CLINICAL STUDY PROTOCOL

Study Title:	A Phase 1b Study to Investigate the Safety, Tolerability, and Pharmacokinetics of Entospletinib (ENTO) as Monotherapy in Japanese Subjects with Relapsed or Refractory Hematologic Malignancies and in Combination with Chemotherapy in Japanese Subjects with Previously Untreated Acute Myeloid Leukemia (AML)	
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404	
IND Number:	Not applicable	
EudraCT Number:	Not applicable	
Clinical Trials.gov Identifier:	NCT03135028	
Indication:	Hematologic Malignancies, Acute Myeloid Leukemia	
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Gilead Clinical Program Manager:	Name: Office Telephone: E-mail:	PPD PPD PPD
Gilead Medical Monitor:	Name: Office Telephone: E-mail:	PPD PPD PPD
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PROTOCOL SYNOPSIS

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

Study Title:	A Phase 1b Study to Investigate the Safety, Tolerability, and Pharmacokinetics of Entospletinib (ENTO) as Monotherapy in Japanese Subjects with Relapsed or Refractory Hematologic Malignancies and in Combination with Chemotherapy in Japanese Subjects with Previously Untreated Acute Myeloid Leukemia (AML)
IND Number: **EudraCT Number:** **Clinical Trials.gov Identifier:**	Not applicable Not applicable NCT03135028
Study Centers Planned:	Approximately 10 centers in Japan
Objectives:	The primary objectives of this study are: • To evaluate the safety and tolerability of ENTO monotherapy in Japanese subjects with relapsed or refractory hematologic malignancies • To evaluate the safety and tolerability of ENTO in combination with cytarabine and daunorubicin (7+3) in Japanese subjects with previously untreated AML who are candidates for chemotherapy The secondary objectives of this study are: • To evaluate the pharmacokinetics (PK) of ENTO in Japanese subjects with relapsed or refractory hematologic malignancies • To evaluate the PK of ENTO in Japanese subjects with previously untreated AML who are candidates for chemotherapy • To evaluate the safety and tolerability of ENTO in combination with age-adjusted high-dose cytarabine (HiDAC) in Japanese subjects with previously untreated AML who are candidates for chemotherapy The exploratory objectives of this study are: CCI

Study Design:

A Phase 1b, open-label, multicenter study evaluating the safety, tolerability, and PK of ENTO as monotherapy in Japanese subjects with relapsed or refractory hematologic malignancies and ENTO in combination with cytarabine and daunorubicin (7+3) in Japanese subjects with previously untreated AML. Up to 24 subjects will be dosed in 2 groups using a rolling 6 design to evaluate 12 subjects for DLT assessment.

Group A: Approximately 6 subjects (approximately 12 subjects if reduced dose level [-1] is also evaluated) with relapsed or refractory hematologic malignancies will receive ENTO monotherapy

Group B: Approximately 6 subjects with previously untreated AML will receive ENTO monotherapy lead-in followed by ENTO in combination with 7+3

The starting ENTO dose level of 400 mg twice daily (BID) is defined as dose level 0. The safety and tolerability of dose level 0 will be assessed in Group A before proceeding with Group B. The dose limiting toxicity (DLT) assessment window for Group A begins on Cycle 1 Day 1 and ends on Cycle 1 Day 28 and for Group B begins on lead-in Cycle 0 Day 1 and ends 28 days from Cycle 1 Day 1 of induction chemotherapy. The subjects in this study should be in hospital during the DLT assessment window, and the window for Group B may be expanded for bone marrow recovery as noted below. During the DLT assessment window, subjects who fail to complete a total of 21 days of ENTO (or in Group B, miss any doses of cytarabine and daunorubicin) for reasons other than a DLT will not be evaluable for DLT assessment and may be replaced in a timely manner as determined by the Gilead Medical Monitor, the Japanese CRO Medical Monitor, and the Principal Investigator.

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

The first 6 subjects in Group A will be enrolled at dose level 0. Once the sixth evaluable subject has completed the DLT assessment window, the safety review team will evaluate the safety data from all enrolled subjects..

- If 0 or 1 out of the 6 subjects experiences a DLT, Group B will open and 6 subjects will be enrolled in Group B at dose level 0
- If $\geq$ 2 out of the 6 subjects experience a DLT, 6 additional subjects will be enrolled in Group A at the reduced dose level -1 (200 mg BID) and Group B will not open

	Group A (ENTO monotherapy) Eligible subjects with relapsed or refractory hematologic malignancies will receive ENTO BID on Days 1-28 of every 28-day cycle and will continue on study treatment as long as the subject is experiencing clinical benefit and does not meet criteria for study treatment discontinuation. Disease assessments will be performed at the end of Cycle 1 on Day 28, as clinically indicated after Cycle 1, at remission/relapse, and End of Treatment (EOT). A bone marrow biopsy and aspirate sample will be collected for disease assessment for subjects with AML. Subjects with hematologic malignancies other than AML will undergo disease assessment using the appropriate clinical, radiographic, and laboratory procedures per the standard of care or institutional practice. **Group B (ENTO + cytarabine + daunorubicin)** Eligible subjects with previously untreated AML will receive ENTO BID as a single agent on Cycle 0 Days 1-14, and will receive ENTO BID in combination with cytarabine on Days 1-7 and IV daunorubicin on Days 1-3 during induction chemotherapy for up to two 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. Up to 4 cycles of 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 up to 4 cycles.
Number of Subjects Planned:	Up to 24 subjects
Target Population:	Japanese subjects with relapsed or refractory hematologic malignancies or previously untreated AML who are fit for chemotherapy, excluding AML with recurrent genetic abnormalities involving chromosomal translocation t(15;17) (q22;q12) and/or the fusion gene PML/RARA (FAB classification M3)
Duration of Treatment:	Subjects may continue to receive ENTO until treatment failure, planned completion of treatment, start of new therapy, unacceptable toxicity, withdrawal of consent by the subject, or withdrawal from study by the investigator.

Main Diagnosis and Disease Eligibility Criteria:

Inclusion Criteria:

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

1) Group A: Subjects age ≥ 18 with relapsed or refractory hematologic malignancies by WHO criteria and who are not eligible to receive standard of care
2) Group B: Subjects age ≥ 18 with previously untreated AML by WHO criteria, who are deemed fit for cytarabine and daunorubicin (7+3) induction chemotherapy and are able to undergo up to 2 cycles of induction chemotherapy, as determined by the treating physician
3) Subjects must have been born in Japan and must not have lived outside of Japan for a period > 1 year in the 5 years prior to Day 1 of study treatment
4) Subjects must be able to confirm the Japanese origin of their maternal and paternal ancestry
5) ECOG performance status less than or equal to 2
6) Life expectancy of at least 3 months
7) Meet required screening laboratory criteria unless disease related, as shown below

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 or Estimated creatinine clearance	< 1.5 x ULN or CrCl ≥ 30 ml/min as calculated by the Cockroft-Gault method
Hematology	Hemoglobin	> 8.0 g/dL (without transfusion support, except if due to disease marrow involvement)
Coagulation	INR[a]	< 1.7
Pregnancy	β-HCG[b]	Negative
Infection	HIV	Negative HIV antibody
	HBV	Negative HBsAg and negative HBc antibody or positive HBc and negative HBV DNA by quantitative PCR
	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 post-menopausal). Female subjects with medically documented ovarian failure must also have serum FSH levels within the institutional postmenopausal range.

8) Left Ventricular Ejection Fraction (LVEF) ≥ 45% confirmed by ECHO or MUGA and no clinical evidence of congestive heart failure
9) Male subjects and female subjects of childbearing potential who engage in heterosexual intercourse must agree to use protocol specified method(s) of contraception as described in Appendix 4
10) Lactating females must agree to discontinue nursing from screening until 30 days (Group A ENTO monotherapy) or 6 months (Group B ENTO + cytarabine + daunorubicin) following the end of relevant systemic exposure
11) Willingness to comply with scheduled visits, drug administration plan, imaging studies, laboratory tests, other study procedures, and study restrictions
12) Have the ability to understand and sign a written informed consent form, which must be obtained prior to initiation of study procedures

Exclusion Criteria:

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

1) Subjects with untreated AML with recurrent genetic abnormalities involving chromosomal translocation t(15;17) (q22;q12) and/or the fusion gene PML/RARA (FAB classification M3)
2) Known active central nervous system or leptomeningeal leukemic involvement. Note: Central nervous system testing (CSF analysis) is required in subjects with suspected involvement based on symptoms at elevated clinical risk, or signs
3) Current therapy with proton pump inhibitors. Note: H2 receptor antagonists and antacids will be allowed for use during the protocol
4) Current therapy with medicines that are strong CYP3A or CYP2C9 inducers, or moderate CYP2C9 inducers. See Section 5.5 Excluded Medication
5) History of active malignancy except for hematologic malignancies and 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, early gastric cancer cured by endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD), or any other cancer that has been in complete remission without treatment for ≥ 5 years prior to enrollment

6) Evidence of ongoing uncontrolled 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
7) Ongoing 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
8) Ongoing (within the past 6 weeks) hepatic encephalopathy
9) Ongoing pneumonitis
10) Ongoing inflammatory bowel disease
11) Ongoing alcohol or drug addiction as determined by investigator
12) Pregnancy or breastfeeding
13) History of prior allogeneic bone marrow progenitor cell or solid organ transplantation
14) Group A: Ongoing therapy for the treatment of hematologic malignancies (including radiotherapy, chemotherapy, tyrosine-kinase inhibitors [TKIs], immunotherapy, or investigational therapy).

    Group B: AML directed therapy prior to enrollment other than hydroxyurea or leukapheresis, if indicated for rapidly rising white blood cell count.

    For Group A, ongoing therapy must be discontinued prior to study drug initiation as follows:

    a) Prior anti-cancer therapy must be discontinued at least 1 week or 5 half-lives (whichever is longer) prior to the initiation of study therapy
    b) Exceptions or modifications to the above are as follows: Medications that are typically part of a maintenance therapy may be administered up to 3 days prior to the first dose (eg, mercaptopurine, methotrexate, steroids for acute lymphoblastic leukemia (ALL)). Tyrosine kinase inhibitors are not permitted to be continued at screening (eg Imatinib) and should be discontinued 3 days prior to first dose of ENTO.

c) CNS prophylaxis in subjects with relapsed ALL should be discontinued at least 1 week prior to first dose of study treatment

d) For biologics (eg, monoclonal antibodies), a washout period of at least 4 weeks or 5 half-lives (whichever is shorter) since the last dose

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

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

16) 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

17) 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

18) Prior treatment with SYK inhibitors

19) 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

20) Known hypersensitivity to ENTO. Also for Group B, known hypersensitivity to cytarabine or daunorubicin, their metabolites, or formulation excipients

Study Procedures/ Frequency:	See Study Procedures Table

Test Product, Dose, and Mode of Administration:	ENTO is available as 200 mg strength tablets and will be administered orally BID approximately every 12 hours while in a fasted state. The selected starting ENTO dose level in Group A is 400 mg BID.
Reference Therapy, Dose, and Mode of Administration:	Induction chemotherapy (Group B): IV daunorubicin 60 mg/m^2 on Days 1- 3 and IV cytarabine 100 mg/m^2 on Days 1-7 for up to 2 cycles. Post-remission chemotherapy (Group B): 3g/m^2 HiDAC administered BID on Days 1, 3, and 5 (≤ 60 years of age) or 1g/m^2 HiDAC administered once daily on Days 1-5 (> 60 years of age) for up to 4 cycles.

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.
Efficacy:	Assessment of clinical response in subjects with hematologic malignancies other than AML will be according to the latest set of published response criteria. Assessment of clinical response in subjects with AML will be according to the modified International Working Group criteria and will include findings on examination of blood, bone marrow and physical examination.
Pharmacokinetics:	Plasma drug concentrations will be analyzed for determination of ENTO PK parameters.
Endpoints:	**Primary Endpoints:** Safety: • Occurrence of AEs and laboratory abnormalities defined as DLTs for ENTO monotherapy in subjects with relapsed or refractory hematologic malignancies • Occurrence of AEs and laboratory abnormalities defined as DLTs for ENTO in combination with cytarabine and daunorubicin in subjects with previously untreated AML who are candidates for chemotherapy

Secondary Endpoints:

