 days before the first administration of study treatment), Cycle 1 Day 14 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. Perform FISH analysis on Screening bone marrow aspirate. If the bone marrow aspirate could not be obtained at Screening, diagnostic samples should be used. A bone marrow aspirate will also be collected at Cycle 0 Day 14 for flow cytometry and biomarker research (see section 6.6.4). Biopsy will be used in the event the aspirate is not collectable or analyzable. If the bone marrow is consistent with Morphologic CR or CRi status per Appendix 5, perform cytogenetics, flow cytometry and FISH or PCR for MRD evaluation as per institutional practice and Appendix 7.

k Peripheral blood samples for PK will be obtained on 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, 2hrs, and 4hrs post-dose of ENTO; Cycle 1 Day 14 at pre-dose and 2hrs post-dose of ENTO.

l Blood samples for biomarker testing will be obtained on Cycle 0 Day 1 at pre-dose and 6hrs post-dose of ENTO or end of day; Cycle 0 Days 8, 14 and Cycle 1 Day 7 at 6hrs post-dose of ENTO or end of day; Cycle 1 Day 14 or at the end of Cycle 1 at the time of blood count recovery (whichever comes first) at 6 hours post-dose of ENTO or end of day; at time of remission/relapse; End of Study Treatment.

m X-ray not to be performed for German sites.

Group A: Phase 2 Dose Expansion (Entospletinib + cytarabine + daunorubicin)

Study Phase	Screening	Cycle 0 Entospletinib Lead-in			Cycle 1 (and Cycle 2, if needed) Entospletinib + 7+3					Post-Remission Entospletinib + cytarabine (3-4 cycles)				Maintenance Entospletinib (up to 12 cycles)		At Blood Count Recovery/ Remission/ Relapse	End of Study Treatment	30-day Follow-up	3-year Long Term Follow-up
Study Day	**Screening**	**1**	**8**	**14**	**1**	**3**	**7**	**14**	**15 to Count Recovery**	**1**	**3**	**5**	**28**	**1**	**28**				
Window (day)	**-14**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**		**±2**	**±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	X	X	X	X	X		X	X	
IxRS Registration	X	X			X					X				X			X		
Smoking status[a]	X	X			X					X				X					
Physical Exam[b]	X	X			X					X				X			X		
Vital Signs[c]	X	X	X	X	X	X	X			X				X			X		
Height and Weight[d]	X				X												X		
ECG[e]	X																		
ECHO/MUGA[f]	X							X											
ECOG Performance Status[g]	X	X						X					X		X		X		
Overall survival, leukemia treatments, and other malignancies																			X (every 6 months)

Study Phase	Screening	Cycle 0 Entospletinib Lead-in			Cycle 1 (and Cycle 2, if needed) Entospletinib + 7+3					Post-Remission Entospletinib + cytarabine (3-4 cycles)				Maintenance Entospletinib (up to 12 cycles)		At Blood Count Recovery/ Remission/ Relapse	End of Study Treatment	30-day Follow-up	3-year Long Term Follow-up
Study Day	**Screening**	**1**	**8**	**14**	**1**	**3**	**7**	**14**	**15 to Count Recovery**	**1**	**3**	**5**	**28**	**1**	**28**				
Window (day)	**-14**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**		**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±7**	**±7**	**± 4 weeks**
X-ray[u]	X																		
Study Treatment																			
Entospletinib Administration[h,i]		X	X	X	X	X	X	X		X	X	X	X	X	X				
IV daunorubicin[h]					X	X													
IV cytarabine[h,i]					X	X	X			X	X	X							
Laboratory Assessments																			
Chemistry[j,k,r]	X	X	X	X			X	X					X		X	X	X		
Hematology[j,k,t]	X	X	X	X			X	X	X				X		X	X	X		
Coagulation[k]	X			X			X	X					X		X		X		
Urinalysis	X																		
Pregnancy Test and FSH[l]	X	X			X					X				X					
HIV/HBV/HCV	X																		
Sparse ENTO PK[m]		X	X	X		X		X				X	X		X				
Intensive ENTO PK[n]							X												
Biomarkers[o]		X	X	X			X	X								X	X		
CCI																			

Study Phase	Screening	Cycle 0 Entospletinib Lead-in			Cycle 1 (and Cycle 2, if needed) Entospletinib + 7+3					Post-Remission Entospletinib + cytarabine (3-4 cycles)				Maintenance Entospletinib (up to 12 cycles)		At Blood Count Recovery/ Remission/ Relapse	End of Study Treatment	30-day Follow-up	3-year Long Term Follow-up
Study Day	**Screening**	**1**	**8**	**14**	**1**	**3**	**7**	**14**	**15 to Count Recovery**	**1**	**3**	**5**	**28**	**1**	**28**				
Window (day)	**-14**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**		**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±7**	**±7**	**± 4 weeks**
Bone Marrow Assessments																			
Biopsy[p]	X							X								X	X		
Aspirate[q]	X			X				X					X		X	X	X		
CCI																			

