Protocol Number: KB-ENTO-3001

Official Title: A Phase 3, Randomized, Double-blind, Placebo-controlled Study to Assess the Efficacy and Safety of Entospletinib in Combination with Intensive Induction and Consolidation Chemotherapy in Adults with Newly Diagnosed Nucleophosmin 1-mutated Acute Myeloid Leukemia

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STATISTICAL ANALYSIS PLAN

A Phase 3, Randomized, Double-blind, Placebo-controlled Study to Assess the Efficacy and Safety of Entospletinib in Combination with Intensive Induction and Consolidation Chemotherapy in Adults with Newly Diagnosed *Nucleophosmin 1*-mutated Acute Myeloid Leukemia

Compound:	Entospletinib (ENTO, formerly known as GS-9973)
Trial Phase:	3
Protocol Number:	KB-ENTO-3001
Protocol Version and Date:	Original Version: 09 April 2021 Version 2: 06 July 2021 Version 2.1: 24 November 2021 (Germany Only) Version 3: 27 January 2022 Version 4: 10 February 2022
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Prepared By:	[redacted] PharPoint Research, Inc. (PharPoint) 1001 Military Cutoff, Suite 301 Wilmington, NC 28405
Prepared For:	Kronos Bio 1300 So. El Camino Real Suite 400 San Mateo, CA 94402

STATISTICAL ANALYSIS PLAN REVIEW AND APPROVAL

This Statistical Analysis Plan has been prepared in accordance with team reviewers' specifications.

Prepared by:

[redacted]
Biostatistician II
PharPoint

Review:

[redacted]
Chief Scientific Officer
PharPoint

[redacted]
Chief Medical Officer
Kronos Bio

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1. GLOSSARY OF ABBREVIATIONS

Abbreviation/Term	Definition
ADL	activities of daily living
AE	adverse event
ALT	alanine aminotransferase
AML	acute myeloid leukemia
ANC	absolute neutrophil count
AST	aspartate aminotransferase
ATC	anatomical therapeutic chemical
β-HCG	beta human chorionic gonadotropin
BID	twice daily
BUN	blood urea nitrogen
C1D1	Cycle 1 Day 1
CBC	complete blood count
CMML	chronic myelomonocytic leukemia
CPK	creatine phosphokinase
CR	complete response
CRh	complete response with hematologic improvement
CRi	complete response with incomplete blood count recovery
CRF	case report form
CSR	clinical study report
DIC	disseminated intravascular coagulation
DMC	data monitoring committee
ECG	electrocardiogram
ECHO	echocardiogram
ECOG PS	Eastern Cooperative Oncology Group Performance Status
eCRF	electronic case report form
EFS	event free survival
ELN	European LeukemiaNet

Abbreviation/Term	Definition
ENTO	Entospletinib
EORTC-QLQ 30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30
EQ-5D-5L	European Quality of Life 5 Dimensions Questionnaire
FISH	fluorescense in situ hybridization
FLT-3	FMS-like tyrosine kinase 3
FSH	follicle stimulating hormone
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HOXA9	homeobox protein
HSCT	hematopoietic stem cell transplant
IDH	isocitrate dehydrogenase
ITD	internal tandem duplication
ITT	intent to treat
IV	intravenous
IWG	International Working Group
IxRS	interactive voice/web response system
LDH	lactate dehydrogenase
LFT	liver function studies
LLN	lower limit of normal
MedDRA	Medical Dictionary for Regulatory Activities
MEIS1	homeobox protein
MFLS	morphologic-free leukemia state
mg	milligrams
mg/m^2	milligrams per meter squared
MRD	measurable residual disease
MUGA	multiple gated acquisition

Abbreviation/Term	Definition
n	number of subjects
N/A	not available
NCI-CTCAE	National Cancer Institute Common Toxicity Criteria for Adverse Events
NPM1	*Nucleophosmin-1*
OS	overall survival
pSYK	phosphorylated spleen tyrosine kinase
PD	progressive disease
PK	pharmacokinetics
PR	partial response
PT	preferred term
QLQ	Quality of Life Questionnaire
SD	stable disease
SOC	system organ class
STD	standard deviation
SUSAR	suspected, unexpected, serious adverse event
SYK	spleen tyrosine kinase
TEAE	treatment-emergent adverse event
TELT	treatment-emergent laboratory toxicity
TESAE	treatment-emergent serious adverse event
TKD	tyrosine kinase domain
ULN	upper limit of normal
WBC	white blood cell
WHO	World Health Organization

2. INTRODUCTION

This document describes the statistical methods and data presentations to be used in the summary of planned analyses of efficacy and safety data from Protocol KB-ENTO-3001. Background information is provided for the overall study design and objectives based on the current version of the protocol. In November 2022, the sponsor terminated this study prior to full enrollment for business reasons. This SAP is intended to describe the study design of the planned study and the analytic methods necessary to generate the safety analyses for the abbreviated Clinical Study Report (CSR). The reader is referred to the study protocol and case report forms (CRFs) for details of study conduct and data collection, the pharmacokinetics (PK) and pharmacodynamics (PD) analysis plan for the description of exploratory PK/PD analyses, and to the Data Monitoring Committee (DMC) charter for the roles and the responsibilities for that committee.

2.1. Study Overview

This is a Phase 3, multi-center, international, double-blind, placebo-controlled study in previously untreated subjects with Acute Myeloid Leukemia (AML) harboring *nucleophosmin-1* (*NPM1*) mutations. Subjects will be randomized 1:1 to receive intensive induction chemotherapy in combination with either the spleen tyrosine kinase (SYK) inhibitor, entospletinib (ENTO), or placebo. Randomization will be stratified by age (<60 or ≥60 years) and anthracycline administered during induction (daunorubicin vs idarubicin). The study will consist of Screening, Induction, Consolidation, End-of-Treatment, and Long-term Follow-up phases.

ENTO (400 mg) or placebo will be administered continuously twice daily (BID) approximately every 12 hours beginning on Cycle 1 Day 1 of induction chemotherapy (**Table 1**) through completion of consolidation (**Table 2**), including while awaiting blood count recovery.

Subjects will undergo bone marrow examination no later than Day 42 of Induction Cycle 1 for assessment of response. Subjects with ≥5% residual leukemic blasts in bone marrow will receive Induction Cycle 2 as outlined in Table 1, which may be administered prior to blood count recovery. Subjects with <5% residual blasts will receive Consolidation Cycle 1 as outlined in Table 2 upon recovery of peripheral blood counts (absolute neutrophil count [ANC] > 1.0 x 10^9/L; platelet count > 100 x 10^9/L).