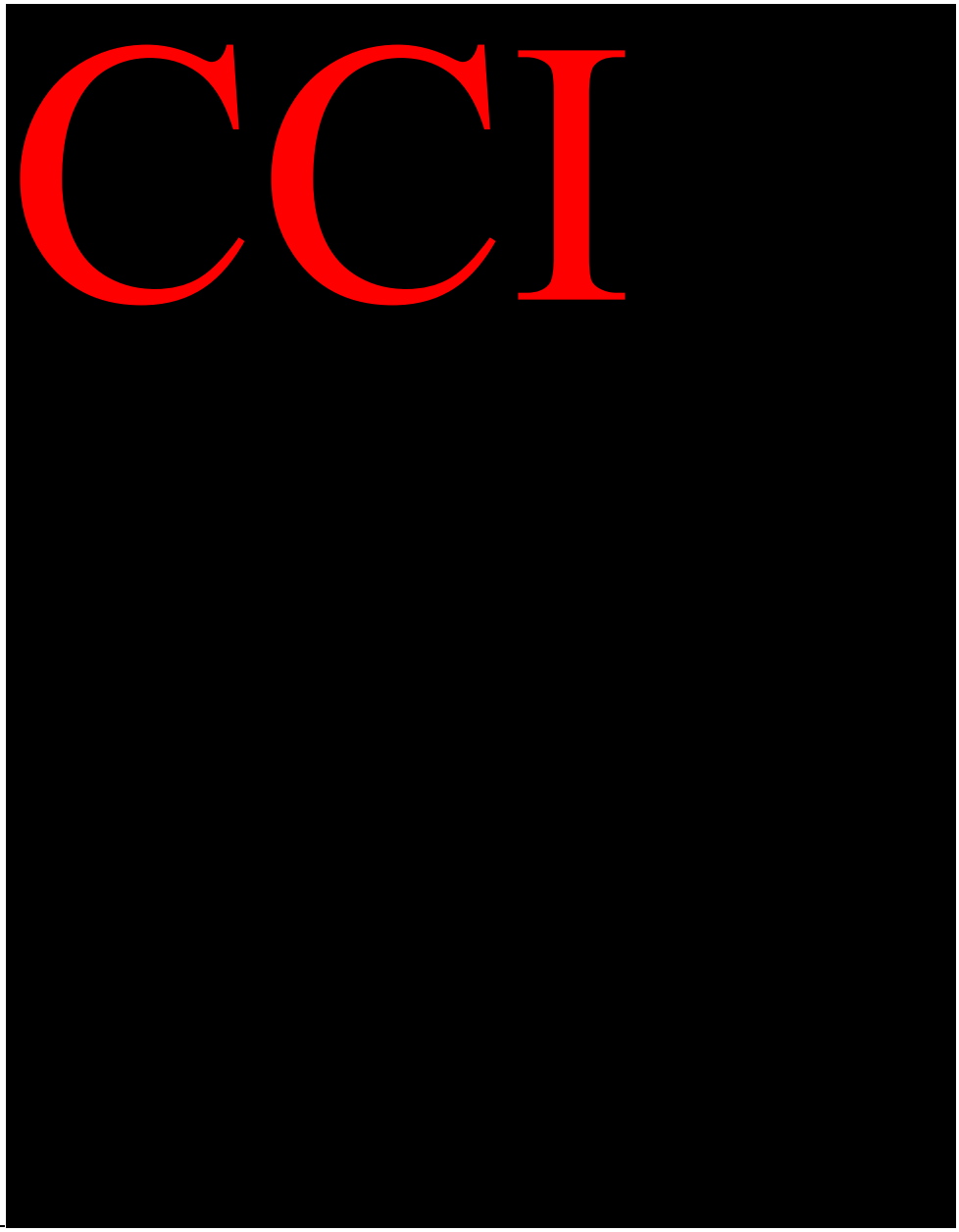
Safety

- Occurrence of AEs, laboratory findings and findings on physical exam not defined as DLTs

Pharmacokinetics

- Determination of the PK parameters of ENTO based on plasma concentrations

Exploratory Endpoints:



Statistical Methods:

Appropriate data analysis sets will be defined. The full-analysis set (FAS) will include all subjects who receive at least 1 dose of study drug (ENTO). The DLT analysis set includes subjects in FAS with sufficient drug exposure or who experience a DLT during the DLT assessment window. Other data sets will be defined and will include 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 for the relevant analysis sets. Descriptive summaries will be prepared to show the number of subjects, mean, standard deviation (StD), 95% confidence intervals (CIs) the mean, median, minimum, and maximum for continuous variables; counts, percentages, and 95% CIs on the percentage for categorical variables. Time-to-event endpoints (eg, 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 with the corresponding 95% CI, the 25%, and 75% percentiles for these endpoints will be provided.

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

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
ADR	adverse drug reaction
AE	adverse event
AKT	protein kinase B (PKB)
ALC	absolute lymphocyte count
ALL	acute lymphoblastic leukemia
ALT	alanine aminotransferase
AM	morning
AML	acute myeloid leukemia
ANC	absolute neutrophil count
ARA-C	cytarabine (Cytosine 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
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
DSPH	Drug Safety and Public Health
EC	ethics committee
EC_{50}	50% effective inhibitory concentration
ECG	electrocardiogram
eCRF	electronic case report form(s)
EDC	electronic data capture
ENTO	entospletinib
EOT	end of treatment
EFS	event free survival
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
HiDAC	high-dose cytarabine

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
IMP	investigational medicinal product
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
LTFU	long term follow up
LVD	longest vertical dimension
MAPK	mitogen-activated protein kinase
MCL	mantle cell lymphoma
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
mL	milliliter
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	overall 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
QD	once-daily
RA	refractory anemia
RBC	red blood cell
REB	research ethics board
RFS	relapse - free survival
RNA	ribonucleic acid
SADR	serious adverse drug reactions
SAE	serious adverse event
SCT	stem cell transplant
SD	stable disease
SD	standard deviation
SDD	spray dried dispersion
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
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. Background

Acute myeloid leukemia (AML) is a biologically heterogeneous disease of the hematopoietic system characterized by clonal accumulation and expansion of immature myeloid cells in the bone marrow {Lowenberg 1999}. A number of clinical factors including age, hyperleukocytosis, prior chemotherapy, and extramedullary or CNS 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 {Mrozek 2008}. 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 {Mrozek 2008}. This predictive value is used to direct initial treatment strategies, including allogeneic transplantation in first CR.

Traditional therapy for AML has remained unchanged over 5 decades and usually consists of a standard chemotherapy regimen of 7 days of cytarabine plus 3 days of an anthracycline (7+3). CR rates to induction chemotherapy range from 20% to 85% with higher CR rates noted in patients younger than 60 years of age and those with good-risk karyotype. Patients with poor-risk karyotype and certain molecular mutations (eg, FLT3-ITD) are typically referred for an allogeneic stem cell transplantation in first CR. Unfortunately, with current treatment strategies, only approximately 40% of the subjects achieve long-term remission. Of those subjects who relapse, only a fraction undergo successful salvage treatment followed by allogeneic hematopoietic stem cell transplant (HSCT) with curative intent. Outcomes for older subjects are far worse and this is related to host and disease related factors. Many older adults may not be candidates for intensive induction chemotherapy with 7+3 or HSCT due to co-morbid illness, poor performance status, and others refuse standard therapy due to concerns of high toxicity and low efficacy. Increasingly, elderly AML patients are being treated with hypomethylating agents like decitabine and azacitidine with CR rates of 20% to 25%. However, even with adaptation of cytogenetically risk-stratified therapies, 20% to 30% of subjects with AML never achieve CR, and greater than 50% of subjects who achieve CR subsequently experience very early disease relapse.

Important factors predictive of prognosis in AML include age, white blood cell count at presentation, the presence of secondary AML (ie, arising after prior chemotherapy or a prior myelodysplastic or myeloproliferative disorder), extramedullary or central nervous system disease, and chromosomal abnormalities {Steelman 2004}. Non-random chromosomal abnormalities, which are identified in approximately 50% to 70% of adult patients with primary acute leukemia, have long been recognized as one of the most important independent prognostic indicators for achievement of CR, duration of first CR, and survival following intensive chemotherapy treatment {Steelman 2004, Stone 2004}. There are several molecular mutations (eg, *FLT3*-ITD, *NPMI*, *IHD1/2*, *DNMT3A*, *MLL*-PTD) and overexpression of genes (eg, *ERG*, *BAALC*) that have a prognostic role in AML disease outcomes {Marcucci 2011}.

Genetic alterations not only represent independent prognosticators, but also may constitute targets for specific therapeutic intervention, including the use of allogeneic transplantation in first CR. The lack of significant advancements in the treatment of AML in adults in the last 40 years highlights the need for development of novel therapeutic strategies.

1.2. Spleen Tyrosine Kinase Biology in AML

SYK is a non-receptor cytoplasmic 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, result in SYK recruitment to the receptor complex and activation 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 {Geahlen 2014, Ruzza 2009}.

SYK has been shown to play an important role as a potential pro-survival factor in hematological malignancies {Geahlen 2014}. SYK activates an array of B-cell responses, including proliferation, survival, differentiation, and apoptosis through key signal transduction pathways downstream of the B-cell receptor (BCR) such as phospholipase C-gamma (PLCγ), phosphoinositide 3-kinase (PI3K), and mitogen-activated protein kinase (MAPK). Additionally, the BCR can deliver antigen-independent signals that have also been postulated to require SYK activity. Antigen-dependent and independent signals have been implicated in the pathogenesis of several B-cell malignancies {Efremov 2011}.

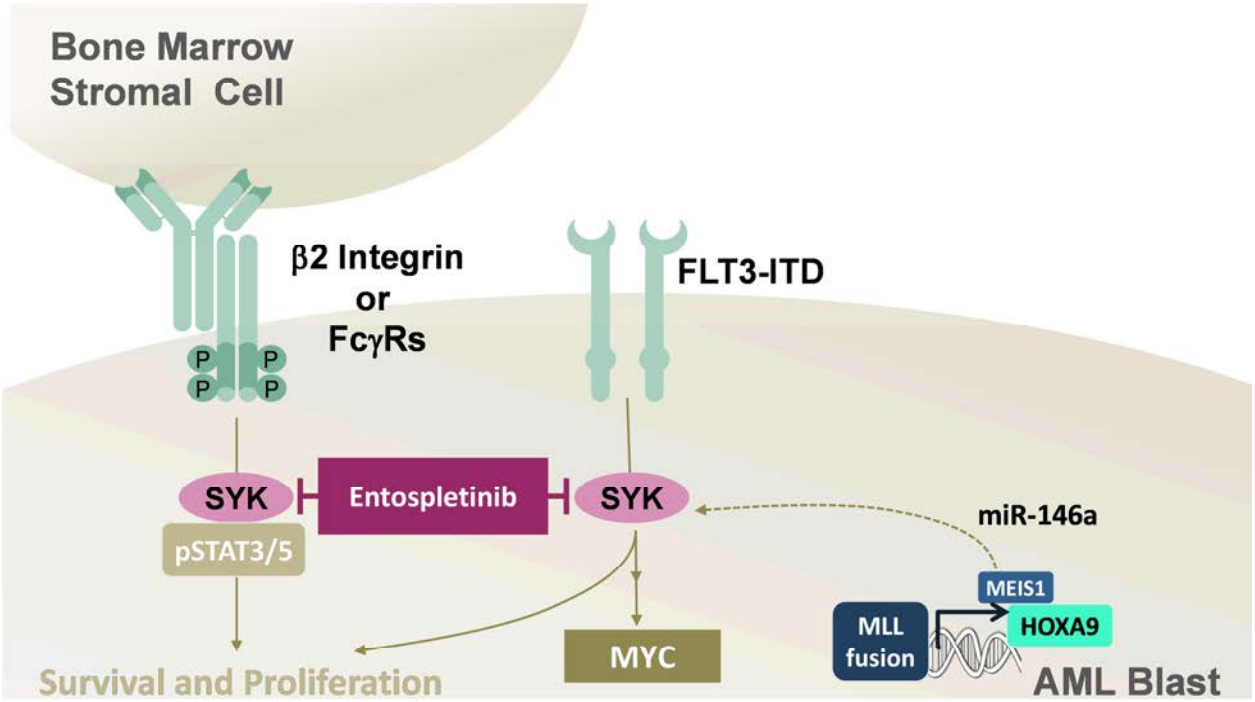
In AML, SYK has been shown to regulate leukemic cell survival and proliferation (Figure 1-1). SYK is expressed in 90% of AML samples and is constitutively activated (pSYK-Y526/6) in AML blasts {Hahn 2009}. High expression of pSYK is associated with increased risk of death following chemotherapy, independent of other AML prognostic indicators such as age, cytogenetics, and white blood cell count {Boros 2015}. In FLT3 mutant AML, SYK is constitutively activated and has been shown to phosphorylate FLT3-ITD and result in up regulation of FLT3 signaling pathways including downstream activation of the signal transducer and activator of transcription 3 and 5 (STAT3 and STAT5) proteins, which are responsible for the proliferation and survival of AML leukemic blasts 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}.

Activation of the SYK signaling pathways in AML occurs through several receptors including stimulation of Fc-γ chain and the β integrins, Mac-1 and Integrin β3. Further, activation of STAT3 and STAT5, which are responsible for the proliferation and survival of AML has been demonstrated to be SYK-dependent {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 CD61/Itgb3 (Integrin B3) impaired homing of primary leukemia cells and induced myeloid differentiation in murine models and in human

leukemia cell lines causing decreased levels of p-SYK in MLL mutated primary cells. Ultimately, integrin signaling through SYK leads to SYK activation affecting transcription, differentiation, and leukemic stem cell survival {Oellerich 2013}.

In an exceptionally high risk group of AML with HOXA9/MEIS1, SYK is critical to leukemic cell survival {Mohr 2016}. HOXA9 and MEIS1 have been found to be over expressed in approximately 30% to 40% of AML cases and expression correlates with poor prognosis {Drabkin 2002, Gao 2016, Heuser 2009, Zangenberg 2009}. High co-expression of HOXA9 and MEIS1 were shown to result in increased SYK protein levels in AML. Non-clinical investigation of this finding in a murine model of HOXA9/MEIS1-induced leukemia demonstrated that genetic knockdown or pharmacologic inhibition of SYK with fostamatinib resulted in a dramatic survival benefit {Mohr 2016}.

Figure 1-1. SYK Regulation of AML Cell Survival and Proliferation



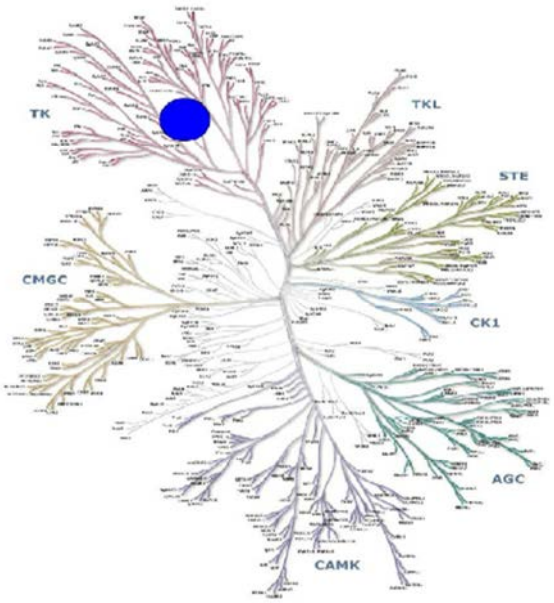
1.3. Entospletinib

Entospletinib (ENTO; GS-9973), a new chemical entity, is a potent and highly selective inhibitor of SYK, being developed by Gilead Sciences, Inc. (Gilead) for oral administration in the treatment of AML. In vitro studies and emerging clinical data suggest that inhibition of SYK may be beneficial in the treatment of certain cancers where SYK-dependent signaling is important for the maintenance and proliferation of malignant cells, including those of AML.