a Collect smoking status at Screening and Day 1 of each cycle.
b After discharge from the hospital, a focused physical exam may be completed at the Investigator's discretion. During Post-remission and Maintenance, a physical exam is to be completed every 2 cycles (eg, Cycle 1 Day 1, Cycle 3 Day 1, etc.)
c Vital signs include measurement of blood pressure, respiratory rate, pulse, temperature, and oxygen saturation level. Vitals signs may be measured daily during hospitalization and at the Investigator's discretion after discharge from the hospital. During Post-remission and Maintenance, vital signs to be performed every 2 cycles (eg, Cycle 1 Day 1, Cycle 3 Day 1, etc.)
d Height and weight will be measured at Screening. Only weight will be measured on Day 1 of induction Cycle 1 (and 2, if needed) and at End of Study Treatment.
e ECG is required at Screening and may be performed at the Investigator's discretion following enrollment.
f An ECHO or MUGA must be performed at Screening and prior to re-induction, if applicable. For German sites only ECHO to be performed, if applicable.
g ECOG performance status to be completed at the end of every 2 cycles on Day 28 during Post-remission and Maintenance (eg, Cycle 2 Day 28, Cycle 4 Day 28, etc.).
h ENTO will be administered orally every 12 hours on Days 1-14 as a single agent in Cycle 0 then in combination with IV daunorubicin (Days 1-3) and IV cytarabine (Days 1-7) during induction chemotherapy of every 14-day cycle (Cycle 1 and up to Cycle 2). Subjects are to continue receiving ENTO while awaiting disease assessment results.
i Subjects will receive 3-4 cycles of 3g/m^2 high dose cytarabine administered every 12 hours on Days 1, 3, and 5 (< 60 years of age) or 1g/m^2 cytarabine administered once daily on Days 1-5 (≥60 years of age) in combination with ENTO every 12 hours on Days 1-28 during Post-remission chemotherapy. Subjects continuing to Maintenance therapy will receive ENTO monotherapy every 12 hours on Days 1-28 for up to 12 cycles.
j Include Total CPK at Screening, Cycle 1 and 2 Day 14, every 2 cycles on Day 28 during Post-remission and Maintenance, and End of Study Treatment (see Table 6-1).
k Chemistry and hematology is collected every 2 cycles from Cycle 1 Day 28 (eg, Cycle 1 Day 28, Cycle 3 Day 28, etc.) during Post-remission and Maintenance therapy.
l A negative serum pregnancy test is required for female subjects (unless surgically sterile or menopausal) at Screening. Female subjects with medically documented ovarian failure must also have serum FSH levels within the institutional postmenopausal range at Screening. A urine pregnancy test will be performed for all females on Day 1 of each cycle (unless surgically sterile or postmenopausal).
m Peripheral blood samples for PK will be obtained on Cycle 1 (and 2, if needed) Day 3 at pre-dose, 2 hours, and 4 hours post-dose of ENTO; all other sparse PK samples will be obtained at pre-dose and 2 hour post-dose of ENTO.
n Intensive peripheral blood samples for PK will be obtained on Cycle 1 Day 7 at 0 (predose), 1, 2, 3, 4, 6, 8 and 12 hours post-dose of ENTO.
o Blood samples for biomarker testing will be obtained on Cycle 0 Days 1, 8, and 14 at pre-dose; Cycle 1 Days 7 and 14 at pre-dose; at time of remission/relapse; End of Study Treatment.

p A bone marrow biopsy will be performed at Screening (within 21 days before the first administration of study treatment), on Cycle 1 Day 14 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. If the bone marrow biopsy could not be obtained at Screening, diagnostic samples should be used. At all bone marrow biopsy time points, slides for biomarker research and disease assessment will be requested from the bone marrow biopsy core. Refer to the most current Covance Lab Manual for collection instructions. If the bone marrow is consistent with Morphologic CR or CRi status per Appendix 5, perform cytogenetics, flow cytometry and FISH or PCR for MRD evaluation as per institutional practice and Appendix 7.

q A bone marrow aspirate will be collected at Screening (within 21 days before the first administration of study treatment), at the end of the monotherapy lead-in period (ie, Cycle 0 Day 14 or after the minimum 5-days of ENTO), prior to chemotherapy, Cycle 1 Day 14 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. Perform FISH analysis on Screening bone marrow aspirate. If the bone marrow aspirate could not be obtained at Screening, diagnostic samples should be used. Subjects with cytogenetic and molecular mutations at Screening must have cytogenetic and molecular mutation testing repeated at subsequent bone marrow examinations (Cycle 0 Day 14, Cycle 1 Day 14, count recovery, End of Study). 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 (see section 6.6.4). 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. Biopsy will be used in the event the aspirate cannot be collected or analyzed (eg, dry-tap, hemodiluted specimen, or lack of spicules). If the bone marrow is consistent with Morphologic CR or CRi status per Appendix 5, perform cytogenetics, flow cytometry and FISH or PCR for MRD evaluation as per institutional practice and Appendix 7.

r Include beta-2 microglobulin at Screening, Cycle 0 Day 14, and induction Cycle 1 (and 2, if needed) Day 28.

s CCI [redacted].

t Collect hematology (complete blood count) starting at CRi bone marrow until complete blood count demonstrates recovery or 14 days after bone marrow collection date, whichever is earlier.

u X-ray not to be performed for German sites.

Group B: Phase 1b Dose Escalation and Safety Run-in (Entospletinib + decitabine or azacitidine)

Study Phase	Screening	Cycle 0 Entospletinib Lead-in			Cycles 1-4 Entospletinib + Hypomethylating agent (2-4 cycles)			Entospletinib + Hypomethylating agent Maintenance (at least 2 cycles)		Entospletinib Maintenance (up to 12 cycles)		Remission/ Relapse	End of Study Treatment	30-day Follow-up	3-year Long Term Follow-up
Study Day	**Screening**	**1**	**8**	**14**	**1**	**8**	**28**	**1**	**28**	**1**	**28**				
Window (day)	**-14**	**±2**	**±2**	**±2**	**±2**	**±2**	**±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	X	X		X	X	
IxRS Registration	X	X			X			X		X			X		
Smoking status[a]	X	X			X			X		X					
Physical Exam	X	X			X			X		X			X		
Vital Signs[b]	X	X	X	X	X	X		X		X			X		
Height and Weight[c]	X				X								X		
ECG	X														
ECHO/MUGA[m]	X														
ECOG Performance Status	X	X			X								X		
X-ray[n]	X														
Overall survival, leukemia treatments, and other malignancies															X (every 6 months)
Study Treatment															
Entospletinib Administration[d,e]		X	X	X	X	X	X	X	X	X	X				
IV decitabine[d,e]					X	X		X							