After completion of Induction Cycle 2 or Consolidation Cycle 1 (hereafter referred to collectively as Chemotherapy Cycle 2), subjects will undergo bone marrow aspiration for assessment of remission status at the investigative site. Bone marrow examination should await recovery of ANC to at least 1.0 x 10^9/L and platelet count to at least 100 x 10^9/L on or before but no later than Day 42 of Chemotherapy Cycle 2 unless leukemic progression is suspected. Subjects who achieve or remain in morphologic complete response (CR) after Chemotherapy Cycle 2 will undergo measurable residual disease (MRD) assessment in peripheral blood and bone marrow aspirate. Subjects who have not achieved morphologic CR last cycle of induction chemotherapy (no later than Day 42 of the last cycle of induction) will be considered treatment failures. *****For subjects with < 5% residual blasts post-Induction Cycle 1, Consolidation Cycle 1 will consist of Chemotherapy Cycle 2. For patients with ≥5% residual blasts post-Induction Cycle 1, Induction Cycle 2 (Table 1) will consist of

Chemotherapy Cycle 2 with consolidation beginning thereafter. All subjects are eligible to receive up to 3 cycles of high dose cytarabine after Chemotherapy Cycle 2.
Figure 1 provides a schematic representation of the study treatment plan from Cycle 1 Day 1 through completion of Chemotherapy Cycle 2

Table 1: Induction Chemotherapy

	Age < 60 years	**Age ≥ 60 years**
Cycle 1:		
Cytarabine[a]	100 mg/m^2 by continuous infusion, Days 1-7	100 mg/m^2 by continuous infusion, Days 1-7
Anthracycline	Daunorubicin, 60 mg/m^2 slow IV push, Days 1-3 ***OR*** Idarubicin, 12 mg/m^2 slow IV push, Days 1-3	Daunorubicin, 60 mg/m^2 by slow IV push, Days 1-3 ***OR*** Idarubicin, 12 mg/m^2 slow IV push, Days 1-3
Cycle 2:		
Cytarabine	1.0 g/m^2, BID Days 1-6	1.0 g/m^2, BID Days 1-6
Anthracycline	Daunorubicin, 60 mg/m^2 slow IV push, Days 1-3 ***OR*** Idarubicin, 12 mg/m^2 slow IV push, Days 1-3	N/A

Abbreviations: BID, twice daily; IV, intravenous; N/A, not administered.

[a] Subjects who are candidates for continuous infusion of cytarabine in Cycle 1 at doses higher than 100 mg/m^2/day are ineligible.

Subjects who achieve MRD negative CR status post-induction will undergo retrospective MRD assessments in peripheral blood every 3 months until morphologic relapse.

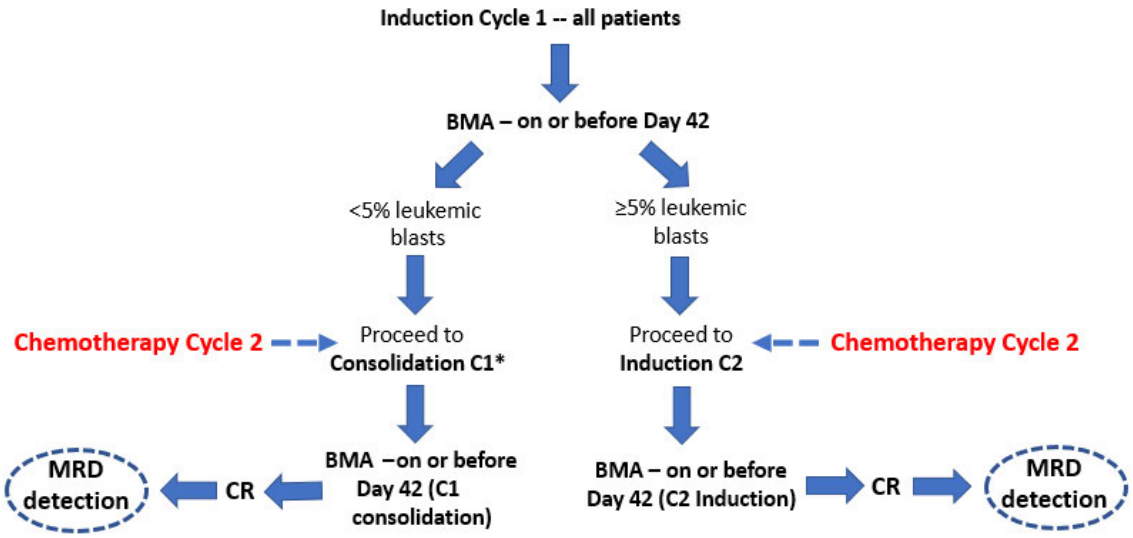
All subjects who achieve morphologic CR, complete response with hematologic improvement (CRh), or complete response with incomplete blood count recovery (CRi) upon completion of Chemotherapy Cycle 2 may initiate or continue consolidation therapy in combination with ENTO or placebo as outlined in Table 2 at the investigator's discretion either instead of or as a bridge to hematopoietic stem cell transplant (HSCT).

Table 2: Treatment Phase - Consolidation

	Age < 60 years	Age ≥ 60 years
Cytarabine	3.0 g/m^2, BID over 3 hours on Days 1, 3 and 5 every 28-35 days for up to 3 cycles*	1.5 g/m^2, BID over 3 hours on Days 1, 3 and 5 every 28-35 days for up to 3 cycles*

*For subjects with < 5% residual blasts post-Induction Cycle 1, Consolidation Cycle 1 will consist of Chemotherapy Cycle 2. For patients with ≥5% residual blasts post-Induction Cycle 1, Induction Cycle 2 (Table 1) will consist of Chemotherapy Cycle 2 with consolidation beginning thereafter. All subjects are eligible to receive up to 3 cycles of high dose cytarabine after Chemotherapy Cycle 2.

Figure 1: Treatment Phase- Cycle 1, Day 1 through Completion of Chemotherapy Cycle 2:



* Following recovery of ANC to >1.0 x 10^9 /L and platelet count to >100 x 10^9/L
BMA, bone marrow aspirate; MRD, measurable residual disease

Following completion of consolidation chemotherapy, all subjects will undergo an End-of-Study Treatment Visit 30 ± 7 days after the last study treatment (either ENTO/placebo or cytarabine, whichever is later) or prior to initiation of follow-on therapy (e.g., maintenance therapy, HSCT) if sooner than 30 ± 7 days after last study treatment.

All subjects regardless of their post-remission status will be followed monthly for 3 months after the End-of-Treatment Visit and thereafter at least once every 3 months for progression/relapse, first salvage therapy, and survival until study termination. Unscheduled study visits at other time points

are permitted in the setting of suspected leukemic recurrence or for evaluation and management of post-treatment sequelae.

2.2. Schedule of Assessments

Study Phase	**Screening**	**Induction (up to 2 Cycles)***					**At Recovery of Blood Counts/Assessment of Remission Status (Post-Induction Cycle 1, Post-Chemotherapy Cycle 2)/ At Relapse**	**Consolidation (up to 3 Cycles)***				**End-of-Study Treatment**	**Long-Term Follow-up** [x]
Study Visit Day [a]	-14 to 0	1	3	7	14	15 until blood count recovery		1	3	5	28 to 35	30 ± 7 days after last study treatment	
Informed consent	X												
IxRS registration/ randomization	X												
Medical/smoking history/ prior medications/AML baseline characteristics [b]	X												
Safety assessments													
Vital signs [c]	X	X	X	X	X			X	X	X	X	X	
Physical examination [d]	X	X			X		X	X			X	X	
Height/weight [e]	X				X			X				X	
ECG [f]	X												
ECHO/MUGA [g]	X											X	
ECOG PS	X	X			X						X	X	
AEs/concomitant medications [h]	X	X	X	X	X			X	X	X	X	X	
Hematology [i]	X	X	X	X	X	X	X	X			X	X	
Clinical chemistries/ LFTs [j]	X	X	X	X	X		X	X			X	X	

Study Phase	**Screening**	**Induction (up to 2 Cycles)***					**At Recovery of Blood Counts/Assessment of Remission Status (Post-Induction Cycle 1, Post-Chemotherapy Cycle 2)/ At Relapse**	**Consolidation (up to 3 Cycles)***				**End-of-Study Treatment**	**Long-Term Follow-up** [x]
Study Visit Day [a]	-14 to 0	1	3	7	14	15 until blood count recovery		1	3	5	28 to 35	30 ± 7 days after last study treatment	
Coagulation [k]	X	X	X	X	X								
Urinalysis [l]	X												
ß-HCG/FSH [m]	X	X						X				X	
HBV/HCV/HIV serologies [n]	X												
Induction therapy													
Study medication (ENTO/Placebo) [o]		→	→	→	→	→	X						
Cytarabine		→	→	→									
Daunorubicin or Idarubicin		→	→										
Consolidation therapy													
Study medication (ENTO/Placebo) [p]								→	→	→	→		
Age-adjusted high dose cytarabine								→	→	→			
Bone marrow evaluations													
Aspirate [q]	X						X						
NPM1-m MRD assessments [r]	X						X					X	X
Pharmacokinetics [s]		X		X	X			X			X		