1.3.1. 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 (Figure 1-2).

Figure 1-2. ENTO 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.

1.3.2. 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.

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.

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, dogs and monkeys was recovered in urine.

ENTO showed good metabolic stability with human hepatic material in vitro. In humans, clearance through metabolism is therefore expected to be slow. 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. These results are consistent with clinical drug interaction studies with potent inhibitors and inducers of CYP3A and CYP2C9.

ENTO is 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. This was confirmed in vivo where ENTO affected the pharmacokinetics of rosuvastatin, a substrate for OATP and BCRP transporters. ENTO is a weak inhibitor of OCT2 and BSEP (IC_{50} 10 µM for each) but does not inhibit MRP1, OAT1, OAT3 or OCT1. 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 was a weak inhibitor of intestinal Pgp in vivo. It is not a substrate of OATP1B1, OATP1B3 or Pgp in vitro but is transported by BCRP.

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.

1.3.3. 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. No carcinogenicity studies have been conducted to date.

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

1.3.4. Clinical Trials of ENTO

As of July 2016, a total of 930 subjects (476 healthy subjects, 7 subjects with rheumatoid arthritis [RA], 10 subjects with impaired hepatic function, 171 subjects with chronic lymphocytic leukemia [CLL], 11 subjects with acute lymphocytic leukemia [ALL], 31 subjects with AML, 223 subjects with non-Hodgkin lymphoma [NHL], and 1 subject with chronic graft-versus-host-disease [cGVHD]) have participated in Phase 1 and Phase 2 clinical studies of ENTO. Of these, 904 subjects were treated with ENTO (450 healthy subjects, 7 subjects with RA, 10 subjects with impaired hepatic function, 171 subjects with CLL, 11 subjects with ALL, 31 subjects with AML, 223 subjects with NHL, and 1 subject with cGVHD).

Study GS-US-339-0102, entitled "A Phase 2, Open Label Study Evaluating the Efficacy, Safety, Tolerability, and PD of ENTO in Subjects with Relapsed or Refractory Hematologic Malignancies" is ongoing and as of the data cutoff date (31 May 2016) had enrolled and treated 265 subjects with either the original ENTO 800 mg Mono-MSA formulation (n=213) or the ENTO 400 mg Bis-MSA SDD formulation (n=52). The Bis-MSA SDD ENTO formulation was introduced later in the course of the study. Consequently, a smaller proportion of subjects had been treated with the Bis-MSA SDD ENTO formulation for more than 12 months compared to the Mono-MSA formulation (9.6%, 5 subjects versus 19.2%, 41 subjects). The Bis-MSA SDD ENTO formulation of ENTO will be used in ongoing and planned clinical trials. AEs ≥ Grade 3 in severity were reported in 185 of 265 subjects (69.8%), and SAEs occurred in 94 subjects (35.5%). Overall, the 3 most common AEs were fatigue (55.8%, 148 subjects), nausea (43.0%, 114 subjects), and diarrhea (41.5%, 110 subjects) and the 3 most common AEs with a worst severity of ≥ Grade 3 were anemia (11.3%, 30 subjects; 4 Grade 4), ALT increased (9.8%, 26 subjects; 8 Grade 4), and neutropenia (9.4%, 25 subjects; 14 Grade 4). The most commonly reported AEs of any grade in the Bis-MSA SDD ENTO treatment group were fatigue (50.0%, 26 subjects); diarrhea (32.7%, 17 subjects); and anemia, cough, nausea (23.1%, 12 subjects each) and the 3 most common AEs with a worst severity of ≥ Grade 3 were anemia (9.6%, 5 subjects; all Grade 3), neutropenia (7.7%, 4 subjects; 2 Grade 4), and sepsis (7.7%, 4 subjects; 2 Grade 4). For additional information, please refer to the current investigator brochure.

Study GS-US-339-1559, entitled "A Phase 1b/2 Study of Entospletinib (GS-9973) Monotherapy and in Combination with Chemotherapy in Patients with Acute Myeloid Leukemia (AML)" is an ongoing Phase 1b/2 open-label study evaluating the efficacy, safety, tolerability, and pharmacodynamics of ENTO administered at doses of 200 and 400 mg twice daily (BID) in combination with chemotherapy in previously untreated AML subjects who are candidates for standard 7+3 chemotherapy (Group A), in combination with decitabine or azacitidine in previously untreated subjects who are not candidates for standard chemotherapy (Group B), and as monotherapy in subjects with previously untreated AML who are not candidates for chemotherapy or in subjects with relapsed or refractory AML (Group C). A total of approximately 205 subjects with previously untreated or relapsed/refractory AML will be dosed in the 3 groups (A, B, and C) in Study GS-US-339-1559, each including a Phase 1b dose escalation phase (3+3) and a Phase 2 dose expansion phase. Based on the evaluation of ENTO in Groups A and C of the Phase 1b portion of the study, the dose level planned for further evaluation in the Phase 2 portion of the study as well as planned studies of ENTO in AML has been determined to be 400 mg BID.

1.3.4.1. GS-US-339-1559 Initial Study Results

Initial Phase 1b results as of 12 Oct 2016 are available from 12 AML subjects enrolled in Study GS-US-339-1559 Group A. Subjects in Group A received ENTO monotherapy BID during a 2-week lead-in period, which continued to be given daily in combination with IV chemotherapy (cytarabine and daunorubicin [7+3]) for up to 2 cycles of induction chemotherapy. All 3 subjects receiving ENTO 200 mg BID and 7 of 9 subjects receiving ENTO 400 mg BID were evaluable for efficacy. 10 of the 12 subjects treated with ENTO had a CR/CRi. The overall CR rate among evaluable subjects was 83% (including CR, cytogenetic complete remission [CRc], or CRi).

A plot of bone marrow blasts over time for all enrolled subjects is provided in Figure 1-3 and a plot of circulating blasts over time is provided in Figure 1-4. ENTO was well tolerated during the 2-week monotherapy lead-in period as evidenced by the lack of dose reductions or interruptions. 1 subject in Group A required hydroxyurea to control blast count. Most subjects showed an improvement in blast count during the ENTO lead-in period (Figure 1-3). One subject (Subject PPD had evidence of increasing circulating blast count through the end of ENTO monotherapy, which may have been due to margination and myeloid differentiation of blasts. This subject obtained a CRi at the end of the first cycle of induction and CR at the end of treatment.

Figure 1-3. **GS-US-339-1559: Group A Bone Marrow Blasts Trajectory Through Induction Treatment (Full Analysis Set)**

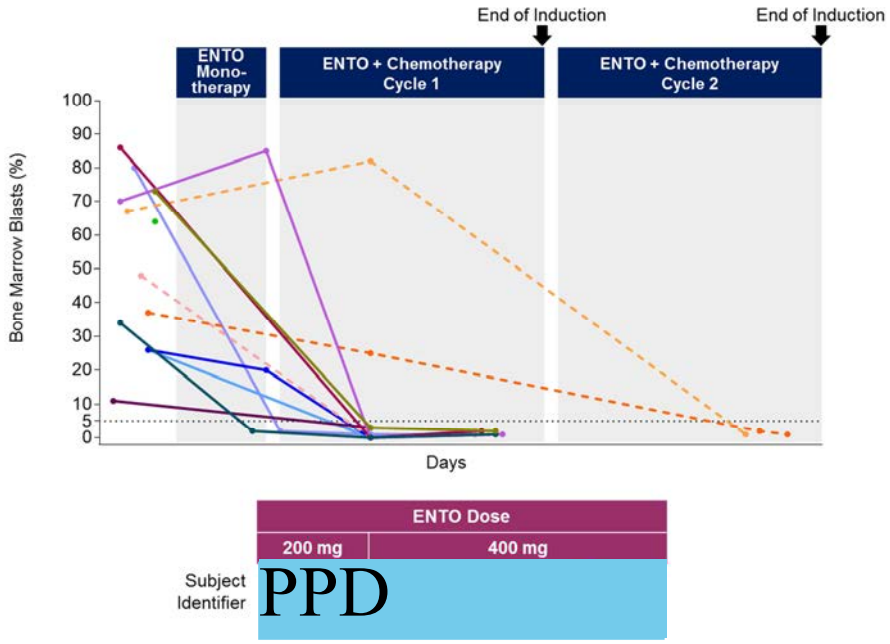
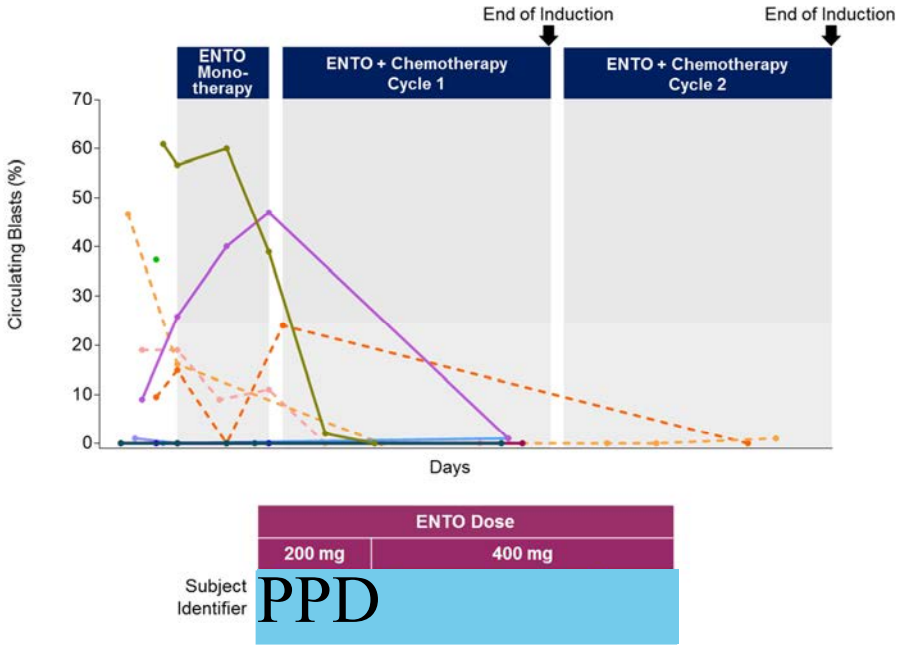


Figure 1-4. **GS-US-339-1559: Group A Circulating Blasts Through Induction Treatment (Full Analysis Set)**



1.3.4.2. Treatment-Emergent Adverse Events in GS-US-339-1559

In Study GS-US-339-1559, treatment-emergent AEs that occurred in Group A are those that have been previously recognized in subjects with AML during chemotherapy induction treatment.

As of 12 October 2016, the most commonly reported treatment-emergent AEs in Group A (ENTO with cytarabine and daunorubicin) occurring in at least 4 subjects across dose levels were as follows: febrile neutropenia (75.0%, 9 subjects), nausea (66.7%, 8 subjects), diarrhea (58.3%, 7 subjects), edema peripheral (75.0%, 6 subjects), and headache (33.3%, 4 subjects).

As of 07 November 2016, the most commonly reported treatment-emergent AEs in Groups B (ENTO with decitabine) and C (ENTO monotherapy) occurring in at least 4 subjects across dose levels were as follows:

- Group B — febrile neutropenia (72.7%, 8 subjects), , nausea (54.5%, 6 subjects), and constipation, device related infection, lung infection(36.4%, 4 subjects each)
- Group C —diarrhea, nausea, and anaemia (28.6%, 4 subjects each)

For additional information, please refer to the current investigator brochure.

1.4. Information about Cytarabine

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 uM, above which the transport is by passive diffusion. To become an active compound ARA-C is converted to ARA-C triphosphate (ARA-CTP) by 3 sequential enzymes, deoxycitidine kinase, deoxycitidine monophosphate kinase, and nucleotide-disphosphate kinase. Competing with these enzymes, there are 2 other enzymes, cytidine deaminize and dCMP deaminase that inactivate ARA-C and ARA-CMP, respectively, to the corresponding 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 the DNA polymerases resulting in termination of the 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 (HiDAC) 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 20 years and is commonly used for AML consolidation.

1.5. Information about 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, preventing the relegation portion of the ligation-religation reaction that topoisomerase II catalyzes. Single strand and double strand DNA breaks results. 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. Dose limiting toxicities for daunorubicin are myelosuppression and cardiotoxicity. Other AEs include mucositis, diarrhea, rash, reversible alopecia, and contact dermatitis. Daunorubicin is also a backbone of AML therapy, commonly delivered by IV bolus for three days during the cytarabine infusion.

1.6. Rationale for This Study

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 vitro and has anti-leukemia activity in AML mouse models. SYK has been shown to be part of the neoplastic progress in AML, as well as in several B-cell malignancies such as NHL and CLL. SYK may also have a role in other hematologic malignancies, such as multiple myeloma {Koerber 2015} and chronic myeloid leukemia {Gioia 2011}. Therefore, it is reasonable to administer ENTO to a wide variety of hematologic malignancies where patients have failed standard therapies. Based on this and the compelling initial findings from Study GS-US-339-1559, Gilead is planning to conduct this Phase 1 clinical trial to evaluate the safety, tolerability, and PK of ENTO monotherapy for Japanese subjects with relapsed or refractory hematologic malignancies and ENTO in combination with cytarabine and daunorubicin for Japanese subjects with previously untreated AML who are candidates for chemotherapy. Data from this study will support the development of ENTO in Japanese subjects.