Study Phase	Screening	Cycle 0 Entospletinib Lead-in			Cycles 1-4 Entospletinib + Hypomethylating agent (2-4 cycles)			Entospletinib + Hypomethylating agent Maintenance (at least 2 cycles)		Entospletinib Maintenance (up to 12 cycles)		Remission/ Relapse	End of Study Treatment	30-day Follow-up	3-year Long Term Follow-up
Study Day	**Screening**	**1**	**8**	**14**	**1**	**8**	**28**	**1**	**28**	**1**	**28**				
Window (day)	**-14**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±7**	**±7**	**± 4 weeks**
IV/SC azacitidine[d,e]					X			X							
Laboratory Assessments															
Chemistry[f]	X	X	X	X		X	X		X		X	X	X		
Hematology	X	X	X	X		X	X		X		X	X	X		
Coagulation	X			X		X							X		
Urinalysis	X														
Pregnancy Test and FSH[g]	X	X			X			X		X					
HIV/HBV/HCV	X														
ENTO PK[h]		X	X	X		X	X		X		X				
Biomarkers[i]		X	X	X		X	X					X	X		
CCI															
Bone Marrow Assessments															
Biopsy[j]	X						X					X	X		
Aspirate[k]	X			X			X		X		X	X	X		
CCI															

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 Cycles 1-4 and at End of Study Treatment.
d ENTO will be administered orally every 12 hours on the following days: Days 1-14 as a single agent in Cycle 0; Days 1-28 in combination with IV decitabine 20mg/m^2 on Days 1-10 or IV/SC azacitidine 75mg/m^2 on Days 1-7 of every 28-day cycle for at least 2 and up to 4 induction cycles (Cycles 1-4); Days 1-28 in combination with IV decitabine 20mg/m^2 on Days 1-5 or IV/SC azacitidine 75mg/m^2 on Days 1-7 of every 28-day cycle for at least 2 cycles (ENTO with decitabine or azacitidine maintenance); Days 1-28 of every 28-day cycle as a single agent for up to 12 cycles (ENTO monotherapy maintenance). Subjects enrolled in the safety run-in will only receive ENTO in combination with azacitidine during induction and maintenance cycles.

e Subjects who achieve < 5% blasts by morphology and flow cytometry may continue beyond induction to ENTO in combination with decitabine or azacitidine maintenance therapy. After 2 cycles, subjects not eligible for SCT will have the option to continue on ENTO in combination with decitabine or azacitidine maintenance or switch to ENTO monotherapy maintenance at anytime. Subjects may continue on ENTO in combination with decitabine or azacitidine maintenance therapy as long as the subject is experiencing benefit and does not meet criteria for study treatment discontinuation. Subjects may continue on ENTO monotherapy maintenance therapy for up to 12 cycles as long as the subject is experiencing benefit and does not meet criteria for study treatment discontinuation.

f Include Total CPK at Screening, Cycle 0 Day 14, Day 28 of every cycle, and End of Study Treatment (see Table 6-1).

g A negative serum pregnancy test is required for female subjects (unless surgically sterile or menopausal) at Screening. Female subjects with medically documented ovarian failure must also have serum FSH levels within the institutional postmenopausal range at Screening. A urine pregnancy test will be performed for all female subjects on Day 1 of each cycle (unless surgically sterile or postmenopausal).

h Peripheral blood samples for PK will be obtained on Cycle 1 Day 8 at pre-dose, 2 hours, and 4 hours post-dose of ENTO; all other PK samples will be obtained at pre-dose and 2 hours post-dose of ENTO.

i Blood samples for biomarker testing will be obtained on Cycle 0 Days 1, 8, and 14 at pre-dose; Cycle 1 Days 8 and 28 at pre-dose; at time of remission/relapse; End of Study Treatment.

j A bone marrow biopsy will be performed at Screening (within 21 days before the first administration of study treatment), at the end of 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. If the bone marrow biopsy could not be obtained at Screening, diagnostic samples should be used. At all bone marrow biopsy time points, slides for biomarker research and disease assessment will be requested from the bone marrow biopsy core. Refer to the most current Covance Lab Manual for collection instructions. If the bone marrow is consistent with Morphologic CR or CRi status per Appendix 5, perform cytogenetics, flow cytometry and FISH or PCR for MRD evaluation as per institutional practice and Appendix 7. If the bone marrow is consistent with Morphologic CRi, reassessment of lineages recovery can occur within 14 days of bone marrow assessment.

k A bone marrow aspirate will be collected at Screening (within 21 days before the first administration of study treatment), 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. Perform FISH analysis on Screening bone marrow aspirate. If the bone marrow aspirate could not be obtained at Screening, diagnostic samples should be used. Subjects with cytogenetic and molecular mutations at Screening must have cytogenetic and molecular mutation testing repeated at subsequent bone marrow examinations (Cycle 0 Day 14, Cycle 1 Day 28, count recovery, End of Study). 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. Biopsy will be used in the event the aspirate cannot be collected or analyzed (eg, dry-tap, hemodiluted specimen, or lack of spicules). 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. If the bone marrow is consistent with Morphologic CR or CRi status per Appendix 5, perform cytogenetics, flow cytometry and FISH or PCR for MRD evaluation as per institutional practice and Appendix 7.

l CCI [redacted]

m For German sites only ECHO to be performed.

n X-ray not to be performed for German sites.