Study Phase	**Screening**	**Induction (up to 2 Cycles)***					**At Recovery of Blood Counts/Assessment of Remission Status (Post-Induction Cycle 1, Post-Chemotherapy Cycle 2)/ At Relapse**	**Consolidation (up to 3 Cycles)***				**End-of-Study Treatment**	**Long-Term Follow-up** [x]
Study Visit Day [a]	-14 to 0	1	3	7	14	15 until blood count recovery		1	3	5	28 to 35	30 ± 7 days after last study treatment	
Peripheral blood biomarker assessments [t]	X	X		X	X		X	X			X	X	
Bone marrow aspirate biomarker assessments [u]	X						X						
Pharmacogenomics (whole blood) [v]	X												
Patient reported outcomes [w]	X						X					X	X
Follow-up for relapse, first salvage therapy, OS [x]													X

Abbreviations: AEs, adverse events; AML, acute myeloid leukemia; β-HCG, beta human chorionic gonadotropin; ECG, electrocardiogram; ECHO, echocardiogram; ECOG PS, Eastern Cooperative Oncology Group Performance Status; FSH, follicle stimulating hormone; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; LFTs, liver function studies; MUGA, multi-gated acquisition; *NPM1*-m, *Nucleophosmin 1*-mutated; MRD, measurable residual disease; OS, overall survival.

***** Subjects with ≥5% residual leukemic blasts in bone marrow aspirate performed no later than Day 42 of Induction Cycle 1 will receive Induction Cycle 2 as outlined in Table 1, which may be administered prior to blood count recovery. Subjects with <5% leukemic blasts will proceed to Consolidation Cycle 1 (Table 2) upon recovery of peripheral blood counts (ANC ≥ 1.0 x 10^9/L; platelet count ≥ 50 x 10^9/L). After completion of Induction Cycle 2 or Consolidation Cycle 1 (i.e., Chemotherapy Cycle 2), subjects will undergo bone marrow examination for assessment of remission status at the investigative site. Patients in morphologic CR post-Chemotherapy Cycle 2 will undergo MRD assessment (see footnote "r" below).

[a] Acceptable windows for study visits/assessments after Cycle 1 Day 1 (C1D1) are ± 1 day; however, study treatment must be administered on the days indicated (e.g., Days 1-7 for cytarabine, and Days 1-3 for daunorubicin or idarubicin in Induction Cycle 1).

[b] The following details minimally, regarding the diagnosis of AML will be collected and recorded on the electronic case report form (eCRF): age and date of diagnosis (month, day, year); AML subtype (*de novo*; AML with myelodysplasia-related changes; therapy associated AML); history of myelodysplastic or myeloproliferative (e.g., chronic myelomonocytic leukemia [CMML] syndrome; history of prior exposure to leukemogenic agents (e.g. alkylating agents, topoisomerase II inhibitors); cytogenetic abnormalities identified by conventional cytogenetic testing and/or fluorescence in situ hybridization (FISH); complete blood count (CBC) with differential; percent blasts (peripheral blood and bone marrow); *NPM1* mutation subtype (A, B, D, other); FMS-like tyrosine kinase 3 (*FLT-3)* mutational status (wild-type; internal tandem duplication [ITD] mutation, tyrosine kinase domain [TKD] mutation, or both).

[c] Vital signs include measurement of blood pressure, respiratory rate, pulse, temperature, and oxygen saturation level by pulse oximetry. After discharge from hospital, assess vital signs at each of the designated time points.

[d] Perform a complete physical examination including neurological exam at Screening. After discharge from the hospital, a targeted physical exam may be performed at each of the designated time points. Subjects ≥60 years old receiving intermediate dose cytarabine or those with impaired renal function are at risk for cerebellar toxicity. Monitor for the occurrence of nystagmus, slurred speech, or dysmetria on each day of cytarabine dosing during Induction Cycle 2 and consolidation. Follow dose modification guidelines outlined in Section 6.5.2 of the protocol or in accordance with institutional care standards in the setting of neurotoxicity.

[e] Height and weight will be measured at Screening. Only weight will be measured thereafter at designated time points.

[f] ECG is required at Screening and thereafter as clinically indicated during treatment.

[g] An echocardiogram (ECHO) or multi-gated acquisition (MUGA) scan must be performed at Screening and at the End-of-Treatment Visit. Consider repeating ECHO or MUGA within 48 hours prior to Induction Cycle 2 for subjects receiving anthracycline in Cycle 2 and at increased risk for cardiac toxicity.

[h] Record all adverse events and concomitant medications through 30 ± 7 days after treatment completion. Thereafter, record only serious adverse events assessed as study medication related.

[i] Includes hemoglobin, hematocrit, white blood cell (WBC) and platelet counts, and WBC differential (neutrophils, bands, lymphocytes, monocytes, eosinophils, basophils, blasts). At times not designated in Table 7, monitor CBC and WBC differential in accordance with institutional care standards until ANC is $\geq 1.0 \times 10^9$/L or persistent leukemia is documented. Monitor platelet counts at times designated in Table 7 and at other times, per institutional care standards until the platelet count is $\geq 100 \times 10^9$/L or persistent leukemia is documented. Monitor CBC and platelet count twice weekly during consolidation and at other times, as clinically indicated.

[j] Includes electrolytes (sodium, potassium, chloride, total CO_2 and/or bicarbonate, calcium, phosphate), liver function studies (aspartate aminotransferase [AST], alanine aminotransferase [ALT], total and direct bilirubin), lactate dehydrogenase (LDH), alkaline phosphatase, blood urea nitrogen [BUN] or serum urea, creatinine, uric acid, glucose, amylase, and lipase. Include total creatine phosphokinase (CPK) at Screening, Day 14 of each induction cycle, and End of Study Treatment. At times not designated in Table 7, monitor electrolytes, LFTs, BUN, creatinine, uric acid, and phosphate in accordance with institutional care standards until the risk of tumor lysis syndrome has abated. For subjects receiving nephrotoxic antimicrobial agents, closer monitoring of renal function throughout the period of hospitalization is recommended, consistent with institutional standards of care.

[k] Includes prothrombin time, activated partial thromboplastin time and international normalized ratio. Perform coagulation panel twice per week during Induction. For subjects with evidence of disseminated intravascular coagulation (DIC), coagulation parameters including fibrinogen should be monitored in accordance with institutional care standards until resolution**.**

[l] Includes dipstick evaluation for pH, glucose, protein, blood, leukocyte esterase and microscopic evaluation for red and white blood cells. After Screening, perform urinalysis as clinically indicated.

[m] A negative serum pregnancy test is required for female subjects (unless surgically sterile or postmenopausal) at Screening. Female subjects with medically documented ovarian failure must also have serum follicle stimulating hormone (FSH) levels within the institutional postmenopausal range at Screening. A urine pregnancy test will be performed for all females (unless surgically sterile or postmenopausal) on Day 1 of each cycle of induction and consolidation and at the End-of-Treatment Evaluation.

[n] HBV/HCV/HIV serology tests include hepatitis B surface antigen (HBsAg), anti-HBs, anti-HBc, anti-HCV, and anti-HIV.[o] Study medication will be administered orally every 12 hours during Induction Cycles 1 and Induction Cycle 2, if administered (see Table 1)

). Subjects are to continue receiving study medication while awaiting blood count recovery and response assessment results.