1.6.1. Rationale for Dose Selection

As of July 2016, a total of 9 evaluable subjects in Group A and 6 evaluable subjects in Group B have received ENTO in the dose escalation phase of Study GS-US-339-1559 at dose levels of 200 mg and 400 mg, and 9 evaluable subjects in Group C have received ENTO at dose levels of 400 mg (n=3) and 800 mg (n=6). To date, no new safety findings have emerged during the course of the study to impact the current safety profile of ENTO. 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. ENTO clinical activity was noted as a single agent at 200 mg and 400 mg and in combination with 7+3 chemotherapy. The time to CR and depth of response (CRc vs. CR vs. CRi) was improved at 400 mg vs. 200 mg in previously untreated subjects. Based on these data, ENTO will be administered at a starting dose of 400 mg BID (PO) in a fasted state in this study.

1.7. Risk/Benefit Assessment for the Study

1.7.1. Potential Risks Based on Nonclinical Safety Data with ENTO

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. In rats treated with 500 mg/kg/day ENTO for 4 weeks, slight villus alteration in the duodenum was noted; this finding was not observed following administration of up to 100 mg/kg/day to rats for 26 weeks. In rabbits and dogs, the predominant organs affected were the GI tract and lymphoid tissues including spleen, lymph nodes, and/or the thymus. At high doses, evidence of lymphoid tissue depletion was noted in rabbits and dogs. Oral administration of ENTO to rats for up to 26 weeks or cynomolgus monkeys for up to 39 weeks showed no evidence of GI toxicity or lymphoid changes at exposures which overlapped with or exceeded those in dogs. 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 increased in any ENTO-treated species. Clinical assessments will monitor for signs and symptoms of infection, hemorrhage, GI disturbances, 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. At dose levels associated with maternal toxicity (reduced body weights and food consumption), decreased fetal weights and delayed ossification were noted in these studies. 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 30 days (Group A ENTO monotherapy) or 6 months (Group B ENTO + cytarabine + daunorubicin) following last treatment administration. Male subjects with female partners of childbearing potential must use condoms during treatment and until 90 days (Group A) or 6 months (Group B) from the last dose of study drug. 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 (Group A) or 6 months (Group B) from the last dose of study drug.

1.7.2. Potential Risks Based on Clinical Safety Data with ENTO

To date, ENTO has been well tolerated. Treatment-emergent AEs commonly reported across the studies involving healthy subjects include headache, somnolence, rash, and GI symptoms (nausea and abdominal pain), all of which were mild and reversible. Increased transaminase levels were noted in some subjects, and these changes were also found to be reversible.

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.

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 and daunorubicin. To mitigate the risk of bone marrow suppression, hematology monitoring will be performed.

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.

The available nonclinical and clinical data support the evaluation of ENTO in eligible subjects with relapsed or refractory hematologic malignancies or previously untreated AML. Given the seriousness of these conditions, the aggregate potential benefits considered in the context of potential risk, support further development of ENTO in Japanese subjects in this Phase 1b study.

1.8. Compliance

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

2. OBJECTIVES

The primary objectives of this study are:

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

The secondary objectives of this study are:

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

The exploratory objectives of this study are:

3. STUDY DESIGN

3.1. Endpoints

The primary endpoints of this study are:

Safety Endpoints:

- Occurrence of AEs and laboratory abnormalities defined as DLTs for ENTO monotherapy in subjects with relapsed or refractory hematologic malignancies
- Occurrence of AEs and laboratory abnormalities defined as DLTs for ENTO in combination with cytarabine and daunorubicin in subjects with previously untreated AML who are candidates for chemotherapy

The secondary endpoints of this study are:

Safety

- Occurrence of AEs, laboratory findings and findings on physical exam not defined as DLTs

Pharmacokinetics

- Determination of the PK parameters of ENTO based on plasma concentrations

The exploratory endpoints of this study are:

3.2. Study Design

A Phase 1b, open-label, multicenter study evaluating the safety, tolerability, and PK of ENTO monotherapy in Japanese subjects with relapsed or refractory hematologic malignancies (Group A) and ENTO in combination with 7 + 3 in Japanese subjects with previously untreated AML (Group B). Approximately 12 subjects will be enrolled to receive ENTO BID as monotherapy or in combination with cytarabine and daunorubicin.

The starting ENTO dose level of 400 mg BID is defined as dose level 0. This dose was chosen from the Phase 1b dose escalation portion of Study GS-US-339-1559 based on clinical activity and tolerability and is currently being explored in the Phase 2 portion of Study GS-US-339-1559 as well as Studies GS-US-339-0102 and GS-US-339-1560. The first 6 subjects will be enrolled in Group A at dose level 0. The safety and tolerability of dose level 0 will be assessed in Group A before proceeding with Group B.

Dose Level	ENTO
-1	200 mg BID
0	400 mg BID

3.2.1. Dose Limiting Toxicities

The DLT assessment window for Group A begins on Cycle 1 Day 1 and ends on Cycle 1 Day 28 and for Group B begins on lead-in Cycle 0 Day 1 and ends 28 days from Cycle 1 Day 1 of induction chemotherapy. The subjects in this study should be in hospital during the DLT assessment window, and the window for Group B may be expanded for bone marrow recovery as noted below. During the DLT assessment window, subjects who fail to complete a total of 21 days of ENTO (or in Group B, miss any doses of cytarabine and daunorubicin) for reasons

other than DLT will not be evaluable for DLT assessment and additional (replacement) subjects may be enrolled in a timely manner to that dose level in order to provide adequate safety data, as determined by the Gilead Medical Monitor, the Japanese CRO Medical Monitor, and the Principal Investigator.

A Grade 4 non-hematologic toxicity attributable to ENTO will be considered a DLT with the exception of alopecia, nausea and vomiting controllable with anti-emetic therapy, line associated venous thrombosis, line associated infection and fatigue.

In subjects without bone marrow evidence of hematologic malignancy (eg, leukemia, lymphoma, or myeloma) by pathological examination, hematologic toxicity will be defined as failure to recover neutrophil count (ANC>500/uL) or platelet count (>25000/uL) within 28 days for Group A and within 8 weeks from chemotherapy initiation for Group B.

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

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 DLTs.

In general, infection will not constitute 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 DLTs unless the toxicity does not resolve to ≤ Grade 2 within 10 days. Subjects in whom ENTO was suspended or dose reduced for a period of more than 10 days will be considered as having a DLT.

Once the sixth evaluable subject has completed the DLT assessment window, the safety review team will evaluate the safety data from all enrolled subjects..

- If 0 or 1 out of the 6 subjects experiences a DLT, Group B will open and 6 subjects will be enrolled in Group B at dose level 0.
- If ≥ 2 out of the 6 subjects experience a DLT, 6 additional subjects will be enrolled in Group A at the reduced dose level -1 (200 mg BID) and Group B will not open.

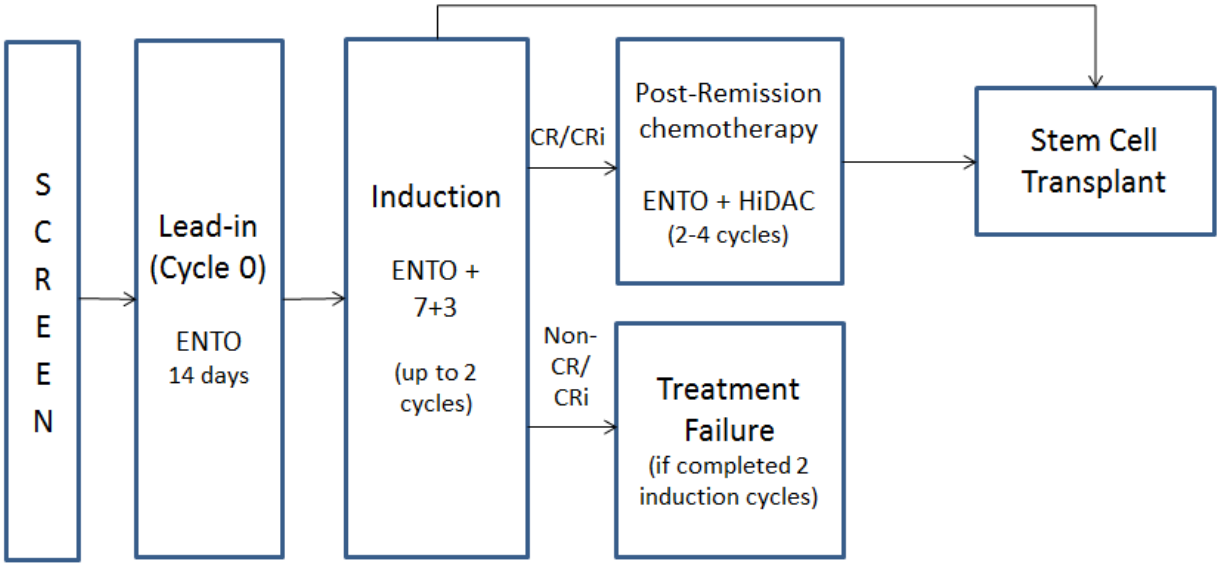
3.2.2. Group A (ENTO monotherapy)

Eligible subjects with relapsed or refractory hematologic malignancies will receive ENTO BID on Days 1-28 of every 28-day cycle and will continue on study treatment as long as the subject is experiencing benefit and does not meet criteria for study treatment discontinuation.

Disease assessments will be performed at the end of Cycle 1 on Day 28, as clinically indicated after Cycle 1, at remission/relapse, and at EOT. A bone marrow biopsy and aspirate sample will be collected for disease assessment for subjects with AML. Subjects with hematologic malignancies other than AML will undergo disease assessment using the appropriate clinical, radiographic, and laboratory procedures per the standard of care or institutional practice.

3.2.3. Group B (ENTO + cytarabine + daunorubicin)

Figure 3-1. Group B Dosing Schema



Lead-in (Cycle 0): Eligible subjects with previously untreated AML will receive ENTO BID on Days 1-14 as a single agent. However, cytarabine and daunorubicin (7+3) treatment (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:

Examples of such situations may include but are not limited to:

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

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 Treatment).

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.

Induction (up to 2 cycles): Following the lead-in cycle, ENTO will continue to be administered BID on Days 1-28 in combination with IV daunorubicin 60 mg/m^2 on Days 1- 3 and IV cytarabine 100 mg/m^2 on Days 1-7 for up to 2 cycles.

Chemotherapy	Dose	Days
IV daunorubicin	60 mg/m^2	1-3
IV cytarabine	100 mg/m^2	1-7

If the Cycle 1 Day 14 bone marrow evaluation has unequivocal evidence of persistent AML, subjects will immediately proceed with Cycle 2. If the bone marrow is hypocellular without evidence of residual leukemia on Day 14, a bone marrow evaluation should be repeated on Day 28 or within 21 days as blood counts recover. Subjects are to continue receiving ENTO BID as they are awaiting disease assessment results and until the completion of induction therapy as determined by bone marrow response. The start of Cycle 2 will depend on the timing of the disease assessment results. Cycle 2 is to be omitted if CR or CRi status is obtained after 1 induction cycle.

If CR/CRi is achieved at the end of Cycle 1 or 2, the subject may proceed to stem cell transplant (SCT) if eligible. Otherwise, the subject will receive post-remission chemotherapy. 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 endpoint criteria, and will be discontinued from the study.

Post-remission chemotherapy (at least 2 cycles, up to 4 cycles): Therapy will be offered to 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. ENTO will be administered BID on Days 1-28 of each 28-day cycle combined with 3g/m^2 high dose cytarabine (HiDAC) administered IV BID on Days 1, 3, and 5 (≤ 60 years of age) or 1g/m^2 HiDAC administered IV once daily on Days 1-5 (> 60 years of age). Careful attention should be paid to the subject's neurological status, particularly cerebellar function prior to each HiDAC dose. The HiDAC doses are the same doses that have been implemented across ENTO clinical studies. Subjects may proceed to allogeneic SCT based on donor availability during post-remission chemotherapy and following completion of post-remission chemotherapy.

Chemotherapy	Subject Age	Dose	Days
HiDAC	≤ 60 years	3g/m^2 BID	1, 3, 5
HiDAC	> 60 years	1g/m^2 once daily	1-5

3.3. Study Treatments

The investigational study drugs (ENTO, daunorubicin, and cytarabine) will be supplied by Gilead Sciences. ENTO 200 mg strength tablets will be self-administered by the subjects enrolled in the trial. Daunorubicin and cytarabine will be administered as described in Section 5.3.2.

3.4. Duration of Treatment

Subjects may continue receiving ENTO until treatment failure, planned completion of treatment, start of new therapy, unacceptable toxicity, withdrawal of consent, or other reasons specified in Section 3.5.1.

3.5. Discontinuation Criteria

3.5.1. 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 A: If there is disease progression or if there has not been an improvement in cytopenias, blast count, peripheral blood or marrow that would suggest clinical benefit, the subject should be removed from study treatment per Investigator discretion. Decisions regarding continuation of ENTO monotherapy in subjects should be determined by the Investigator.
- Group A: Requires continued treatment with hydroxyurea after Cycle 1
- Group B: If a CR or CRi is not achieved by the end of induction Cycle 2, the subject will be considered to have refractory leukemia, to meet the definition of treatment failure and study endpoint criteria, and will be discontinued from the study treatment

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

- 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 the last study visit (see Section 6.8.3, Long term follow up)

- Subjects with noncompliance to study treatment administration, study procedures, or study requirements that increase risk or substantially compromise the interpretation of study results should be withdrawn from study treatment.

- Pregnancy or breastfeeding begins during the study

- 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.