Group B: Phase 2 Dose Expansion Randomization (Entospletinib + decitabine or azacitidine)

Study Phase	Screening	Cycle 0 Entospletinib Lead-in			Cycles 1-4 Entospletinib + Hypomethylating agent (2-4 cycles)			Entospletinib + Hypomethylating agent Maintenance (at least 2 cycles)		Entospletinib Maintenance (up to 12 cycles)		Remission/ Relapse	End of Study Treatment	30-day Follow-up	3-year Long Term Follow-up
Study Day	**Screening**	**1**	**5**		**1**	**8**	**28**	**1**	**28**	**1**	**28**				
Window (day)	**-14**	**±2**	**±2**		**±2**	**±2**	**±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	X		X	X	
IxRS Registration	X	X			X			X		X			X		
Smoking status[a]	X	X			X			X		X					
Physical Exam	X	X			X			X		X			X		
Vital Signs[b]	X	X	X		X	X		X		X			X		
Height and Weight[c]	X				X								X		
ECG	X														
ECHO/MUGA[m]	X														
ECOG Performance Status	X	X			X								X		
X-ray[n]	X														
Overall survival, leukemia treatments, and other malignancies															X (every 6 months)
Study Treatment															
Entospletinib Administration[d,e]		X	X		X	X	X	X	X	X	X				
IV decitabine[d,e]					X	X		X							

Study Phase	Screening	Cycle 0 Entospletinib Lead-in			Cycles 1-4 Entospletinib + Hypomethylating agent (2-4 cycles)			Entospletinib + Hypomethylating agent Maintenance (at least 2 cycles)		Entospletinib Maintenance (up to 12 cycles)		Remission/ Relapse	End of Study Treatment	30-day Follow-up	3-year Long Term Follow-up
Study Day	**Screening**	**1**	**5**		**1**	**8**	**28**	**1**	**28**	**1**	**28**				
Window (day)	**-14**	**±2**	**±2**		**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±7**	**±7**	**± 4 weeks**
IV/SC azacitidine[d,e]					X			X							
Laboratory Assessments															
Chemistry[f]	X	X	X			X	X		X		X	X	X		
Hematology	X	X	X			X	X		X		X	X	X		
Coagulation	X		X			X							X		
Urinalysis	X														
Pregnancy Test and FSH[g]	X	X			X			X		X					
HIV/HBV/HCV	X														
ENTO PK[h]		X	X			X	X		X		X				
Biomarkers[i]		X	X			X	X					X	X		
CCI															
Bone Marrow Assessments															
Biopsy[j]	X						X					X	X		
Aspirate[k]	X		X				X		X		X	X	X		
CCI															

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 Cycles 1-4 and at End of Study Treatment.
d ENTO will be administered orally every 12 hours on the following days: Days 1-5 as a single agent in Cycle 0; Days 1-28 in combination with IV decitabine 20mg/m^2 on Days 1-10 or IV/SC azacitidine 75mg/m^2 on Days 1-7 of every 28-day cycle for at least 2 and up to 4 induction cycles (Cycles 1-4); Days 1-28 in combination with IV decitabine 20mg/m^2 on Days 1-5 or IV/SC azacitidine 75mg/m^2 on Days 1-7 of every 28-day cycle for at least 2 cycles (ENTO with decitabine or azacitidine maintenance); Days 1-28 of every 28-day cycle as a single agent for up to 12 cycles (ENTO monotherapy maintenance).

e Subjects who achieve < 5% blasts by morphology and flow cytometry may continue beyond induction to ENTO in combination with decitabine or azacitidine maintenance therapy. After 2 cycles, subjects not eligible for SCT will have the option to continue on ENTO in combination with decitabine or azacitidine maintenance or switch to ENTO monotherapy maintenance at anytime. Subjects may continue on ENTO in combination with decitabine or azacitidine maintenance therapy as long as the subject is experiencing benefit and does not meet criteria for study treatment discontinuation. Subjects may continue on ENTO monotherapy maintenance therapy for up to 12 cycles as long as the subject is experiencing benefit and does not meet criteria for study treatment discontinuation.

f Include Total CPK at Screening, Cycle 0 Day 5, Day 28 of every cycle, and End of Study Treatment (see Table 6-1).

g A negative serum pregnancy test is required for female subjects (unless surgically sterile or menopausal) at Screening. Female subjects with medically documented ovarian failure must also have serum FSH levels within the institutional postmenopausal range at Screening. A urine pregnancy test will be performed for all female subjects on Day 1 of each cycle (unless surgically sterile or postmenopausal).

h Peripheral blood samples for PK will be obtained on Cycle 1 Day 8 at pre-dose, 2 hours, and 4 hours post-dose of ENTO; all other PK samples will be obtained at pre-dose and 2 hours post-dose of ENTO.

i Blood samples for biomarker testing will be obtained on Cycle 0 Days 1 and 5 at pre-dose; Cycle 1 Days 8 and 28 at pre-dose; at time of remission/relapse; End of Study Treatment.

j A bone marrow biopsy will be performed at Screening (within 21 days before the first administration of study treatment), at the end of 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. If the bone marrow biopsy could not be obtained at Screening, diagnostic samples should be used. At all bone marrow biopsy time points, slides for biomarker research and disease assessment will be requested from the bone marrow biopsy core. Refer to the most current Covance Lab Manual for collection instructions. If the bone marrow is consistent with Morphologic CR or CRi status per Appendix 5, perform cytogenetics, flow cytometry and FISH or PCR for MRD evaluation as per institutional practice and Appendix 7. If the bone marrow is consistent with Morphologic CRi, reassessment of lineages recovery can occur within 14 days of bone marrow assessment.

k A bone marrow aspirate will be collected at Screening (within 21 days before the first administration of study treatment), 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. Perform FISH analysis on Screening bone marrow aspirate. If the bone marrow aspirate could not be obtained at Screening, diagnostic samples should be used. Subjects with cytogenetic and molecular mutations at Screening must have cytogenetic and molecular mutation testing repeated at subsequent bone marrow examinations (Cycle 0 Day 5, Cycle 1 Day 28, count recovery, End of Study). 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. Biopsy will be used in the event the aspirate cannot be collected or analyzed (eg dry-tap, hemodiluted specimen, or lack of spicules). 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. If the bone marrow is consistent with Morphologic CR or CRi status per Appendix 5, perform cytogenetics, flow cytometry and FISH or PCR for MRD evaluation as per institutional practice and Appendix 7.

l CCI [redacted].

m For German sites only ECHO to be performed.

n X-ray not to be performed for German sites.