[p] Subjects who achieve CR, CRh or CRi post-Chemotherapy Cycle 2 may receive **consolidation** chemotherapy in combination with study medication (see Table 2**)**. Subjects are to continue receiving study medication while awaiting blood count recovery. The number of cycles of consolidation (up to 3) will be at the investigator's discretion.

[q] A bone marrow aspirate will be performed at Screening (within 14 days before the first administration of study treatment) for confirmation of diagnosis, morphology (spicule prep), cytogenetics/FISH and *NPM1* and *FLT-3* mutational status. **In cases in which an adequate bone marrow aspirate cannot be obtained at Screening (eg, due to dry tap, hypocellularity or hemodilution), a trephine bone marrow biopsy is mandated**. Bone marrow aspirates are required in Induction Cycle 1 (up to but no later than Day 42) and again post-Chemotherapy Cycle 2 (no later than Day 42) to assess remission status. Thereafter, perform bone marrow examination for confirmation of suspected leukemic relapse.

[r] *NPM1*-m allelic frequency will be assessed in peripheral blood and bone marrow aspirate in a central laboratory at the following time points: Screening; post-Chemotherapy Cycle 2 for subjects in CR (no later than Day 42, **for MRD assessment**); and at the End of Study Treatment visit (***peripheral blood only***). MRD will be assessed retrospectively on peripheral blood in subjects who achieve MRD negative CR post-Chemotherapy Cycle 2, every 3 months during long term follow-up until morphologic relapse.

[s] Blood sampling for pharmacokinetic assessments will be performed at the following time points: **Cycle 1 (Induction):** Day 1 between 2- and 4-hours post-study medication dose, Day 7 predose only, Day 14 predose and between 2- and 4-hours post-study medication dose; **Cycle 3 (Consolidation):** Day 1 predose and between 2- and 4-hours post-study medication dose, Day 28-35 predose and between 2- and 4-hours post-study medication dose. All predose samples must be obtained within 60 minutes before the first daily dose of study medication (Protocol Section 8.7).

[t] Blood samples for biomarker assessments including (but not limited to) other somatic mutations will be obtained at Screening; **Cycle 1 (Induction)**, Day 1 (predose and 2 hours post-dose), Day 7 and Day 14 (predose only) prior to the first daily dose of study medication; **Cycle 3 (Consolidation)** Day 1 (predose) and Day 28-35 (predose); at time of post-Chemotherapy Cycle 2; relapse; and End of Study Treatment. See Protocol Section 8.9 for a description of planned biomarker assessments.

[u] Bone marrow aspirate samples for biomarker assessments including (but not limited to) other somatic mutations will be obtained at Screening; post-Chemotherapy Cycle 2; and at relapse.

[v] Whole blood will be collected during Screening for evaluation of CYP2C9 and cytidine deaminase polymorphisms. Examinations of other germline genes implicated in leukemogenesis may be conducted for comparison with corresponding genes in the leukemic clone. See Protocol Section 8.9 for additional details.

[w] Includes the European Quality of Life 5 Dimensions Questionnaire (EQ-5D-5L) and the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC-QLQ 30).

[x] All subjects regardless of post-remission status will be followed monthly for 3 months after the End-of-Treatment Visit and thereafter at least once every 3 months for progression/relapse, first salvage therapy, and overall survival until study termination.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To evaluate the efficacy of ENTO compared to placebo when added to chemotherapy in previously untreated *NPM1*-m AML, as defined by the rate of molecularly defined MRD.	• MRD negative CR rates after completion of 2 cycles of chemotherapy plus either ENTO or placebo. *Note:* MRD negative CR requires CR as defined by the European Leukemia Network (ELN) 2017 criteria (with minor modification for neutrophil and platelet count thresholds as defined by International Working Group [IWG]) as assessed by study site investigators, and MRD negativity (<0.01%) in bone marrow as measured by a molecular *NPM1*-m assay (e.g., by next generation sequencing) in a central laboratory upon recovery of peripheral blood counts following completion of 2 cycles of chemotherapy (i.e., no later than Day 42 of Cycle 2).
Secondary	
• To evaluate the efficacy of ENTO compared to placebo when added to chemotherapy in previously untreated *NPM1*-m AML, as defined by relapse-free, event-free, and overall survival.	• Event-free survival, defined as the time from randomization to the earliest occurrence of induction treatment failure, relapse from CR, or death from any cause. *Note:* Induction treatment failure is failure to achieve morphological CR after completion of the last cycle of induction chemotherapy (no later than Day 42 of the last cycle of induction). • Relapse-free survival, defined as the time from CR until relapse or death from any cause as assessed by study site investigators.

	• Overall survival defined as the time from enrollment until death from any cause.
• To evaluate the efficacy of ENTO compared to placebo when added to chemotherapy in previously untreated *NPM1*-m as defined by CR rate.	• CR rates after 2 cycles of chemotherapy, as defined by ELN 2017 criteria (with minor modification for neutrophil and platelet count thresholds as defined by IWG) as assessed by study site investigators.
• To evaluate the safety of ENTO compared to placebo when added to intensive chemotherapy.	• Type, incidence, severity, and outcome of adverse events; changes from baseline in safety laboratory assessments, ECGs, ECHO/MUGA scans, ECOG PS.
Exploratory	
• To explore the predictive value of potential biomarkers that correlate with differential outcomes (CR, MRD negativity, event-free and overall survival) among ENTO- vs placebo-treated subjects.	• Baseline expression levels of homeobox protein (*HOXA9/MEIS1)* and other relevant genes in leukemic cells from peripheral blood and bone marrow aspirate using standard expression profiling platforms (e.g., Nanostring® or next-generation sequencing) for correlations with response and progression. • Mutational profiling in leukemic cells using standard platforms like next generation sequencing for correlations with response and progression. • Targeted protein/phosphoprotein profiling (e.g., phosphorylated spleen tyrosine kinase (pSYK) expression) in leukemic cells at baseline for correlations with response and progression. • Extent of ENTO target engagement as measured by pSYK expression/expression of other relevant genes for correlation with response and progression. • Level of concordance for MRD for *NPM1*-m in leukemic cells derived from bone marrow aspirate and peripheral blood. • Log reduction in *NPM1*-m alleles in bone marrow post-induction compared with baseline for correlation with response and progression.
• To assess the value of MRD detection as a prognosticator of relapse.	• Longitudinal assessment of peripheral blood for detection of *NPM1*-m alleles among subjects who achieve MRD-negative CR post-Chemotherapy Cycle 2 using standard

	molecular platforms (eg, next-generation sequencing) for correlation with morphologic relapse.
• To further assess the PK of ENTO in combination with intensive induction therapy for population PK modeling. • To explore the relationship between CYP2C9 genetic polymorphisms and ENTO exposure. • To assess the relationship (if any) between cytidine deaminase polymorphisms and safety and efficacy outcomes.	• Population-based PK parameter assessment. • Identification of CYP2C9 polymorphism and population-based PK analysis. • Correlation between cytidine deaminase polymorphisms and selected safety metrics and efficacy outcomes, described above.
• To compare changes in quality-of-life measures over time among subjects treated with ENTO compared to placebo when added to intensive induction therapy in previously untreated NPM1-m AML.	• EQ-5D-5L and EORTC-QLQ 30 over time.

Abbreviations: AML, acute myeloid leukemia; CR, complete remission; ECG, electrocardiogram; ECHO, echocardiogram; ECOG PS, Eastern Cooperative Oncology Group Performance Status; ELN, The European Leukemia Network; EORTC-QLQ 30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EQ-5D-5L, European Quality of Life 5 Dimensions Questionnaire; MRD, measurable residual disease; MUGA, multigated acquisition; *NPM1*-m, nucleophosmin-1 mutated; PK, pharmacokinetics; pSYK, phosphorylated spleen tyrosine kinase.