- Initiation of non-study specific anti-cancer therapy

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

3.5.2. Discontinuation of Study

Discontinuation from the study may occur in the following instances:

- If, in the investigator's opinion and in consultation with Gilead, it is determined not to be in the subject's best interest to continue

- Pregnancy or breastfeeding begins during the study

- Death

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

- Withdrawal of consent

- Lost to follow-up

3.6. End of Treatment

Subjects will be removed from study treatment when any of the criteria listed in Section 3.5.1 apply. The End of Treatment (EOT) visit should be completed when a subject discontinues study treatment and prior to initiating a new therapy.

4. SUBJECT POPULATION

4.1. Number of Subjects and Subject Selection

Approximately 12 Japanese subjects with relapsed or refractory hematologic malignancies or previously untreated AML who meet the eligibility criteria will be enrolled to receive ENTO BID as monotherapy or in combination with cytarabine and daunorubicin.

4.2. Inclusion Criteria

Subjects must meet all of the following applicable inclusion criteria to be eligible for participation in this study.

1) Group A: Subjects age $\geq$ 18 with relapsed or refractory hematologic malignancies by WHO criteria and who are not eligible to receive standard of care

2) Group B: Subjects age $\geq$ 18 with previously untreated AML by WHO criteria, who are deemed fit for cytarabine and daunorubicin (7+3) induction chemotherapy and are able to undergo up to 2 cycles of induction chemotherapy, as determined by the treating physician

3) Subjects must have been born in Japan and must not have lived outside of Japan for a period > 1 year in the 5 years prior to Day 1 of study treatment

4) Subjects must be able to confirm the Japanese origin of their maternal and paternal ancestry

5) ECOG performance status less than or equal to 2

6) Life expectancy of at least 3 months

7) Meet required screening laboratory criteria unless disease related, as shown below

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 or Estimated creatinine clearance	< 1.5 x ULN or CrCl ≥ 30 ml/min as calculated by the Cockroft-Gault method
Hematology	Hemoglobin	≥ 8.0 g/dL (without transfusion support, except if due to disease marrow involvement)
Coagulation	INR[a]	< 1.7
Pregnancy	β-HCG[b]	Negative
Infection	HIV	Negative HIV antibody
	HBV	Negative HBsAg and negative HBc antibody or positive HBc and negative HBV DNA by quantitative PCR
	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 post-menopausal). Female subjects with medically documented ovarian failure must also have serum FSH levels within the institutional post-menopausal range.

8) Left Ventricular Ejection Fraction (LVEF) ≥ 45% confirmed by ECHO or MUGA and no clinical evidence of congestive heart failure

9) Male subjects and female subjects of childbearing potential who engage in heterosexual intercourse must agree to use protocol specified method(s) of contraception as described in Appendix 4

10) Lactating females must agree to discontinue nursing from screening until 30 days (Group A ENTO monotherapy) or 6 months (Group B ENTO + cytarabine + daunorubicin) following the end of relevant systemic exposure

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

12) 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 previously untreated AML with recurrent genetic abnormalities involving chromosomal translocation t(15;17) (q22;q12) and/or the fusion gene PML/RARA (FAB classification M3)

2) Known or suspected 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) Current therapy with proton pump inhibitors. Note: H2 receptor antagonists and antacids will be allowed for use during the protocol.

4) Current therapy with medicines that are strong CYP3A or CYP2C9 inducers, or moderate CYP2C9 inducers. See Section 5.5 Excluded Medication.

5) History of active malignancy except for hematologic malignancies and 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, early gastric cancer cured by endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD), or any other cancer that has been in complete remission without treatment for ≥ 5 years prior to enrollment

6) Evidence of ongoing uncontrolled 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.

7) Ongoing 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.

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

9) Ongoing pneumonitis

10) Ongoing inflammatory bowel disease

11) Ongoing alcohol or drug addiction as determined by investigator

12) Pregnancy or breastfeeding

13) History of prior allogeneic bone marrow progenitor cell or solid organ transplantation

14) Group A: Ongoing therapy for the treatment of hematologic malignancies (including radiotherapy, chemotherapy, tyrosine-kinase inhibitors [TKIs], immunotherapy, or investigational therapy).

    Group B: AML directed therapy prior to enrollment other than hydroxyurea or leukapheresis, if indicated for rapidly rising white blood cell count.

    For Group A, ongoing therapy must be discontinued prior to study drug initiation as follows:

    a) Prior anti-cancer therapy must be discontinued at least 1 week or 5 half-lives (whichever is longer) prior to the initiation of study therapy

    b) Exceptions or modifications to the above are as follows: Medications that are typically part of a maintenance therapy may be administered up to 3 days prior to the first dose (eg, mercaptopurine, methotrexate, steroids for acute lymphoblastic leukemia (ALL)). Tyrosine kinase inhibitors are not permitted to be continued at screening (eg Imatinib) and should be discontinued 3 days prior to first dose of ENTO.

    c) CNS prophylaxis in subjects with relapsed ALL should be discontinued at least 1 week prior to first dose of study treatment

    d) For biologics (eg, monoclonal antibodies), a washout period of at least 4 weeks or 5 half-lives (whichever is shorter) since the last dose

       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

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

16) 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

17) 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

18) Prior treatment with SYK inhibitors

19) 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

20) Known hypersensitivity to ENTO. Also for Group B subjects, known hypersensitivity to cytarabine or daunorubicin, their metabolites, or formulation excipients

5. INVESTIGATIONAL MEDICINAL PRODUCTS

5.1. Description and Handling

5.1.1. Formulation

ENTO tablets, 200 mg strength, are 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.

Daunorubicin is administered by IV infusion or IV bolus during Group B induction therapy and is supplied in vials of 20 mg. Each vial contains a red freeze-dried powder of 20 mg (titer) daunorubicin hydrochloride and 100 mg D-mannitol. .

Cytarabine is administered by IV infusion during Group B induction and post-remission chemotherapy. For induction therapy, cytarabine may be supplied in vials of 20 mg, 40 mg, 60 mg, 100 mg or 200 mg solution for injection or concentrate solution for infusion. The pharmacy manual should be referenced for information on the actual vial sizes that will be supplied. If the 100 mg vials are supplied, each vial will contain a 5 ml solution for injection with a concentrate for solution for infusion containing 100 mg cytarabine (20 mg/ml). Each 100 mg vial will also contain a sodium-S-lactate solution (50%), sodium chloride, and water for injections. For post-remission therapy, cytarabine is supplied in vials of 1 g solution for infusion with 20 mL solution that contains 1000 mg cytarabine (50 mg/mL). Each 1 g vial contains sodium-S-lactate solution (50%) and water for injections as a clear, colorless to yellowish solution free of particles.

5.1.2. Packaging and Labeling

Study drug (ENTO [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.

Gilead will supply daunorubicin and/or cytarabine to each site as study drug and details regarding the packaging and labeling will be provided separately in the pharmacy manual.

Study drugs to be distributed to centers in Japan shall be labeled to meet applicable requirements of the Pharmaceuticals and Medical Devices Agency (PMDA) and/or other local regulations.

5.1.3. Storage and Handling

Study drug (ENTO) 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 through inhalation when handling.

Daunorubicin and cytarabine will be supplied as study drug and the site should handle and store them in accordance with the pharmacy manual.

5.2. Premedication

No specific premedications or supporting medications are required in conjunction with ENTO administration. All subjects should receive anti-microbial, anti-fungal, and anti-viral prophylaxis per institutional guidelines.

For cytarabine and daunorubicin, the site should reference the pharmacy manual.

5.3. Dosage and Administration

5.3.1. Entospletinib

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. Subjects should also be instructed to contact the site staff or investigators if the incorrect dose of ENTO is taken.

ENTO will be administered orally (PO) BID approximately every 12 hours while in a fasted state. Ideally, ENTO should be taken at approximately the same times each day. 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.

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.

5.3.1.1. Guidelines for ENTO Dose Modifications

Recommendations for dose modifications based on the type and severity of AEs or laboratory abnormalities are provided in Table 5-1. The dose adjustment recommendations are based on the CTCAE grade of specific toxicities. However, exceptions are expected for subjects who initiate study treatment with low blood counts. Clinical judgement should apply, and in cases of uncertainty, the study medical monitor should be contacted.

The dose modification instructions focus on the types of events most commonly attributed to ENTO or other drugs that target B-cell receptor signaling pathways. The recommendations provided in Table 5-1 comprise only guidelines; variations from these recommendations may be warranted based on an investigator's individual judgement in considering potential risks, benefits, and therapeutic alternatives available to each subject.

Table 5-1. ENTO Dose Modification Guidelines

<table>
<tr><th>Adverse Event</th><th>Grade 1</th><th>Grade 2</th><th>Grade 3</th><th>Grade 4</th></tr>
<tr><td>Neutropenia</td><td colspan="3">Maintain current dose level and schedule.</td><td>Continue dosing at same or lower dose level at investigator discretion.</td></tr>
<tr><td>Thrombocytopenia</td><td colspan="3">Maintain current dose level and schedule.</td><td>Continue dosing at same or lower dose level at investigator discretion.</td></tr>
<tr><td rowspan="2">Dermatological</td><td colspan="2" rowspan="2">Maintain current dose level and schedule.</td><td>Withhold dosing until ≤ Grade 1. Resume dosing at current dose level.</td><td>Withhold dosing until Grade ≤1.</td></tr>
<tr><td>If re-challenge at current dose level results in recurrence, may resume dosing at same or lower dose level at investigator discretion.</td><td>May resume at lower dose level or discontinue dosing at investigator discretion</td></tr>
<tr><td rowspan="3">Hepatic (elevations in ALT, AST, or bilirubin)

Note: If subject has febrile neutropenia, rule out infectious cholecystitis and other infectious causes.</td><td>(ALT/AST≤3xULN) (Direct Bilirubin ≤1.5xULN)</td><td>(ALT/AST>3-5xULN) (Direct Bilirubin >1.5-≤3xULN)</td><td>(ALT/AST>5-20xULN) (Direct Bilirubin >3-10xULN)</td><td>(ALT/AST>20xULN) (Direct Bilirubin >10xULN)</td></tr>
<tr><td>Maintain current dose level and schedule.</td><td>Maintain current dose level and schedule. Monitor ALT, AST, ALP, and direct bilirubin at least 1x per week.</td><td>Withhold dosing. Monitor ALT, AST, ALP, and direct bilirubin at least 1x per week until all abnormalities are Grade ≤1.</td><td>Withhold dosing. Monitor ALT, AST, ALP, and direct bilirubin at least 1x per week until all abnormalities are Grade ≤1.</td></tr>
<tr><td>If direct bilirubin was Grade <3, resume dosing at same dose level. If direct bilirubin was Grade ≥3, resume at lower dose level.</td><td>If direct bilirubin was Grade <4, resume dosing at lower dose level. If direct bilirubin was Grade 4, discontinue dosing.</td></tr>
<tr><td>Pneumonitis (dyspnea, cough, hypoxia and/or diffuse interstitial pattern or ground-glass opacities on chest CT and no obvious infectious cause)
Note: If subject has febrile neutropenia, rule out bacterial /fungal pneumonia.</td><td>Maintain current dose level and schedule.</td><td>Withhold dosing until Grade ≤1.

May resume at initial or lower dose level at investigator discretion.</td><td colspan="2">Withhold dosing until Grade ≤1.

May resume at lower dose level or discontinue dosing at investigator discretion.</td></tr>
<tr><td>Other Study Drug Related, Non-hematological AEs</td><td colspan="2">Maintain current dose level and schedule</td><td colspan="2">Withhold dosing until Grade ≤1.

May resume dosing at initial or lower dose level or discontinue dosing at investigator discretion.</td></tr>
</table>

5.3.2. Cytarabine and Daunorubicin

During induction chemotherapy, IV cytarabine 100 mg/m^2 will be administered on Days 1-7 of each cycle. During post-remission chemotherapy, age-adjusted HiDAC will be administered. Subjects ≤ 60 years of age will receive 3 g/m^2 HiDAC BID on Days 1, 3, and 5 of each cycle and subjects > 60 years of age will receive 1 g/m^2 HiDAC once daily on Days 1 to 5 of each cycle.

IV daunorubicin 60 mg/m^2 will be administered on Days 1-3 of each cycle of induction chemotherapy.

The site should administer cytarabine and daunorubicin in accordance with the pharmacy manual.

5.4. Prior and Concomitant Medications

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

Nausea and/or vomiting should be treated with maximal medical therapy, which should include a 5HT3 receptor antagonist, unless otherwise contraindicated.

Strong consideration should be given to transfusing subjects with markedly compromised hemoglobin levels (< 8 g/dL) unless contraindicated.

The use of myeloid growth factors during induction chemotherapy is not permitted but during post-remission chemotherapy may be used per guidelines for use in AML. During the DLT assessment period, primary prophylaxis with granulocyte-colony stimulating factor (G-CSF) is not permitted.

5.5. Excluded 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.

Subjects who initiate therapy with excluded medications will be discontinued from the trial. The following therapies are not permitted at any point during the trial beginning with the first dose of study treatment.

- rEPO is not permitted at any time on the study.
- No other direct anti-leukemia therapy is permitted.
- Palliative radiation therapy may not be administered while the subject is on study.
- 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.

- Proton Pump Inhibitors since they are likely to decrease exposure to ENTO. Use of a proton pump inhibitor should be avoided for 7 days prior to study drug administration.
  Note: H2 blockers and antacids will be allowed for use during the protocol

- Co-administration of strong CYP3A and CYP2C9 inducers, and moderate CYP2C9 inducers are contraindicated 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 5-2.

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 5-2. Contraindicated 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, vonoprazan	

* Not yet approved in Japan

In a study in healthy volunteers, ENTO 400 mg BID increased rosuvastatin exposure by approximately 3.8-fold, which may theoretically increase the risk of AEs. The following restrictions apply to the use of HMG-CoA reductase inhibitors with ENTO:

HMG-CoA reductase inhibitor	Dose Adjustment Required
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

* Not yet approved in Japan

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.