Group C: Phase 1b Dose Escalation (Entospletinib Monotherapy)

Study Phase	Screening	Cycle 1				Subsequent Cycles		Remission/ Relapse	End of Study Treatment	30 Day Follow-Up	3-year Long Term Follow-up
Study Day	Screening	1	8	14	28	1	28				
Window (day)	-14	±2	±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	
Physical Exam	X	X		X		X			X		
Vital Signs[a]	X	X	X	X	X	X			X		
Height and Weight[b]	X	X				X			X		
ECG	X										
ECHO/MUGA[k]	X										
ECOG Performance Status	X	X		X		X			X		
X-ray[l]	X										
Overall survival, leukemia treatments, and other malignancies											X (every 6 months)
Study Treatment											
Entospletinib Administration[c]		X	X	X	X	X	X				
Laboratory Assessments											
Chemistry[d]	X	X	X	X	X	X	X	X	X		
Hematology	X	X	X	X	X	X	X	X	X		
Coagulation	X	X				X			X		
Urinalysis	X										
Pregnancy Test and FSH[e]	X	X				X					
HIV/HBV/HCV	X										

Study Phase	Screening	Cycle 1				Subsequent Cycles		Remission/ Relapse	End of Study Treatment	30 Day Follow-Up	3-year Long Term Follow-up
Study Day	Screening	1	8	14	28	1	28				
Window (day)	-14	±2	±2	±2	±2	±2	±2	±2	±7	±7	± 4 weeks
Bone Marrow Assessments											
Biopsy[f]	X				X		X	X	X		
Aspirate[g]	X				X		X	X	X		
PK[h]		X	X	X	X						
Biomarkers[i]		X	X	X	X			X	X		
Pharmacodynamics (BAT assay)[j]		X	X	X	X		X		X		
CCI											

a Vital signs include measurement of blood pressure, respiratory rate, pulse, temperature, and oxygen saturation level.
b Height and weight will be measured at Screening. Only weight will be measured on Day 1 of each cycle and at End of Study Treatment.
c ENTO monotherapy will be administered orally every 12 hours for every 28-day cycle
d Include Total CPK at Screening, Day 28 of every cycle, and End of Study Treatment (see Table 6-1).
e A negative serum pregnancy test is required for female subjects (unless surgically sterile or menopausal) at Screening, and a negative urine 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. A urine pregnancy test will be performed for all female subjects on Day 1 of each subsequent cycle (unless surgically sterile or menopausal).
f A bone marrow biopsy will be performed at Screening (within 21 days before the first administration of study treatment), 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. If the bone marrow biopsy could not be obtained at Screening, diagnostic samples should be used. At all bone marrow biopsy time points, slides for biomarker research and disease assessment will be requested from the bone marrow biopsy core. Refer to the most current Covance Lab Manual for collection instructions. If the bone marrow is consistent with Morphologic CR or CRi status per Appendix 5, perform cytogenetics, flow cytometry and FISH or PCR for MRD evaluation as per institutional practice and Appendix 7.
g A bone marrow aspirate will be collected at Screening (within 21 days before the first administration of study treatment), 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. Perform FISH analysis on Screening bone marrow aspirate. If the bone marrow aspirate could not be obtained at Screening, diagnostic samples should be used. 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 (see section 6.6.4). 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. Biopsy will be used in the event the aspirate is not collectable or analyzable. If the bone marrow is consistent with Morphologic CR or CRi status per Appendix 5, perform cytogenetics, flow cytometry and FISH or PCR for MRD evaluation as per institutional practice and Appendix 7.
h Peripheral blood samples for PK will be obtained on Cycle 1 Days 1, 8, 14 and 28 at pre-dose and 2hrs post-dose of ENTO.
i Blood samples for biomarker testing will be obtained on Cycle 1 Days 1, 8, 14, and 28 at pre-dose; at time of remission/relapse; End of Study Treatment.
j To be collected only for subjects dosed with 400 mg and 800 mg ENTO during phase 1b. Peripheral blood samples for pharmacodynamics (BAT Assay) will be obtained on Cycle 1 Days 1, 8, 14 and 28 at pre-dose and 2hrs post-dose of ENTO and may be collected at pre-dose on Day 28 of subsequent cycles and at End of Study Treatment.
k For German sites only ECHO to be performed.
l X-ray not to be performed for German sites.

Group C: Phase 2 Dose Expansion (Entospletinib Monotherapy)

Study Phase	Screening		Cycle 1				Subsequent Cycles		Remission/ Relapse	End of Study Treatment	30 Day Follow-Up	3-year Long Term Follow-up
Study Day	**Screening**	**1**	**5**	**8**	**14**	**28**	**1**	**28**				
Window (day)	**-14**	**±2**	**±2**	**±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	
IxRS Registration	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[l]	X											
ECOG Performance Status	X	X			X		X			X		
X-ray[m]	X											
Overall survival, leukemia treatments, and other malignancies												X (every 6 months)
Study Treatment												
Entospletinib Administration[d]		X	X	X	X	X	X	X				
Laboratory Assessments												
Chemistry[e]	X	X		X	X	X	X	X	X	X		
Hematology	X	X		X	X	X	X	X	X	X		
Coagulation	X	X					X			X		
Urinalysis	X											
Pregnancy Test and FSH[f]	X	X					X					
HIV/HBV/HCV	X											