The study was terminated early at the request of the sponsor. Therefore, the endpoints described above could not be conducted. See **Section 8** for details.

4. GENERAL STATISTICAL CONSIDERATIONS

4.1. Statistical Hypothesis

Due to the study termination, no formal statistical testing will be performed.

4.2. Sample Size

Based on a completed study of newly diagnosed AML subjects treated with ENTO, it is anticipated that 87% of *NPM1*-m subjects will achieve CR (Walker et al, 2020). Based on analysis of a historical dataset from the Cancer and Leukemia Group B Alliance (Mims et al, 2021) showing a 68% CR rate in 107 *NPM1*-mutated/*FLT3-ITD* negative patients ≥ 60 years of age treated with 7+3 induction, a conservative estimate of 70% CR rate for placebo is assumed for sample size determination. The MRD negative rate among placebo subjects achieving CR is assumed to be 60% (Ivey et al, 2016). Alternatively, it is hypothesized that 80% of subjects with CR receiving ENTO will be MRD negative.

Approximately 180 subjects will be randomized with a randomization ratio of 1:1. A sample size of 90 subjects per group will provide > 97% power to detect a difference in the MRD negative CR rate of 28% (87% x 80% = 70% for ENTO vs 70% x 60% = 42% for placebo) with a 2-sided alpha level of 0.05 (PASS 2008: Two sample test of Proportion Module). Up to 10% over enrollment is allowed in order to account for technical or logistical barriers (e.g., inadequate bone marrow aspirate or poor sample quality) related to the ascertainment of MRD status in patients who achieve CR post-Chemotherapy Cycle 2.

Assuming the two-year event free survival (EFS) rate for the control group is 63% (hazard rate of 0.231), a total of 124 events (70 in the placebo arm, 54 in the ENTO arm) would be sufficient to provide 80% power to detect a hazard ratio of 0.6 for EFS (PASS 2008: log rank tests (Lakatos) [Hazard Rate] module) assuming 2-sided alpha = 0.05 and a total study duration of 60 months.

The study was terminated early with a final sample size of 15 randomized subjects.

4.3. Measures to Minimize Bias: Randomization and Masking

Subjects will be randomized 1:1 to study medication (ENTO or placebo) using an Interactive Voice/Web Response System (IxRS) and randomization schedule prepared by a non-study statistician using PharPoint standard operating procedure BIO002. The randomization will be stratified by age (<60 years vs ≥60 years) and anthracycline administered during induction (daunorubicin or idarubicin). All subjects, study site personnel, and the Sponsor's clinical trial management staff and their designees will be blinded to treatment assignment.

Under certain circumstances, members of the DMC may be unblinded to treatment assignment for individual subjects or treatment arm, in order to better assess safety and efficacy trends that could potentially underlie the basis for specific recommendations to modify the study. The criteria and procedures for unblinding at the DMC are outlined in the DMC Charter. Investigators will also have the ability to unblind the study medication assignment for individual patients in circumstances where this

information is critical for the assessment and management of specific adverse events, including suspected, unexpected, serious adverse events (SUSARs) and Grade 5 AEs assessed as at least possibly related to study medication. The investigator will have the capability to unblind the study medication assignment for individual patients without prior authorization from the study medical monitor or Sponsor and will access this information via the IxRS. Upon unblinding the medication assignment for a specific patient, the investigator must notify the study's medical monitor as soon as possible thereafter.

4.4. Handling of Data

4.4.1. Strata and Covariates

No adjustments for strata and covariates will be implemented.

4.4.2. Examination of Subject Subsets

No planned analysis of subject subsets will be conducted.

4.4.3. Multiple Testing and Comparisons

No statistical inference is planned.

4.4.4. Definitions and Data Derivations

Age
Age is defined as the age in years at time of informed consent recorded on the Demographics page of the CRF.

Study Medication
Study medication refers to ENTO/placebo.

Study Treatment
Study treatment refers to ENTO/placebo and/or chemotherapy.

Time since AML Diagnosis
Time since AML diagnosis, expressed in weeks, will be calculated as (date of randomization – date of AML diagnosis +1)/7.

Cycle 1 Day 1 (Baseline)
Cycle 1 Day 1 (C1D1) is defined as the earliest day that the first dose of any component of study treatment is administered.

Baseline Value
Baseline value is defined as the last observation of an assessment prior to the first dose of study treatment.

Study Day
Study Day is defined relative to C1D1. For events prior to C1D1, Study Day is calculated as:

Study Day = event date – date of C1D1

For events occurring on or after C1D1, Study Day is calculated as:

Study Day = event date – date of C1D1 + 1

Post-Baseline Value
Any assessment occurring after the initiation of study treatment will be considered a post-baseline value. For assessments occurring on C1D1 where no time of assessment is captured, the value will be considered as post-baseline if the assessment was not planned as part of the set of screening assessments (e.g., an assessment taken on C1D1 where no time was recorded but not designated as a screening assessment will be considered a post-baseline assessment whereas a laboratory assessment on C1D1 without a time but designated as a screening assessment will be considered as such).

Change from Baseline
Change from baseline will be determined for post-baseline assessments (where applicable) as:

Post-baseline value – baseline value

Days on Study Medication
Days on study medication is the number of days from C1D1 (or the first day of study medication, if later) to the date of the last dose of study medication as recorded on the Study treatment- Oral administration page of the CRF.

Days on Study Treatment
Days on study treatment is the number of days from the start of study treatment (either study medication or chemotherapy) to the date of the last dose of study treatment as recorded on the Study treatment- Oral administration or Study treatment- IV administration pages of the CRF.

Days on Study
Days on Study is the number of days from C1D1 to the date of completion or study discontinuation on the End of Study page of the CRF.

Cumulative Dose of ENTO
Cumulative dose of ENTO is defined as the sum of the doses administered to a patient measured in milligrams (mg). For subjects receiving placebo, this is set to 0 mg.

Cumulative Dose of Chemotherapy
The cumulative dose of each chemotherapy agent is defined as the sum of the doses administered to a patient measured in milligrams per meter squared (mg/m^2). Cumulative chemotherapy administration will be calculated separately for Induction and Consolidation.

Actual Dose Intensity (mg/m^2)
The actual dose intensity will be defined separately for each chemotherapy component by phase (Induction, Consolidation) and treatment cycle (as the cumulative dose / duration).

Relative Dose Intensity
Relative dose is set to 100*(Actual Dose Intensity/ (Expected Cumulative Dose / 28)).

Completed Chemotherapy Cycle
A chemotherapy cycle is considered completed if at least one of the assigned chemotherapy agents in the regimen has been completed per protocol. Information regarding premature discontinuation of chemotherapy will be as recorded on the Study treatment – IV administration pages of the CRF.