5.6. Accountability for IMP

The investigator is responsible for ensuring adequate accountability of all used and unused IMP. This includes acknowledgement of receipt of each shipment of IMP (quantity and condition). All used and unused IMP dispensed to subjects must be returned to the site.

Study drug (ENTO, cytarabine and daunorubicin) accountability records will be provided to each study site to:

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

5.6.1. Investigational Medicinal Products Return or 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 and described in the text that follows. Additional information is provided in the study procedures manual.

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

6.1. Subject Enrollment

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.

6.2. Study Procedure Descriptions

6.2.1. Informed Consent

All subjects must sign and date the most recent Independent Ethics Committee (IEC) approved informed consent form before any study procedures are performed. For subjects < 20 years of age, both the subject and the subject's legal representative must sign and date the informed consent form before any study procedures are performed.

Subjects who screen fail must re-sign the informed consent, in the event any screening procedures will be performed outside of the screening window from the time of the first informed consent.

6.2.2. Medical History

A complete medical history will be obtained by the investigator or qualified designee at screening and recorded on the eCRF. Medical history will include information on the subject's significant past medical events (eg, prior hospitalizations or surgeries), a review of the disease under study, prior anti-cancer therapies, and any concurrent illnesses.

6.2.3. Prior and Concomitant Medications

All medications taken up to 30 days prior to the screening visit will be recorded on the eCRF. In addition, supportive therapies given during the course of the study (eg, blood transfusion, growth factor) should be collected and 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 and non-prescription medications, pre-infusion medications (eg, anti-emetics), and vitamins and minerals.

6.2.4. Physical Examination

The investigator or qualified designee will perform a complete physical examination at designated time points during the study (Refer to Appendix 2). Pre-dose abnormal findings will be reported on the medical history page of the eCRF. Any changes from the pre-dose baseline physical examination that represent a clinically significant deterioration will be documented on the AE page of the eCRF. The Screening physical examination will be complete physical examinations, thereafter, a modified physical examination will be performed to monitor for any changes, and will also include weight and assessment of disease-related clinical signs and symptoms.

6.2.5. Vital Signs

Vital signs will include blood pressure, respiratory rate, pulse, temperature and oxygen saturation. All measurements will be recorded on the appropriate eCRF page with appropriate source documentation. Any abnormal measurements may be repeated and reported as AEs if appropriate. All measures of blood pressure will be performed using standard sphygmomanometry. Measurements of blood pressure should be taken per institutional guidelines.

6.2.6. Electrocardiogram

12-lead electrocardiograms (ECGs) reporting ventricular rate, PR, QRS, QT, and QTc intervals will be obtained at the applicable study visits (Appendix 2).

Subjects should be resting quietly and free of distraction (eg, television, conversation) for 10 minutes prior to ECG collection and ECGs should be collected over a 5 minute window at each time point.

The investigator or qualified designee will review all ECGs. The ECG tracings will be maintained in the source documentation of each subject and the appropriate data reported on the eCRF.

6.2.7. Echocardiogram

Echocardiograms will be performed at the time points listed in the Study Procedures Table (Appendix 2). Multigated acquisition (MUGA) scans are also acceptable. However, the same modality must be used throughout study participation.

Abnormal echocardiogram findings that are considered clinically significant by the investigator should be reported as AEs and recorded in the AE eCRF if the finding meets the definition of an AE.

6.2.8. ECOG Performance Status

ECOG Performance Status is an investigator assessment of the impact of the disease on the subject's activities of daily living. ECOG assessments will be performed at the time points listed in the Study Procedures Table (Appendix 2 and Appendix 3). ECOG will be scored using the scale index in Appendix 5.

6.2.9. Adverse Events

Subjects will be assessed for AEs per guidelines in the National Cancer Institute (NCI) CTCAE (see Section 8.6.2) at the time points outlined in Appendix 2. Any AEs reported after informed consent is obtained and throughout the study will be recorded on the eCRF with appropriate source documentation. The subject will be assessed for AEs until approximately 30 days after the last dose of study treatment.

Please refer to Section 7 for additional information on AE reporting.

6.2.10. Laboratory Assessments

Screening laboratory samples should be obtained within 14 days prior to the Cycle 1 Day 1 (Group A) or Cycle 0 Day 1 (Group B) ENTO dose. Local laboratory complete blood count (CBC) assessments may be collected as required for dose adjustments and medical management throughout the study. Local laboratory assessments resulting in a dose change will be reported on the eCRF.

The central laboratory will be responsible for chemistry, hematology, coagulation, urinalysis, and serum pregnancy testing per Table 6-1 and the Study Procedures Tables (Appendix 2 and Appendix 3) and storage of other study samples. If central laboratory results are not available, local laboratories may be used for dosing decisions. Other tests listed in Table 6-1 may be performed by a designated laboratory, and the virology and urine pregnancy testing may be performed by the local laboratory. Any sample collected per the Study Procedures Tables (Appendix 2 and Appendix 3) may be analyzed for any tests necessary to ensure subject safety. Specific instructions for processing, labeling, and shipping samples will be provided in the central laboratory manual. The date and time of sample collection will be recorded in the subject's source documentation and reported to the central laboratory.

The date and time of previous ENTO dose will be recorded in the subject's source documentation on days where PK is collected. WBC differentials will be reported as absolute counts. All laboratory tests must be reviewed for clinical significance by the investigator or qualified designee. The analytes listed in Table 6-1 will be tested.

Table 6-1. Analytes

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]	Hemoglobin Hematocrit Red Blood Cell (RBC) count White Blood Cell (WBC) Count Neutrophils Lymphocytes Monocytes Eosinophils Basophils Platelets	Pharmacokinetic Sampling
	Coagulation	
	Prothrombin time APTT INR	
Pregnancy Testing	**Virology**	
Serum Qualitative β-HCG and FSH[a] Urine pregnancy test	Hep B Hep C HIV	

a Screening only. Serum FSH also required for female subjects with medically documented ovarian failure.
b Screening for Groups A and B. See Appendix 2 for additional Group A timepoints and Appendix 3 for additional Group B timepoints.

All female subjects of childbearing potential (as defined in Appendix 4) will have serum pregnancy and FSH testing (for female subjects with medically documented ovarian failure) at screening. The results must be confirmed as negative for pregnancy prior to administration of the first dose of study drug.

Female subjects of childbearing potential urine pregnancy tests will be performed monthly and at EOT.

6.2.11. Pharmacokinetic Samples

PK samples will be collected at the time points listed below for each group. ENTO plasma concentrations will be determined using a validated assay. The date and time of ENTO dosing will be collected prior to and on the day of PK sampling.

6.2.12. Chest X-ray

A chest x-ray to screen for infiltrates or other evidence of infection must be completed prior to initiating study treatment.

6.2.13. Bone Marrow Biopsy and Aspirate

Bone marrow aspirate/biopsy samples will be assessed by a local hematopathologist for disease assessment. For subjects with AML, bone marrow aspirate samples for molecular mutational testing of leukemia will be shipped to a central lab. Results of the molecular mutational testing will be disclosed to the investigator but these results will not be used for clinical decision making in the conduct of this study. Biopsy will be used in the event the aspirate cannot be collected or analyzed (eg, dry-tap, hemodiluted specimen, or lack of spicules).

6.2.14. Biological Sample Storage

PK samples and bone marrow aspirate samples (for mutational testing of leukemia) at the conclusion of this study may be retained in storage by the Sponsor for a period of up to 10 years for purposes of this study before being destroyed. Samples will be destroyed by internationally accepted means (eg, incineration). The sample storage period will be in accordance with the IRB/EC-approved Informed Consent Form. Samples other than the PK samples and bone marrow aspirate samples (for mutational testing of leukemia) will not be retained.

6.3. Screening Visit

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 (and other clinical, radiographic, and laboratory procedures required for subjects with hematologic malignancies other than AML) 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
- Performance status
- 12-lead ECG
- ECHO or MUGA

- Obtain blood samples for:
  - Chemistry
  - Hematology
  - Coagulation
  - Serum pregnancy test (female subjects of childbearing only) and FSH (for female subjects with medically documented ovarian failure)
  - HIV/HBV/HCV
- Urinalysis
- Chest X-ray
- Subjects with AML will undergo a bone marrow aspirate and biopsy for disease assessment within 21 days before the first administration of study treatment Cytogenetic testing will be locally performed and molecular mutation testing of leukemia for FLT3, NPM1, and CEBPA will be centrally performed.
- Subjects with hematologic malignancies other than AML will undergo the appropriate clinical, radiographic, and laboratory procedures per the standard of care or institutional practice for disease assessment within 21 days before the first administration of study treatment
- Record any serious adverse events (SAEs) and all AEs related to protocol mandated procedures occurring after signing of the consent form

Subjects meeting all of the applicable 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 SAEs, as well as any AEs related to protocol-mandated procedures on the AE case report form (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 eCRF. See Section 7 for additional details.

6.4. Treatment Assessments – Group A (ENTO Monotherapy)

Subjects with relapsed or refractory hematologic malignancies who have met all eligibility criteria will come to the clinic on Cycle 1 Day 1 to perform study required procedures prior to dosing. Review prior/ concomitant medications and record AEs at each clinic visit.

6.4.1. Cycle 1

- ENTO will be administered BID on Days 1-28 as a single agent
- Obtain current smoking status (Day 1)
- Physical examination (Days 1 and 14)
- Vital signs; including blood pressure, respiratory rate, pulse, temperature, oxygen saturation level (Days 1, 8, 14, and 28)
- Weight (Day 1)
- Performance status (Days 1 and 14)
- Urine pregnancy test (prior to dose on Day 1; female subjects of childbearing potential only)
- Obtain blood samples for:
  - Chemistry (Days 1 (pre-dose), 8, 14, and 28)
  - Hematology (Days 1 (pre-dose), 8, 14, and 28)
  - Coagulation (Days 14 and 28)
  - Sparse PK (Days 1, 14, and 28 at pre-dose and 2 hours post-dose of ENTO)
  - Intensive PK (Day 8 at pre-dose, 1, 2, 3, 4, 6, 8, and 12 hours post-dose of ENTO)

  Note: ENTO should be held until the pre-dose blood samples have been drawn. Record the approximate time of the last two doses of ENTO on PK collection days and the time the PK blood samples are obtained
- Subjects with AML will undergo a bone marrow biopsy and aspirate for disease assessment (histopathological evaluation) (~8mL) at the end of Cycle 1 on Day 28. Subjects with cytogenetic and molecular mutations at screening must have cytogenetic and molecular mutation testing repeated.
- Subjects with hematologic malignancies other than AML will undergo the appropriate clinical, radiographic, and laboratory procedures per the standard of care or institutional practice for disease assessment at the end of Cycle 1 on Day 28

6.4.2. Subsequent Cycles

- ENTO will be administered BID on Days 1-28 as a single agent

- Obtain current smoking status (Day 1 of each cycle)
- Physical examination (Day 1 of each cycle)
- Vital signs; including blood pressure, respiratory rate, pulse, temperature, oxygen saturation level (Day 1 of each cycle)
- Weight (Day 1 of each cycle)
- Performance status (Day 1 of each cycle)
- Urine pregnancy test (prior to dose on Day 1 of each cycle; female subjects of childbearing potential only)
- Obtain blood samples for:
  - Chemistry (Day 28 of each cycle)
  - Hematology (Day 28 of each cycle)
  - Coagulation (Day 28 of each cycle)
  - Sparse PK (Day 28 of each cycle at pre-dose and 2 hours post-dose of ENTO)

  Note: ENTO should be held until the pre-dose blood samples have been drawn. Record the approximate time of the last two doses of ENTO on PK collection days and the time the PK blood samples are obtained
- Subjects with AML will undergo a bone marrow biopsy and aspirate for disease assessment (histopathological evaluation) (~8mL) as clinically indicated
- Subjects with hematologic malignancies other than AML will undergo the appropriate clinical, radiographic, and laboratory procedures per the standard of care or institutional practice for disease assessment as clinically indicated

6.5. Treatment Assessments – Group B (ENTO + cytarabine + daunorubicin)

Subjects with previously untreated AML who have met all eligibility criteria will come to the clinic on Cycle 0 Day 1 to perform study required procedures prior to dosing. Review prior/ concomitant medications and record AEs at each clinic visit.

6.5.1. Lead-in (Cycle 0)

- ENTO will be administered BID on Days 1-14 as a single agent
- Vital signs; including blood pressure, respiratory rate, pulse, temperature, oxygen saturation level

- Physical examination (Day 1)
- Obtain current smoking status (Day 1)
- Performance status (Day 1)
- Urine pregnancy test (prior to dose on Day 1; female subjects of childbearing potential only)
- Obtain blood samples for:
  - Chemistry (Days 1 (pre-dose), 8, and 14)
  - Hematology (Days 1 (pre-dose), 8, and 14)
  - Coagulation (Day 14)
  - Sparse PK (Days 1, 14 at pre-dose and 2 hours post-dose of ENTO)
  - Intensive PK (Day 8 at pre-dose, 1, 2, 3, 4, 6, 8, and 12 hours post-dose of ENTO)

  Note: ENTO should be held until the pre-dose blood samples have been drawn. Record the approximate time of the last two doses of ENTO on PK collection days and the time the PK blood samples are obtained
- A bone marrow aspirate sample for disease assessment (histopathological evaluation) (~8mL) will be collected at completion of the lead-in cycle, which is anticipated to occur on Cycle 0 Day 14. The bone marrow aspirate sample must be collected prior to starting 7+3 treatment (Cycle 1). Subjects with cytogenetic and molecular mutations at screening must have cytogenetic and molecular mutation testing repeated.