Study Phase	Screening		Cycle 1				Subsequent Cycles		Remission/ Relapse	End of Study Treatment	30 Day Follow-Up	3-year Long Term Follow-up
Study Day	**Screening**	**1**	**5**	**8**	**14**	**28**	**1**	**28**				
Window (day)	**-14**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±7**	**±7**	**± 4 weeks**
ENTO PK[g]		X		X	X	X		X				
Biomarkers[h]		X		X	X	X			X	X		
CCI												
Bone Marrow Assessments												
Biopsy[i]	X					X		X	X	X		
Aspirate[j]	X					X		X	X	X		
CCI												

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 End of Study Treatment.
d ENTO will be administered orally every 12 hours 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..
e Include Total CPK at Screening, Day 28 of every cycle, and End of Study Treatment (see Table 6-1).
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. Urine pregnancy tests will be performed for all female subjects on Day 1 of each subsequent cycle (unless surgically sterile or menopausal).
g Peripheral blood samples for PK will be obtained on Cycle 1 Days 1, 8, 14 and 28, and Day 28 of subsequent cycles at pre-dose and 2hrs post-dose of ENTO.
h Blood samples for biomarker testing will be obtained on Cycle 1 Days 1, 8, 14, and 28 at pre-dose; at time of remission/relapse; End of Study Treatment.
i A bone marrow biopsy will be performed at Screening (within 21 days before the first administration of study treatment), 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. If the bone marrow biopsy could not be obtained at Screening, diagnostic samples should be used. At all bone marrow biopsy time points, slides for biomarker research and disease assessment will be requested from the bone marrow biopsy core. Refer to the most current Covance Lab Manual for collection instructions. If the bone marrow is consistent with Morphologic CR or CRi status per Appendix 5, perform cytogenetics, flow cytometry and FISH or PCR for MRD evaluation as per institutional practice and Appendix 7. If the bone marrow is consistent with Morphologic CRi, reassessment of lineages recovery can occur within 7 to 14 days of bone marrow assessment.
j A bone marrow aspirate will be collected at Screening (within 21 days before the first administration of study treatment), 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. Perform FISH analysis on Screening bone marrow aspirate. If the bone marrow aspirate could not be obtained at Screening, diagnostic samples should be used. 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 (see Section 6.6.4) 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. Biopsy will be used in the event the aspirate cannot be collected or analyzed. If the bone marrow is consistent with Morphologic CR or CRi status per Appendix 5, perform cytogenetics, flow cytometry and FISH or PCR for MRD evaluation as per institutional practice and Appendix 7.
k CCI .
l For German sites only ECHO to be performed.
m X-ray not to be performed for German sites.

Appendix 3. Management of Clinical and Laboratory Adverse Events

Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4
Dermatological	Maintain current dose level and schedule.	Maintain current dose level and schedule.	Withhold dosing until ≤ Grade 1. Resume dosing at current dose level. If re-challenge at current dose level results in recurrence, may resume dosing at same or lower dose level at investigator discretion.	Withhold dosing until Grade ≤ 1 May resume at lower dose level or discontinue dosing at investigator discretion.
Gastrointestinal Inflammation-Diarrhea	Provide anti-diarrheal per PI discretion (eg, loperamide) and maintain current dose level and schedule	Provide anti-diarrheal per PI discretion (eg, loperamide). Withhold dosing until Grade ≤ 1. Resume dosing at current dose level. If re-challenge results in recurrence, may resume at initial or lower dose level at investigator discretion. Consider addition of anti-inflammatory (eg, sulfasalazine, budesonide).	Provide anti-diarrheal per PI discretion (eg, loperamide). Withhold dosing until Grade ≤ 1. Resume at lower dose level. Consider addition of anti-inflammatory (eg, sulfasalazine, budesonide).	Provide anti-diarrheal per PI discretion (eg, loperamide). Withhold dosing until Grade ≤ 1. May resume at lower dose level or discontinue dosing at investigator discretion. Consider addition of anti-inflammatory (eg, sulfasalazine, budesonide).
Hepatic (elevations in ALT, AST, or bilirubin)	ALT/AST≤3xULN) (Direct Bilirubin ≤1.5xULN)	(ALT/AST >3-5xULN) (Direct Bilirubin >1.5-≤3xULN)	Withhold dosing. Monitor ALT, AST, ALP, and direct bilirubin at least 1x per week until all abnormalities are Grade ≤ 1.	Withhold dosing. Monitor ALT, AST, ALP, and direct bilirubin at least 1x per week until all abnormalities are Grade ≤ 1
	Maintain current dose level and schedule	Maintain current dose level and schedule	If direct bilirubin was Grade < 3, resume dosing at same dose level. If direct bilirubin was Grade ≥ 3, resume at lower dose level.	If direct bilirubin was Grade <4, resume dosing at lower dose level. If direct bilirubin was Grade 4, discontinue dosing.

Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4
Pneumonitis (dyspnea, cough, hypoxia and/or diffuse interstitial pattern or ground-glass opacities on chest CT and no obvious infectious cause)	Maintain current dose level and schedule. Consider Pneumocystis therapy	Withhold dosing until Grade $\leq$ 1. Consider systemic corticosteroids and Pneumocystis treatment. May resume at initial or lower dose level at investigator discretion.	Withhold dosing until Grade $\leq$ 1. May resume dosing at initial or lower dose level or discontinue dosing at investigator discretion.	Discontinue study treatment
Other Study Drug Related, Non hematological Adverse Events	Maintain current dose level and schedule	Maintain current dose level and schedule	Withhold dosing until Grade < 1. May resume dosing at initial or lower dose level or discontinue dosing at investigator discretion	Withhold dosing until Grade < 1. May resume dosing at initial or lower dose level or discontinue dosing at investigator discretion

Appendix 4. Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Requirements

1) Definitions

a. Definition of Childbearing Potential

For the purposes of this study, a female born subject is considered of childbearing potential following the initiation of puberty (Tanner stage 2) until becoming post-menopausal, unless permanently sterile or with medically documented ovarian failure.