Response Criteria
Criteria for responses as outlined below and assessed by the investigator are based on the ELN 2017 definitions (Döhner et al 2017) with minor modification for neutrophil and platelet count thresholds as defined by the IWG and as applicable to the current study:

CR*
CR requires all the following:

- Bone marrow blasts < 5%
- Absence of circulating blasts and blasts with Auer rods
- Absence of extramedullary disease (i.e., leukemia outside of bone marrow confirmed by biopsy)
- Absolute neutrophil count > 1.0 x 10^9/L (1000/μL)
- Platelet count > 100 x 10^9/L (100,000/μL)

*Note: *MRD positive or unknown*

Complete Response with Hematologic Improvement (CRh)**
CRh requires all the CR criteria, except for residual thrombocytopenia and/or neutropenia and is defined as:

- Bone marrow blasts < 5%
- Absence of circulating blasts and blasts with Auer rods
- Absence of extramedullary disease
- Absolute neutrophil count > 0.5 x 10^9/L (500/μL)
- Platelet count > 50 x 10^9/L (50,000/μL)

Complete Response with Incomplete Blood Count Recovery (CRi)**
CRi requires all the CR criteria, except for residual neutropenia or thrombocytopenia and is defined as:

- Bone marrow blasts < 5%
- Absence of circulating blasts and blasts with Auer rod
- Absence of extramedullary disease

- Absolute neutrophil count ≤ 1.0 x 10^9/L (1000/μL) or platelet count ≤ 100 x 10^9/L (100,000/μL)

*Note: **If subjects meet criteria for both CRh and CRi, they should be classified as CRh*

Morphologic-free Leukemia State (MLFS)***

- Bone marrow blasts < 5%
- Absence of blasts with Auer rods
- Absence of extramedullary disease
- No hematologic recovery required

*Note: *** Marrow should not be merely "aplastic"; at least 200 cells should be enumerated or cellularity on bone marrow biopsy should be at least 10% of normal*.

Partial Response (PR)

PR meets all hematologic criteria of CR:

- Absolute neutrophil count > 1.0 x 10^9/L (1000/μL)
- Platelet count > 100 x 10^9/L (100,000/μL), and
- Residual bone marrow blast percentage of 5% to 25%
- Reduction of bone marrow blast percentage by ≥ 50% compared with pretreatment

Stable Disease (SD)

Absence of MRD negative CR, CR, CRh, CRi, PR, MLFS and criteria for PD not met.

Progressive Disease (PD)

Evidence for an increase in bone marrow blast percentage and/or circulating blast counts as defined by at least one of the following:

- 50% increase in bone marrow blasts over baseline (a minimal absolute 15% increase is required in cases with < 30% blasts at baseline), or
- Persistent bone marrow blast percentage > 70% over ≥ 3 months without at least a 100% improvement in ANC to an absolute level > 0.5 x 10^9/L (500/μL) and/or platelet count to > 50 x 10^9/L (50,000/μL) without transfusion, or
- 50% increase in circulating blasts to > 25 x 10^9/L (>25,000/μL) in the absence of Differentiation Syndrome,**** or
- New extramedullary disease

**** Certain targeted therapies, for example, those inhibiting mutant isocitrate dehydrogenase (IDH) proteins, other kinase or targets may cause a transient increase in the percentage of bone marrow blasts accompanied by an increase in circulating blasts (differentiation syndrome). In the setting of therapy with such compounds, an increase in blasts may not necessarily indicate progressive disease. Such instances should be discussed with the study medical monitor on a case-by-case basis.

Recurrence

Recurrence for subjects with prior MRD-CR, morphological CR, CRh, CRi, or MLFS is defined as one of the following:

- Morphologic relapse as defined by the reappearance of circulating blasts or ≥ 5% blasts in the bone marrow not attributable to any other cause. *Note: In the setting of recent treatment, if there are no circulating blasts and the bone marrow contains 5 to 20% blasts, a bone marrow aspirate/biopsy should be repeated within 1 week to distinguish relapse from bone marrow regeneration.*
- Reappearance of cytologically or biopsy documented extramedullary disease, including new CNS disease or other new sites of extramedullary involvement. *Note: The reappearance of a cytogenetic or molecular abnormality would be considered a cytogenetic or molecular relapse. In the absence of morphologic relapse, this would not be considered a recurrence.*

Evaluation of response is recorded on the Response Assessment eCRF, and documentation of recurrence (relapse) is recorded on the Relapse Assessment eCRF.

Adverse Event
An AE is defined as any untoward medical occurrence in a clinical study subject, temporally associated with the use of study treatment, whether or not considered related to the study treatment.

Treatment-emergent Adverse Event (TEAE)
A TEAE is any adverse event beginning or worsening from C1D1 through 30 days following study treatment completion.

Treatment-emergent Laboratory Toxicity (TELT)
A TELT is a laboratory abnormality as defined in the National Cancer Institute - Common Toxicity Criteria for Adverse Events (NCI-CTCAE) v5.0 (NCI 2017, which occurs on or after the start of study treatment and up to 30 days following discontinuation of all study treatment and is at least 1 grade shift from the baseline value. TELTs are determined programmatically from laboratory assessments recorded in the relevant CRF pages.

Concomitant Medications
Concomitant medications are those medications taken on or after the initiation of study treatment. This includes medications started prior to the initiation of ENTO/placebo and continued after the initiation of ENTO/placebo. These medications will be recorded in the Prior and Concomitant Medications page of the CRF.

Prior Medications
Prior medications are those medications taken and discontinued prior to the initiation of study treatment. These medications will be recorded in the Prior and Concomitant Medications page of the CRF.

4.4.5. Presentations by Study Visit

All study visits should be scheduled relative to C1D1 regardless of any treatment interruptions. Visits will be presented according to the visit designation as recorded in the CRF. Unscheduled and Early Termination Visits will be excluded from by visit presentations. All data will be presented in data listings.

4.4.6. Missing Data

Every effort will be made to obtain required data at each scheduled evaluation from all subjects who have been randomized. In situations where it is not possible to obtain all data, it may be necessary to impute missing data. AEs with missing causal relationship will be assessed as related to study treatment. AEs with missing severity will be included in the denominator for all grade events of the same preferred term (PT) but will not be included in the numerator for any severity when reporting the frequency of events by severity. See Section 4.4.4.4 for details of imputing missing dates. See Section 6.4 for details of imputing missing efficacy endpoints.

Unless otherwise specified, all other missing data will not be imputed.

4.4.6.1. Imputation for Alphanumeric Data

Should there be instances where a clinical laboratory parameter is reported with imbedded non-numeric characters, such as, for example, "<0.1" or ">10", the data will be imputed for quantitative summaries. The actual values as reported in the database will be presented in data listings.

For incorporation in quantitative summaries, the following imputation rules will be employed:

The limit of quantitation will be increased by one level of precision in the direction of the symbol that precedes the value. For example, "< 0.1" will be imputed to "0.09", while ">0.1" will be imputed to "0.11", and ">10" will be imputed to "10.1".

4.4.6.2. Incomplete or Missing Dates

An incomplete date occurs when the exact date an event started or ended cannot be obtained. The database contains data fields for month, day, and year. A date is incomplete if at least one of these three fields is not known.

For many of the planned analyses, a complete date is necessary to determine if the event should be included in the analysis (i.e., if the event is treatment-emergent) or to establish the duration of an event. In such cases, incomplete or missing dates will be imputed.

For the purposes of handling partially reported start and stop dates for an event the following algorithm will be applied:

- Missing start day, but month and year present:

If the event occurs in the same month and year as the initiation of study treatment, then the start day of the event will be assigned to C1D1. For example, if an AE occurred in December 2021, and C1D1 study treatment administration was on 8 December 2021 then the date of AE onset would be set to 8 December 2021.

Otherwise, the start day will be set to the first day of the month.

- Missing start day and month, but year present:

  If an event occurs in the same year as the initiation of study treatment, then the start date of the event will be assigned to C1D1. For example, in the event a subject started study treatment on 20 January 2022 and had an AE starting in 2022 with no Month and Day indicated, the AE date would be set to 20 January 2022.

  Otherwise, the start day and month will be set to 01 January. Thus, for AEs with a start date of 2022 and initiation of study treatment in 2021, the AE start date would be 01 January 2022.

- Missing start day, month, and year will be set to C1D1.
- Missing end day, but month and year present:

  The day will be set to the last day of the month.

- Missing end day and month, but year present:

  The end day and month will be set to 31 December of that year or the study treatment completion date, if earlier.

If any imputed date causes the end date to occur prior to the start date of the event, the start date of the event will be used for the imputation of the end date. In subject data listings, start and stop dates of events will be displayed as reported on the CRF (i.e., imputed values will not be listed).