6.5.2. Induction

- ENTO will continue to be administered BID on Days 1-28 in combination with IV cytarabine 100 mg/m^2 daily on Days 1-7 and IV daunorubicin 60 mg/m^2 daily on Days 1-3 of each 28-day cycle. Subjects will receive at least 1 cycle of induction chemotherapy but no more than 2 cycles.
- Vital signs; including blood pressure, respiratory rate, pulse, temperature, oxygen saturation level (Days 1, 3, and 7 of each cycle)
- Weight (Day 1 of each cycle)
- Performance status (Day 28 of each cycle)
- Physical exam (Day 1 of each cycle)

- Obtain smoking status (Day 1 of each cycle)
- Urine pregnancy test (Day 1 of each cycle; female subjects of childbearing potential only)
- Obtain blood samples for:
  - Chemistry (Days 7, 14, and 28 of each cycle)
  - Hematology (Days 7, 14, and 28 of each cycle; local hematology (complete blood count) daily from Day 15 until count recovery for subjects with hypocellular bone marrow and no evidence of residual leukemia on Day 14)
  - Coagulation (Days 7, 14, and 28 of each cycle)
  - Sparse PK (Day 3 of each cycle at pre-dose, 2, and 4 hours post-dose of ENTO; Days 14 and 28 of each cycle at pre-dose and 2 hours post-dose of ENTO)
  - Intensive PK (Day 7 [Cycle 1 only] at pre-dose, 1, 2, 3, 4, 6, 8, and 12 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 two 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 (and Cycle 2 Day 14 if needed) for disease assessment (~8mL). Subjects with cytogenetic and molecular mutations at screening must have cytogenetic and molecular mutation testing repeated on Cycle 1 Day 14 (or at count recovery).
  - If the Cycle 1 Day 14 bone marrow evaluation has unequivocal evidence of persistent AML, subjects will immediately proceed with Cycle 2
  - If the bone marrow is hypocellular (≤ 20% cellularity) without evidence of residual leukemia on Day 14, a bone marrow evaluation must be repeated on Day 28 or within 21 days (eg, no later than Day 35) as blood counts recover prior to proceeding to SCT or post-remission chemotherapy. Subjects are to continue receiving ENTO BID as they are awaiting disease assessment results and until the completion of induction chemotherapy as determined by bone marrow response. Cycle 2 is to be omitted if CR or CRi status is achieved after 1 induction cycle.
  - If CR/CRi is achieved at the end of Cycle 1 or 2 as demonstrated on the bone marrow aspirate and biopsy, the subject may proceed to SCT if eligible. Otherwise, the subject will receive post-remission chemotherapy.

— 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 endpoint criteria, and will be discontinued from study treatment

6.5.3. Post-remission chemotherapy

- ENTO will continue to be administered BID on Days 1-28 in combination with age-adjusted HiDAC for at least 2 cycles and up to 4 cycles

  — For subjects ≤ 60 years of age, 3 g/m^2 HiDAC will be administered BID on Days 1, 3, and 5 of each 28-day cycle

  — For subjects > 60 years of age, 1 g/m^2 HiDAC will be administered once daily on Days 1-5 of each 28-day cycle

- Vital signs; including blood pressure, respiratory rate, pulse, temperature, oxygen saturation level (Day 1 of each cycle)

- Weight (Day 1 of each cycle)

- Performance status (Day 28 of each cycle)

- Physical exam (Day 1 of each cycle)

- Obtain smoking status (Day 1 of each cycle)

- Urine pregnancy test (on Day 1 of each cycle; female subjects of childbearing potential only)

- Obtain blood samples for:

  — Chemistry (Day 28 of each cycle)

  — Hematology (Day 28 of each cycle)

  — Coagulation (Day 28 of each cycle)

  — Sparse PK (Days 5 and 28 of each cycle at 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 two doses of ENTO on PK collection days and the time the PK blood samples are obtained

- Obtain bone marrow aspirate at Cycle 2 Day 28 and Cycle 4 Day 28, or as clinically indicated for disease assessment (~8mL)

During and following completion of post-remission chemotherapy, subjects may proceed to SCT based on donor availability.

6.6. Assessments for Premature Discontinuation from Study

If a subject prematurely discontinues study treatment (see Section 3.5.1, Discontinuation of Study Treatment), every attempt should be made to keep the subject in the study and continue to perform the required study-related follow-up and procedures (see Sections 6.8). If this is not possible or acceptable to the subject or investigator, the subject may be withdrawn from the study and no further study-related follow-up and procedures will be performed.

6.7. End of Treatment

Subjects will be removed from study treatment when any of the criteria listed in Section 3.5.1 apply. The following procedures will be conducted when a subject discontinues study treatment and prior to initiating a new therapy.

- Review concomitant medications
- Review any AEs
- Performance status
- Physical exam
- Vital signs; including blood pressure, respiratory rate, pulse, temperature, oxygen saturation level
- Weight
- Obtain blood samples for:
  - Chemistry
  - Hematology (with differential)
  - Coagulation
- Urine Pregnancy Test (for females of childbearing potential)
- Subjects with AML will undergo a bone marrow aspirate and biopsy for disease assessment (~8mL) (if not performed within the last 2 weeks). Subjects with cytogenetic and molecular mutations at screening must have cytogenetic and molecular mutation testing repeated.
- Subjects with hematologic malignancies other than AML will undergo the appropriate clinical, radiographic, and laboratory procedures per the standard of care or institutional practice for disease assessment (if not performed within the last 2 weeks)

6.8. Follow-up

6.8.1. Remission/Relapse

Subjects with AML who achieve remission or relapse should undergo a bone marrow aspirate and biopsy for disease assessment (~8mL) and have a blood sample obtained for hematology. Subjects with cytogenetic and molecular mutations at screening must have cytogenetic and molecular mutation testing repeated.

Subjects with hematologic malignancies other than AML will undergo the appropriate clinical, radiographic, and laboratory procedures per the standard of care or institutional practice for disease assessment.

6.8.2. 30-day Follow-up

Subjects will be contacted by telephone 30 days (± 7 days) after the last dose of ENTO to assess AEs and review concomitant medications. The 30-day follow-up visit may be substituted by a scheduled study visit if it occurs within the same window.

6.8.3. Long Term Follow-up

Long term follow-up (LTFU) for OS begins after EOT or the last study visit if EOT does not occur. Subjects will be contacted by telephone or during a routine clinic visit every 6 months (± 4 weeks) to gather leukemia treatments, other malignancies, and survival for up to 3 years after EOT or the last study visit. Every attempt should be made to keep the subject in LTFU for OS.

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 AE 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
- 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) 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 may be profoundly anemic and thrombocytopenic secondary to bone marrow involvement by their AML or from the myelosuppressive effects of chemotherapy. These subjects will thus require transfusional support with red cells and platelets per institutional guidelines and therefore may require hospitalization for transfusions.

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 IMP 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 Section 7.1. If the laboratory abnormality is part of a syndrome, record the syndrome or diagnosis (eg, anemia), not the laboratory result (ie, decreased hemoglobin).

For specific information on handling of clinical laboratory abnormalities in this study, please refer to Section 7.1.3.

7.2. Assessment of Adverse Events and Serious Adverse Events

The investigator or qualified subinvestigator 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 Drugs and Procedures

The investigator or qualified subinvestigator is responsible for assessing the relationship to IMP therapy using clinical judgment and the following considerations:

- **No:** Evidence exists that the AE 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 AE 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 AE has an etiology other than the study procedure.
- **Yes:** The AE 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 (see Section 8.6.2). 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 drug initiation:

After informed consent, but prior to initiation of study medication, the following types of events should be reported on the case report form (eCRF): all SAEs and AEs 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 IMP must be reported to the eCRF database as instructed.

All AEs should be followed up until resolution or until the AE 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 eCRF database and Gilead Drug Safety and Public Health (DSPH) 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 but within 30 days of the last dose of study IMP, 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 DSPH.

- All AEs and SAEs will be recorded in the eCRF database within the timelines outlined in the 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 DSPH and Gilead Japan DSPH 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 SAE reporting form and submit within 24 hours to Gilead DSPH. Fax: PPD or email: 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 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. 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 Section 7.1. If the laboratory abnormality is part of a syndrome, record the syndrome or diagnosis (eg, anemia), not the laboratory result (ie, decreased hemoglobin).

7.6. 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. See Section 8.6.2.

7.7. Special Situations Reports

7.7.1. Definitions of Special Situations

Special situation reports include all reports of medication error, abuse, misuse, overdose, reports of AEs 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.

7.7.2. Instructions for Reporting Special Situations

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 drug follow-up period, to Gilead DSPH (Fax: PPD or email: PPD using the pregnancy report form within 24 hours of becoming aware of the pregnancy.

Refer to the eCRF completion guidelines for full instructions on the mechanism of pregnancy reporting.

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 Section 7.3. Furthermore, any SAE occurring as an adverse pregnancy outcome post study must be reported to Gilead DSPH.

The subject should receive appropriate monitoring and care until the conclusion of the pregnancy. The outcome should be reported to Gilead DSPH 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 DSPH. Gilead DSPH contact information is as follows:
Email: PPD and Fax: PPD

Pregnancies of female partners of male study subjects exposed to Gilead or other study drugs must also be reported and relevant information should be submitted to or Gilead DSPH 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 DSPH. Fax number: PPD or email: PPD

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

7.7.3. Reporting Other Special Situations

All other special situation reports must be reported on the special situations report form and forwarded to Gilead DSPH 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.

Refer to Section 7.7 and the eCRF completion guidelines for full instructions on the mechanism of special situations reporting.

All clinical sequelae in relation to these special situation reports will be reported as AEs or SAEs at the same time using the AE 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 of this study are:

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

The secondary objectives of this study are:

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

The exploratory objectives of this study are:

CCI

8.1.2. Primary Endpoints

The primary endpoints of this study are:

Safety Endpoints:

- Occurrence of AEs and laboratory abnormalities defined as DLTs for ENTO monotherapy in subjects with relapsed or refractory hematologic malignancies
- Occurrence of AEs and laboratory abnormalities defined as DLTs for ENTO in combination with cytarabine and daunorubicin in subjects with previously untreated AML who are candidates for chemotherapy

8.1.3. Secondary Endpoints

The secondary endpoints of this study are:

Safety

- Occurrence of AEs, laboratory findings and findings on physical exam not defined as DLTs

Pharmacokinetics

- Determination of the PK parameters of ENTO based on plasma concentrations

8.1.4. Other Endpoints of Interest

The exploratory endpoints of this study are:

CCI

8.2. Analysis Conventions

8.2.1. Analysis Sets

8.2.1.1. Full-Analysis Set (FAS)

Full-Analysis Set (FAS) includes all subjects who receive at least 1 dose of study drug (ENTO). This analysis set will be used in the analyses of subject characteristic, drug exposure, safety, and efficacy.

8.2.1.2. DLT Analysis Set

DLT Analysis Set includes all subjects in FAS who receive sufficient drug exposure (Section 3.2) or experience a DLT during the DLT assessment window.

8.2.1.3. Pharmacokinetic Analysis Sets

Pharmacokinetic Analysis Sets include all subjects in FAS who have necessary baseline and post-treatment assessments in order to provide interpretable results for the specific parameters of interest.

8.3. Data Handling Conventions

By-subject listings will be created for important variables from each eCRF module. Summary tables for continuous variables will contain the following statistics: N (the number of subject in group), n (the number of subjects with assessment), 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, dose level, duration of study treatment, reasons of study treatment discontinuation, and reasons of study discontinuation. Available information on subjects who are screened but are not treated may be listed separately.

Subject demographic and baseline characteristics will be listed and summarized by dose level based on Full Analysis set.

8.5. Efficacy Analysis

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

Complete Remission Rate and Composite Complete Remission Rate and other response rate variables will be described. In the analyses of Complete Remission Rate and Composite Complete Remission Rate by induction completion, subjects who do not have evaluable post-treatment assessment to characterize response will be counted as non-responder. For all analyses, the corresponding 95% exact CIs will be presented.

Time-to-Event Endpoints

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. In addition, the estimated rate at 6- month, 12-month, 2-year, and 3-year will be reported.

The following censoring rules will be applied:

RFS: For subjects who are not known to have relapsed or died by the end of the study or data cutoff, RFS is censored on the date of the last available disease assessment.

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

OS: For subjects who are not known to have died by the end of the study or data cutoff, OS is censored on the last dates on which the subjects are known to be alive.

Analysis of Complete Remission Duration and Composite Complete Remission Duration will be analyzed using cumulative incidence by considering death without relapse as competing risks. The estimate of the cumulative incidence of relapse (CIR) will be reported with the associated

95% CI. For subjects who die without report of relapse, Complete Remission Duration and Composite Complete Remission Duration are censored on the date of death, regardless of cause. For subjects with no report of relapse by the end of the study or data cutoff date, the Remissions are censored on the date of the last available disease assessment.

Continuous Endpoints

TTR will be summarized using descriptive statistics.

Categorical Endpoints

For the analysis of Proportion of bridging to SCT, subjects who do not have evaluable post-treatment assessment to characterize response will be counted as non-responder. For this analysis, the corresponding 95% exact CIs will be provided.

8.6. Safety Analysis

All safety data collected on or after the date that ENTO is first dosed up to 30 days after the permanent discontinuation of study treatment will be summarized by dose level.

8.6.1. Extent of Exposure

Descriptive information will be provided by phase and dose level regarding the number of doses of study treatment prescribed the total number of doses taken, duration of treatment, and the number 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 AEs will be listed. The AE summarization will focus on treatment-emergent AEs. Treatment-emergent AEs are defined as AEs that onset in the period from the first dose of study treatment to 30 days after the permanent discontinuation of study treatment or that lead to permanent study treatment discontinuation.

AEs that occur before the first dose of study treatment or >30 days after study treatment discontinuation will be included in data listings.