Women are considered to be in a postmenopausal state when they are ≥ 54 years of age with cessation of previously occurring menses for ≥ 12 months without an alternative cause. In addition, women of any age with amenorrhea of ≥ 12 months may also be considered postmenopausal if their follicle stimulating hormone (FSH) level is in the postmenopausal range and they are not using hormonal contraception or hormonal replacement therapy.

Permanent sterilization includes hysterectomy, bilateral oophorectomy, or bilateral salpingectomy in a female subject of any age.

b. Definition of Male Fertility

For the purposes of this study, a male born subject is considered fertile after the initiation of puberty unless permanently sterile by bilateral orchidectomy or medical documentation.

2) Contraception Requirements for Female Subjects

a. Study Drug Effects on Pregnancy and Hormonal Contraception

ENTO is contraindicated in pregnancy as the risks of treatment with ENTO during pregnancy have not been evaluated. ENTO has insufficient data to exclude the possibility of a clinically relevant interaction with hormonal contraception that results in reduced contraception efficacy. Therefore, contraceptive steroids are not recommended as a contraceptive method either solely or as a part of a contraceptive regimen. Please refer to the latest version of the investigator's brochure for additional information.

b. Contraception Requirements for Female Subjects of Childbearing Potential

The inclusion of female subjects of childbearing potential requires the use of highly effective contraceptive measures. They must also not rely on hormone-containing contraceptives as a form of birth control during the study. They must have a negative serum pregnancy test at Screening and negative urine pregnancy test on Cycle 0 Day 1 (Cycle 1 Day 1 for Group C) prior to dosing. Pregnancy tests will be performed at 28 day intervals thereafter until the end of study treatment. Female subjects must agree to one of the following from Screening until 30 days following the end of relevant systemic exposure or as recommended in the prescribing information for other co-administered study drugs (whichever is later).

- Complete abstinence from intercourse of reproductive potential. Abstinence is an acceptable method of contraception only when it is in line with the subject's preferred and usual lifestyle.

Or

- Consistent and correct use of one of the following methods of birth control listed below.
  - Intrauterine device (IUD) with a failure rate of < 1% per year
  - Tubal sterilization
  - Essure micro-insert system (provided confirmation of success 3 months after procedure)
  - Vasectomy in the male partner (provided that the partner is the sole sexual partner and had confirmation of surgical success 3 months after procedure)

Female subjects must also refrain from egg donation and in vitro fertilization during treatment and until at least 30 days after the end of relevant systemic exposure or as recommended in the prescribing information for other co-administered study drugs (whichever is later).

3) Contraception Requirements for Male Subjects

It is theoretically possible that a relevant systemic concentration may be achieved in a female partner from exposure of the male subject's seminal fluid. Therefore, male subjects with female partners of childbearing potential must use condoms during treatment and until 90 days after the end of relevant systemic exposure or as recommended in the prescribing information for other co-administered study drugs (whichever is later). Additional contraception recommendations should also be considered if the female partner is not pregnant.

Male subjects must also refrain from sperm donation during treatment and until at least 90 days after the end of relevant systemic exposure or as recommended in the prescribing information for other co-administered study drugs (whichever is later).

4) Unacceptable Birth Control Methods

Birth control methods that are unacceptable include periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM). Female condom and male condom should not be used together.

5) Procedures to be Followed in the Event of Pregnancy

Subjects will be instructed to notify the investigator if they become pregnant at any time during the study, or if they become pregnant within 30 days of last study drug dose. Subjects who become pregnant or who suspect that they are pregnant during the study must report the information to the investigator and discontinue study drug immediately. Subjects whose partner has become pregnant or suspects she is pregnant during the study must report the information to the investigator. Instructions for reporting pregnancy, partner pregnancy, and pregnancy outcome are outlined in Section 7.6.2.1.

Appendix 5. International Working Group Criteria for AML {Cheson 2003}

Assessment of clinical response will be made according to the International Working Group criteria {Cheson 2003}. The major criteria for judging response will include physical examination and examination of blood and bone marrow. All laboratory studies that are abnormal prior to study will be repeated to document the degree of maximal response.

Early Treatment Assessment (ETA)

- Evaluation is made at approximately 7-10 days after completing the last dose of the initial course of treatment (ie, Group A Cycle 1 Day 14)
- Guides subsequent treatment (eg, need for or timing of second induction course)

Morphologic Leukemia-free State (MLFS)

MLFS requires all of the following:

- < 5% blasts in bone marrow aspirate
- No extramedullary disease
- No blasts with Auer rods detected

Morphologic Complete Remission (CR)

CR requires all of the following:

- < 5% blasts in bone marrow aspirate
- Neutrophils ≥ 1,000/μL
- Platelets ≥ 100,000/μL
- No extramedullary disease
- No blasts with Auer rods detected
- Independent of transfusions

Cytogenetic Complete Remission (CRc)

CRc requires all of the following:

- < 5% blasts in bone marrow aspirate
- Neutrophils ≥ 1,000/μL

- Platelets ≥ 100,000/μL
- No extramedullary disease
- No blasts with Auer rods detected
- Independent of transfusions
- Reversion to a normal karyotype with an abnormal karyotype at the time of diagnosis

Morphologic CR with incomplete blood count recovery (CRi)

CRi requires all of the following:

- < 5% blasts in bone marrow aspirate
- Neutrophils < 1,000/μL or Platelets < 100,000/μL
- No extramedullary disease
- No blasts with Auer rods detected

If blood counts recover within 14 days of a bone marrow evaluation that is consistent with CRi, the patient will be considered CR at the time when both neutrophil and platelet count recover (neutrophils ≥ 1,000/μL, platelets ≥ 100,000/μL).