4.5. Timing of Analyses

A single DMC analysis occurred in September 2022.

A final analysis will be conducted once the database is cleaned and locked.

5. ANALYSIS SETS

The following analysis populations will be defined for this study: Intent-to-Treat Analysis Set and Safety Analysis Set.

5.1. Intent-To-Treat Analysis Set

The Intent-to-Treat (ITT) Analysis Set consists of all subjects who are randomized. The ITT analysis set will be the primary population for efficacy analyses.

5.2. Safety Analysis Set

The Safety Analysis Set consists of all subjects who receive at least one dose of study medication. Subjects in this population will be analyzed according to the treatment they received, regardless of the treatment to which they were randomized. The Safety Analysis Set will be used for all summaries of safety data.

6. STATISTICAL METHODS

Descriptive statistical methods will be used to summarize the data from this study. Unless stated otherwise, the term "descriptive statistics" refers to number of subjects (n), mean, median, standard deviation , interquartile range, minimum, and maximum for continuous data and frequency and percentage for categorical data. The term "treatment group" refers to the randomized assignment: ENTO or placebo. Unless otherwise specified, data summaries and analyses described below will be reported by treatment group. All data collected during the study will be included in data listings. Unless otherwise noted, the data will be sorted first by treatment, patient number, and then by assessment date for each patient number. The number of subjects screened, enrolled, treated, and discontinued from study drug will be summarized along with the primary reason for study treatment discontinuation. The number of subjects in each analysis population will be presented by treatment group.

6.1. Demographics and Baseline Characteristics

Demographic data including age (years), sex, race, ethnicity, geographic region (North America, South America, European Union, Asia Pacific), (height (cm), weight (kg), and body surface area (m^2) will be summarized for the ITT Analysis Set.

All information pertaining to AML diagnosis as collected on the eCRF will be listed.

6.2. Medical History

All clinically relevant prior or concurrent medical conditions will be mapped to system organ class (SOC) and PT using the version of Medical Dictionary for Regulatory Activities (MedDRA) in effect at the time of database lock. The number and percent of subjects in the ITT Analysis Set reporting each medical condition will be summarized according to SOC and PT.

All medical history will be listed.

6.3. Exposure to Treatment

The number of days on oral study drug and cumulative dose will be summarized by treatment group for the Safety Analysis Set. Additionally, the number of chemotherapy cycles completed and the relative dose intensities for each chemotherapy agent will be presented by treatment group, separately for Induction and Consolidation and presented by cycle and overall. Drug administration details will be listed.

6.4. Efficacy

No analysis of protocol defined primary or secondary efficacy endpoints will be generated. A summary of the investigator assessment of response after two cycles of chemotherapy will be summarized by treatment group for the Safety Analysis Set as this analysis was previously generated for the DMC.

6.5. SAFETY ANALYSIS

Descriptive summaries will be generated for safety data including TEAEs as well as changes from baseline in laboratory assessments (figure only), and graded laboratory toxicities. All adverse events will be graded for severity using NCI-CTCAE as follows:

- Grade 1 (Mild): asymptomatic or mild symptoms; clinical or diagnostic observation only; intervention not indicated
- Grade 2 (Moderate): minimal, local, or non-invasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL)
- Grade 3 (Severe): Medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL
- Grade 4 (Life-threatening): Urgent intervention indicated required to remove or abrogate risk of death
- Grade 5: Death related to AE

6.5.1. Adverse Events

Adverse events will be mapped to the MedDRA version in effect at the time of database lock. TEAEs will be summarized by treatment group using system organ class and preferred term.

If a subject experiences multiple events that map to a single preferred term, the event of greatest severity will be assigned to the preferred term for the appropriate summaries. Subjects with events mapping to multiple preferred terms within the same system organ class will be counted once at the system organ class level.

Separate summaries for treatment-emergent serious adverse events (TESAEs), TEAEs by severity, TEAEs related to study medication, TEAEs leading to ENTO/placebo dose reduction, interruption, discontinuation, and TEAEs with an outcome of death will be generated.

Missing onset dates will be imputed as previously outlined in Section 4.4.4.4.

6.5.2. Clinical Laboratory Assessments

Laboratory toxicities will be graded for severity using NCI-CTCAE Version 5.0 (see section Appendix B for more details about laboratory grading). The frequency and percentage of subjects experiencing treatment-emergent toxicities will be summarized by treatment group. Shifts from baseline toxicity grades to worst post-treatment toxicity grades will be presented by treatment group.

Figures of observed values by study visit will be produced for the following hematology and clinical chemistry parameters of interest: hemoglobin, white blood cells, lymphocytes, ANC, platelets, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, total bilirubin, direct bilirubin, indirect bilirubin, creatinine, urea nitrogen, percent leukemic blasts, and lactate dehydrogenase.

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6.5.3. Prior and Concomitant Medications

Prior and concomitant medications will be classified using World Health Organization (WHO) Drug Dictionary codes and Anatomical Therapeutic Chemical (ATC) Classification for therapeutic indication. ATC Level 4 will be utilized as the drug classification. Prior and concomitant medications will be listed.

6.5.4. Vital Signs and Pulse Oximetry

Vital signs include systolic and diastolic blood pressures, respiratory rate, pulse, temperature. Vital signs and pulse oximetry will be listed.

6.5.5. Electrocardiograms

Triplicate 12-lead ECGs will be obtained at Screening.

ECG data will be listed.

6.5.6. Echocardiograms/Multigated Acquisition Scan

An ECHO or MUGA scan will be performed at screening and at the end-of-treatment visit. For subjects receiving anthracycline in Induction Cycle 2, the ECHO or MUGA scan may be repeated within 48 hours prior to Cycle 2, Day 1 in subjects at increased risk for cardiotoxicity. ECHO data will be listed.

6.5.7. Physical Examinations

Physical examination will include body weight, height (at screening only) and a full neurological examination. These data will be presented in listing format.

6.5.8. ECOG Performance Status

ECOG PS score at each visit will be presented in a data listing.

7. PROTOCOL DEVIATIONS

All protocol deviations will be reviewed by the project team prior to unblinding to identify subjects with important protocol deviations.

All deviations from the study protocol will be available from the clinical team.

8. CHANGES IN THE PLANNED ANALYSES

As the study was terminated prior to the enrollment of 180 subjects, analyses of the efficacy and exploratory endpoints described in the protocol will not be conducted. These deviations will be documented in the final CSR.

9. REFERENCES

DHHS (2009). "Guidance for Industry: Drug-Induced Liver Injury: Premarketing Clinical Evaluation."

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Ivey A, Hills RK, Simpson MA, et al. Assessment of Minimal Residual Disease in Standard-Risk AML. N Engl J Med. 2016;374(5):422-433.

Mims AS, Kohlschmidt J, Borate U, et al. A precision medicine classification for treatment of acute myeloid leukemia in older patients. J Hematol Oncol. 2021;14(1):96.

Walker AR, Byrd JC, Blachly JS, et al. Entospletinib in Combination with Induction Chemotherapy in Previously Untreated Acute Myeloid Leukemia: Response and Predictive Significance of HOXA9 and MEIS1 Expression. Clin Cancer Res. 2020; 26(22):5852-5859.