AEs will be classified using Medical Dictionary for Regulatory Activities (MedDRA) with descriptions by System Organ Class, High-Level Group Term, High Level Term, Preferred Term, and Lower-Level Term. The severity of AEs will be graded by the investigator according to the CTCAE, Version 4.03 (http://www.hrc.govt.nz/sites/default/files/CTCAE%20manual%20-%20DMCC.pdf), whenever possible. If a CTCAE criterion does not exist for a specific type of AE, the grade corresponding to the appropriate adjective will be used by the investigator to describe the maximum intensity of the AE: Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), Grade 4 (life threatening), or Grade 5 (fatal). The relationship of the AE to study treatment will be categorized as related or unrelated.

Treatment-emergent AEs will be summarized by presenting the number and percentage of subjects with treatment-emergent AEs by severity grade. Subjects who report multiple treatment-emergent AEs under the same Preferred Term (or System Organ Class) are counted only once under the worst severity grade. The summary will be presented in decreasing frequency of System Organ Class and Preferred Term of the 'Total' column. Within the same frequency, the AEs are ordered in the alphabetical order of System Organ Class and Preferred Term. Separate listings and summaries will be provided for the following types of treatment-emergent AEs:

- Study treatment related AEs
- AEs with severity ≥ Grade 3
- AEs leading to study treatment interruption and/or dose modification
- AEs leading to study treatment discontinuation
- Study treatment related SAEs
- DLT
- DLT rates and their 90% CI

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 laboratory data summarization will focus on treatment-emergent laboratory abnormalities. Treatment-emergent laboratory abnormalities are defined as abnormalities that, compared to baseline, worsens by >=1 grade in the period from the first dose of study treatment to 30 days after the permanent discontinuation of study treatment. If baseline data are missing, any graded abnormality will be considered as treatment-emergent. Laboratory abnormalities that occur before the first dose of study treatment or >30 days after the permanent discontinuation of study treatment will be included in data listings.

Hematological, serum chemistry, coagulation, and urinalysis 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 based on subjects' age, sex, etc.

Hematological, serum chemistry, coagulation assessments and their changes from baseline will be summarized by presenting the number and percentage of subjects by severity grade. For laboratory tests without CTCAE scale, the summary will present the number and percentage of subjects below, within, and above the normal ranges. Subjects will be counted only once for a given laboratory test under the worst severity grade during a period of interest (eg, during the study or from baseline to a particular visit).

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

8.7. Pharmacokinetic Analysis

Concentrations of ENTO and its metabolites (if applicable) in plasma will be determined using a validated bioanalytical assay. Calculated pharmacokinetic parameters will include AUC_{tau}, C_{max}, T_{max}, $t_{1/2}$, and C_{tau} (if applicable). Pharmacokinetic parameters will be listed and summarized for ENTO and its metabolites (if applicable) using descriptive statistics (eg, sample size, arithmetic mean, geometric mean, % coefficient of variation, standard deviation, median, minimum, and maximum). Plasma concentrations of ENTO and its metabolites (if applicable) over time will be plotted in semi logarithmic and linear formats as mean ± standard deviation.

8.8. Sample Size

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

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

8.9. Timing of Analyses

8.9.1. Interim Analyses

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

8.9.2. Final Analysis

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

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 subinvestigators 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 subinvestigator's) participation in the study. The investigator and subinvestigator 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. Independent Ethics Committee (IEC) 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). The investigator will not begin any study subject activities until approval from the IEC has been documented and provided as a letter to the investigator.

Before implementation, the investigator will submit to and receive documented approval from the IEC if any modifications are made to the protocol or any accompanying material to be provided to the subject after initial 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 IEC-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 byIEC or local requirements.

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, IEC, 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, 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 two 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, IEC 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 AEs 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. The Eligibility Criteria eCRF should be completed only after all data related to eligibility have been received. 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 IEC, 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 IEC in accordance with local requirements and receive documented IEC 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 eCRF.

The monitor is responsible for routine review of the 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 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

Both the sponsor and the investigator reserve the right to terminate the study at any time. Should this be necessary, both parties 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.

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11. APPENDICES

Appendix 1. Investigator Signature Page

GILEAD SCIENCES, INC.
333 LAKESIDE DRIVE
FOSTER CITY, CA 94404

STUDY ACKNOWLEDGEMENT

A Phase 1b Study to Investigate the Safety, Tolerability, and Pharmacokinetics of Entospletinib (ENTO) as Monotherapy in Japanese Subjects with Relapsed or Refractory Hematologic Malignancies and in Combination with Chemotherapy in Japanese Subjects with Previously Untreated Acute Myeloid Leukemia (AML)

GS-US-429-4104, Amendment 3, 23 August 2017

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

PPD

Medical Monitor

PPD

Signature

23 AUG 2017

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 Table: Group A (ENTO Monotherapy)

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

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

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

Appendix 3. Study Procedures Table: Group B (ENTO + cytarabine + daunorubicin)

Study Phase	Screening	Lead-in Cycle 0			Induction Cycle 1 (if needed Cycle 2)						Post-remission chemotherapy (up to Cycle 4)				Relapse	End of Treatment (EOT)	30-day Follow-up	Long Term Follow-up
Study Day	**Screening**	**1**	**8**	**14**	**1**	**3**	**7**	**14**	**15 to count recovery**	**28**	**1**	**3**	**5**	**28**	**NA**	**NA**	**NA**	**NA**
Window (day)	**-14**	**NA**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**NA**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±7**	**±7**	**± 4 weeks**
General and Safety Assessments																		
Informed Consent	X																	
Medical & Medication History	X																	
Adverse Events/ Concomitant Medications	X	X	X	X	X	X	X	X		X	X	X	X	X		X	X	
Smoking status[a]	X	X			X						X							
Physical Exam[b]	X	X			X						X					X		
Vital Signs[c]	X	X	X	X	X	X	X				X					X		
Height and Weight[d]	X				X						X					X		
ECG[e]	X																	
ECHO/MUGA[f]	X							X		X								
Performance Status[g]	X	X						X		X				X		X		
Overall survival, leukemia treatments, and other malignancies																		X (every 6 months)
Chest X-ray	X																	
Study Treatment																		
ENTO Administration[h,i,]		X	X	X	X	X	X	X		X	X	X	X	X				
IV daunorubicin[j]					X	X												
IV cytarabine[h,i,]					X	X	X				X	X	X					

Study Phase	Screening	Lead-in Cycle 0			Induction Cycle 1 (if needed Cycle 2)						Post-remission chemotherapy (up to Cycle 4)				Relapse	End of Treatment (EOT)	30-day Follow-up	Long Term Follow-up
Study Day	**Screening**	**1**	**8**	**14**	**1**	**3**	**7**	**14**	**15 to count recovery**	**28**	**1**	**3**	**5**	**28**	**NA**	**NA**	**NA**	**NA**
Window (day)	**-14**	**NA**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**NA**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±7**	**±7**	**± 4 weeks**
Laboratory Assessments																		
Chemistry[j,k]	X	X	X	X			X	X		X				X		X		
Hematology[k, r]	X	X	X	X			X	X	X	X				X	X	X		
Coagulation[k]	X			X			X	X		X				X		X		
Urinalysis	X																	
Serum Pregnancy Test and FSH[l]	X																	
Urine Pregnancy Test[m]		X			X						X					X		
HIV/HBV/HCV	X																	
Sparse PK[n]		X		X		X		X		X			X	X				
Intensive PK[o]			X				X											
Bone Marrow Assessments																		
Biopsy[p]	X			X				X		X					X	X		
Aspirate[q]	X			X				X		X				X	X	X		

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 chemotherapy, a physical exam is to be completed on Cycle 1 Day 1 and Cycle 3 Day 1.
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.
d Height and weight will be measured at screening. Only weight will be measured on Day 1 of each induction cycle, Day 1 of each post-remission chemotherapy cycle, and at EOT.
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 if applicable, prior to starting induction Cycle 2 (on Cycle 1 Day 14 or 28).
g During post-remission chemotherapy, performance status to be completed on Cycle 2 Day 28 and Cycle 4 Day 28.
h ENTO will be administered BID 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 28-day cycle (Cycle 1 and up to Cycle 2). Subjects are to continue receiving ENTO BID as they are awaiting disease assessment results.

i During post-remission chemotherapy, subjects will receive 2-4 cycles of 3g/m^2 HiDAC administered every 12 hours on Days 1, 3, and 5 (≤ 60 years of age) or 1g/m^2 HiDAC administered once daily on Days 1-5 (> 60 years of age) in combination with ENTO BID on Days 1-28.
j Include Total CPK at screening, Day 14 of induction Cycle 1 (and Cycle 2, if applicable), Day 28 of post-remission chemotherapy Cycles 1 and 3, and EOT.
k During post-remission chemotherapy, collect Chemistry, Hematology, and Coagulation on Day 28 of Cycles 1 and 3 only.
l A negative serum pregnancy test is required for female subjects (unless surgically sterile or post-menopausal). Female subjects with medically documented ovarian failure must also have serum FSH levels within the institutional post-menopausal range.
m For females of childbearing potential, urine pregnancy tests will be done on Day 1 of each cycle and at EOT.
n Peripheral blood samples for sparse PK will be collected at pre-dose and 2hrs post-dose of ENTO on Cycle 0 Days 1 and 14, Days 14 and 28 of each induction cycle, and Days 5 and 28 of each post-remission chemotherapy cycle. Sparse PK will also be collected at pre-dose, 2, and 4 hours post-dose of ENTO on Day 3 of each induction cycle.
o Peripheral blood samples for intensive PK will be collected on Cycle 0 Day 8 and induction Cycle 1 Day 7 at 0 (pre-dose), 1, 2, 3, 4, 6, 8, and 12 hours post-dose of ENTO.
p A bone marrow biopsy will be performed at screening (within 21 days before the first administration of study treatment), Cycle 0 Day 14, Day 14 of each induction cycle (if hypocellular on Day 14, must repeat on Day 28 or within 21 days as blood counts recover prior to proceeding to post-remission chemotherapy or SCT), relapse, and EOT (if not performed within the last 2 weeks) for disease assessment. Subjects with cytogenetic and molecular mutations at screening must have cytogenetic and molecular mutation testing repeated at Cycle 0 Day 14, Cycle 1 Day 14 (or at count recovery), relapse, and EOT.
q A bone marrow aspirate (~8mL) will also be collected for disease assessment at the bone marrow biopsy time-points noted above as well as post-remission chemotherapy 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.
r For subjects without evidence of residual leukemia on Day 14 of induction chemotherapy, local hematology (complete blood count) to be collected daily from Day 15 of induction chemotherapy until complete blood count demonstrates recovery.

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 $\geq$ 54 years of age with cessation of previously occurring menses for $\geq$ 12 months without an alternative cause. In addition, women of any age with amenorrhea of $\geq$ 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 and are without an alternative medical cause for amenorrhea.

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 a malformation effect is unknown, taking into consideration class effects, genotoxic potential, or a strong suspicion of human teratogenicity/fetotoxicity in early pregnancy based on non-clinical data. ENTO has insufficient data to exclude the possibility of a clinically relevant interaction with hormonal contraception that results in reduced contraception efficacy. 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 have a negative serum pregnancy test at Screening and a negative urine pregnancy test on the Baseline/Day 1 visit prior to enrollment. Pregnancy tests will be performed at monthly intervals thereafter. Female subjects must agree to one of the following methods from Screening until 30 days (Group A ENTO monotherapy) or 6 months (Group B ENTO + cytarabine + daunorubicin) following the end of relevant systemic exposure.

Individual Methods	Combination Methods	
	Hormone Methods (choose one and use with a barrier method)	**Barrier Methods (use both OR choose one and use with a hormone method)**
Intrauterine Devices (IUDs) • Copper T 380A IUD*,** • LNg 20 IUD*, *** **Tubal Sterilization***	**Estrogen and Progesterone** • Oral contraceptives* • Transdermal patch • Vaginal ring **Progesterone** • Injection • Implant*	• Diaphragm with spermicide* OR Cervical cap with spermicide • Male condom (with* or without spermicide*)
	Partner's vasectomy must be used with a hormone or barrier method.	

Abbreviation: IUD = intrauterine device
* Approved in Japan
** Sold in Japan as Copper T 380 IUD
*** Sold in Japan as Minera 52mg

Female subjects must also refrain from egg donation and in vitro fertilization during treatment and until at least 30 days (Group A) or 6 months (Group B) after the end of relevant systemic exposure.

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 (Group A) or 6 months (Group B) after the end of relevant systemic exposure. 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 (Group A) or 6 months (Group B) after the end of relevant systemic exposure.

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 (Group A) or 6 months (Group B) 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 7.7.

Appendix 5. 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
Severely 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 6. Modified International Working Group Criteria for AML

Assessment of clinical response in Group B 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 (i.e. Cycle 1 Day 14)
- Guides subsequent treatment (eg, need for or timing of second induction course)

Morphologic Complete Remission (CR)

CR requires all of the following:

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

Cytogenetic Complete Remission (CRc)

CRc requires all of the following:

- < 5% blasts in bone marrow aspirate
- Neutrophils ≥ 1,000/UL
- Platelets ≥ 100,000/UL
- No extramedullary disease
- No blasts with Auer rods detected
- Reversion to a normal karyotype with an abnormal karytype 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/uL or Platelets < 100,000/uL
- No extramedullary disease
- No blasts with Auer rods detected

Partial Remission (PR)

PR requires all of the following:

- ≥ 50% decrease in blasts in bone marrow aspirate to a range of 5-25%
- Neutrophils ≥ 500/uL
- Platelets ≥ 50,000/uL

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. Subjects who survive ≥ 7 days following completion of initial treatment, with evidence of persistent leukemia by blood and/or bone marrow examination.
- Death in Aplasia: Subjects who survive ≥ 7 days following completion of initial treatment, but dies while cytopenic, with an aplastic or hypoplastic marrow obtained within 7 days of death, without evidence of persistent leukemia
- Death from Indeterminate cause: Subjects who die before completion of treatment or < 7 days following completion of initial treatment; subjects who die ≥ 7 days following completion of initial treatment with no peripheral blood blasts, but no bone marrow examination is available; subjects 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.