Partial Remission (PR)

PR requires all of the following:

- ≥ 50% decrease in blasts in bone marrow aspirate to a range of 5-25%
- Neutrophils ≥ 1,000/μL
- Platelets ≥ 100,000/μL
- Independent of transfusions
- A value of ≤ 5% blasts may also be considered a PR if Auer rods are detected

Treatment Failure (TF)

Treatment failure will be classified as one of the following:

- Resistant disease: Failure to achieve a complete remission (CR, CRc, or CRi) or partial remission. Patients who survive ≥ 7 days following completion of initial treatment, with evidence of persistent leukemia by blood and/or bone marrow examination.

- Death in Aplasia: Patients who survive ≥ 7 days following completion of initial treatment, but die while cytopenic, with an aplastic or hypoplastic marrow obtained within 7 days of death, without evidence of persistent leukemia

- Death from Indeterminate cause: Patients who die before completion of treatment or < 7 days following completion of initial treatment; patients who die ≥ 7 days following completion of initial treatment with no peripheral blood blasts, but no bone marrow examination is available; patients who fail to complete the first cycle of therapy

Relapse

Relapse is defined as:

- Evidence of morphologic relapse with the reappearance of leukemic blasts in the peripheral blood, blasts with Auer rods, ≥ 5% blasts in the bone marrow, or evidence of extramedullary disease not attributable to any other cause. In the setting of recent treatment, if there are no circulating blasts and the bone marrow contains 5-20% blasts, a bone marrow biopsy should be repeated within 1 week to distinguish relapse from bone marrow regeneration.

- The reappearance of cytologically proven extramedullary disease also indicates relapse. Reappearance of a cytogenetic abnormality is considered a cytogenetic relapse. Evidence of bone marrow morphologic involvement or extramedullary disease required.

Appendix 6. Performance Scales: Karnofsky & ECOG Scores {Oken 1982}

Karnofsky Status	Karnofsky Grade	ECOG Grade	ECOG Status
Normal, no complaints	100	0	Fully active, able to carry on all pre-disease performance without restriction
Able to carry on normal activities. Minor signs or symptoms of disease	90	0	Fully active, able to carry on all pre-disease performance without restriction
Normal activity with effort	80	1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work, office work
Care for self. Unable to carry on normal activity or to do active work	70	1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work, office work
Requires occasional assistance, but able to care for most of his needs	60	2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
Requires considerable assistance and frequent medical care	50	2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
Disabled. Requires special care and assistance	40	3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
Severly disabled. Hospitalisation indicated though death nonimminent	30	3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
Very sick. Hospitalisation necessary. Active supportive treatment necessary	20	4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
Moribund	10	4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
Dead	0	5	Dead

Appendix 7. Minimal Residual Disease (MRD) Level Definition {Sanchez-Garcia 2013}

MRD Level (by flow cytometry)	% of Leukemia Cells
No Measurable	≤ 0.01
Low	> 0.01 and ≤ 0.1
Intermediate	> 0.1 and ≤ 1
High	> 1

Appendix 8. 2017 European Leukemia Network (ELN) Risk Stratification by Genetics[a] {Dohner 2017}

Risk Category	Genetic Abnormality
Favorable	t(8;21)(q22;q22.1); *RUNX1-RUNX1T1* inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11* Mutated *NPM1* without *FLT3*-ITD or with *FLT3*-ITD$^{low(c)}$ Biallelic mutated *CEBPA*
Intermediate	Mutated *NPM1* and *FLT3*-ITD$^{high(c)}$ Wild type *NPM1* without *FLT3*-ITD or with *FLT3*-ITD$^{low(c)}$ (w/o adverse risk genetic lesions) t(9;11)(p21.3;q23.3); *MLLT3-KMT2A*[d] Cytogenetic abnormalities not classified as favorable or adverse
Adverse	t(6;9)(p23;q34.1); *DEK-NUP214* t(v;11q23.3); *KMT2A* rearranged t(9;22)(q34.1;q11.2); *BCR-ABL1* inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2,MECOM(EVI1)* -5 or del(5q); -7; -17/abn(17p) Complex karyotype,[e] monosomal karyotype[f] Wild type *NPM1* and *FLT3*-ITD$^{high(c)}$ Mutated *RUNX1*[g] Mutated *ASXL1*[g] Mutated *TP53*[h]

a Frequencies, response rates and outcome measures should be reported by risk category, and, if sufficient numbers are available, by specific genetic lesions indicated.
b Prognostic impact of a marker is treatment-dependent and may change with new therapies.
c Low, low allelic ratio (<0.5); high, high allelic ratio (>0.5); semi-quantitative assessment of *FLT3*-ITD allelic ratio (using DNAfragment analysis) is determined as ratio of the area under the curve (AUC) "*FLT3*-ITD" divided by AUC "*FLT3*-wild type";recent studies indicate that acute myeloid leukemia with *NPM1* mutation and *FLT3*-ITD low allelic ratio may also have a more favorable prognosis and patients should not routinely be assigned to allogeneic hematopoietic-cell transplantation.
d The presence of t(9;11)(p21.3;q23.3) takes precedence over rare, concurrent adverse-risk gene mutations.
e Three or more unrelated chromosome abnormalities in the absence of one of the World Health Organization-designated recurring translocations or inversions, ie, t(8;21), inv(16) or t(16;16), t(9;11), t(v;11)(v;q23.3), t(6;9), inv(3) or t(3;3); AML with *BCR-ABL1*.
f Defined by the presence of one single monosomy (excluding loss of X or Y) in association with at least one additional monosomy or structural chromosome abnormality (excluding core-binding factor AML).
g These markers should not be used as an adverse prognostic marker if they co-occur with favorable-risk AML subtypes.
h *TP53* mutations are significantly associated with AML with complex and monosomal karyotype.