10. PROPOSED TABLES, LISTINGS, AND FIGURES

Summary Tables

1	Subject Disposition
2	Demographics and Baseline Disease Characteristics
3	Exposure to Study Medication and Chemotherapy
4	Summary of Responses after Two Cycles of Chemotherapy
5	Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, and Greatest Severity
6	Summary of Treatment-Related Adverse Events by System Organ Class and Preferred Term
7	Summary of Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
8	Summary of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
9	Summary of Treatment-Emergent Severity Graded Laboratory Abnormalities

Figures

1	Chemistry Parameters Over Time
2	Hematology Parameters Over Time

Data Listings

1	Subject Disposition
2	Treatment-Emergent Adverse Events
3	Treatment-Emergent Severity Graded Laboratory Abnormalities
4.1	Demographics
4.2	AML Diagnosis
5.1	Study Treatment - IV/Infusion Administration Details
5.2	Study Treatment - Oral Administration Details
6	Response Assessment after Two Cycles of Chemotherapy
7	Vital Signs, Height, and Weight
8	Electrocardiogram
9	Physical Examinations
10	ECOG Performance Status
11	Echocardiogram/MUGA for LVEF Assessment
12	General Medical History
13	Prior and Concomitant Medications
14	Prior Leukemogenic Agent Exposure

Appendix A: Programming Conventions

- Statistical software: The statistical analyses will be conducted with the SAS® software package version 9.4 or higher.

- Verification procedures: All analyses will be subject to formal verification procedures. Specifically, results will be verified utilizing independent programming prior to issuance of the draft statistical report. All documents will be verified by the lead statistician to ensure accuracy and consistency of analyses.

- Page orientation, margins, and fonts: Summary tables, listings, and figures will appear in landscape orientation. There should be a minimum of a 1" boundary on the upper (bound) edge, and a minimum of a 1.0" boundary on the remaining three edges. Output should be printed in Courier New with a point size of 8. Titles may be printed using a larger font (e.g., Arial point size 10).
- Identification of analysis population: Every summary table and figure should clearly specify the analysis population being summarized. Listings will be prepared for all subjects enrolled.
- Group headers: In the summary tables, the group headers will identify the treatment group and the within-group sample size for the indicated analysis population. Of note, the header's sample size does not necessarily equal the number of subjects actually summarized within any given summary module; some subjects in the analysis population may have missing values and thus may not be summarized.
- Suppression of percentages corresponding to null categories: When count data are presented as category frequencies and corresponding percentages, the percent should be suppressed when the count is zero in order to draw attention to the non-zero counts.
- Presentation of sample sizes: Summary modules should indicate, in one way or another, the number of subjects actually contributing to the summary statistics presented in any given summary module. As mentioned above, this may be less than the number of subjects in the analysis population.
    - ♦ In the quantitative modules describing continuous variables (and thus presenting sample size, means, and standard deviations), the sample size should be the number of non-missing observations.
    - ♦ For categorical variables that are presented in frequency tables, the module should present the total count in addition to the count in each category. Percentages should be calculated using this total as the denominator, and the percentage corresponding to the sum itself (that is, 100%) should be presented so as to indicate clearly to a reviewer the method of calculation.
- Sorting: Listings will be sorted by treatment group, patient number, and date, if applicable. If a listing is sorted in a different manner, a footnote will indicate as such.

- General formatting rules: Rounding for all variables will occur only as the last step, immediately prior to presentation in listings, tables, and figures. No intermediate rounding will be performed on derived variables. The standard rounding practice of rounding numbers ending in 0-4 down and numbers ending in 5-9 up will be employed.
- The presentation of numerical values will adhere to the following guidelines:
  - Raw measurements will be reported to the number of significant digits as captured electronically or on the CRFs.
  - Standard deviations will be reported to two decimal places beyond the number of decimal places the original parameter is presented.
  - Means, medians, first and third quartiles will be reported to one decimal place beyond the number of decimal places the original parameter is presented.
  - Calculated percentages will be reported with no decimals.
- Dates will be formatted as DDMMMYYYY. Partial dates will be presented on data listings as recorded on CRFs.
  - Time will be presented according to the 24-hour clock (HHMM).

Appendix B: Programming Modified NCI-CTCAE Grading for Laboratory Abnormalities

Category	Analyte Name	CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4
Chemistry	Albumin	Hypoalbuminemia	<LLN - 3 g/dL	<3 - 2 g/dL	<2 g/dL	-
Chemistry	Amylase	Serum amylase increased	>ULN - 1.5 x ULN	>1.5 - 5.0 x ULN	>5.0 x ULN	-
Chemistry	Alanine Aminotransferase	Alanine aminotransferase increased	>ULN - 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal
Chemistry	Alkaline Phosphatase	Alkaline phosphatase increased	>ULN - 2.5 x ULN if baseline was normal; 2.0 - 2.5 x baseline if baseline was abnormal	>2.5 - 5.0 x ULN if baseline was normal; >2.5 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal
Chemistry	Aspartate Aminotransferase	Aspartate aminotransferase increased	>ULN - 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal

Category	Analyte Name	CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4
Chemistry	Bilirubin (Total or Direct)	Blood bilirubin increased	>ULN - 1.5 x ULN if baseline was normal; > 1.0 - 1.5 x baseline if baseline was abnormal	>1.5 - 3.0 x ULN if baseline was normal; >1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 10.0 x ULN if baseline was normal; >3.0 - 10.0 x baseline if baseline was abnormal	>10.0 x ULN
Chemistry	Calcium Corrected for Albumin	Hypocalcemia	<LLN - 8.0 mg/dL	<8.0 - 7.0 mg/dL	<7.0 - 6.0 mg/dL	<6.0 mg/dL
		Hypercalcemia	>ULN - 11.5 mg/dL	>11.5 - 12.5 mg/dL	>12.5 - 13.5 mg/dL	>13.5 mg/dL
Chemistry/ Lipid Profile	Cholesterol	Cholesterol high	>ULN - 300 mg/dL	>300 - 400 mg/dL	>400 - 500 mg/dL;	>500 mg/dL
Chemistry	Creatine Kinase	CPK increased	>ULN - 2.5 x ULN	>2.5 x ULN - 5 x ULN	>5 x ULN - 10 x ULN	>10 x ULN
Chemistry	Creatinine	Creatinine increased	>ULN - 1.5 x ULN	>1.5 - 3.0 x baseline or >1.5 - 3.0 x ULN	>3.0 x baseline or >3.0 - 6.0 x ULN	>6.0 x ULN
Chemistry	GGT	GGT increased	>ULN - 2.5 x ULN if baseline was normal; 2.0 - 2.5 x baseline if baseline was abnormal	>2.5 - 5.0 x ULN if baseline was normal; >2.5 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal

Category	Analyte Name	CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4
Chemistry	eGFR or CrCL	eGFR decreased/CrCL decreased	<LLN – 60 ml/min/1.73 m2	<60 – 30 ml/min/1.73 m2	<30 - 15 ml/min/1.73 m2	<15 ml/min/1.73 m2
Chemistry	Glucose	Hypoglycemia	<LLN - 55 mg/dL	<55 - 40 mg/dL	<40 - 30 mg/dL	<30 mg/dL
Chemistry	Lipase	Serum lipase increased	>ULN - 1.5 x ULN	>1.5 - 5.0 x ULN	>5.0 x ULN	-
Chemistry	Magnesium	Hypermagnesemia	>ULN - 3.0 mg/dL	-	>3.0 - 8.0 mg/dL mmol/L	>8.0 mg/dL
		Hypomagnesemia	<LLN - 1.2 mg/dL	<1.2 - 0.9 mg/dL	<0.9 - 0.7 mg/dL	<0.7 mg/dL
Chemistry	Potassium	Hyperkalemia	>ULN - 5.5 mmol/L	>5.5 - 6.0 mmol/L	>6.0 - 7.0 mmol/L	>7.0 mmol/L
		Hypokalemia	<LLN - 3.0 mmol/L	-	<3.0 - 2.5 mmol/L	<2.5 mmol/L
Chemistry	Sodium	Hypernatremia	>ULN - 150 mmol/L	>150 - 155 mmol/L;	>155 - 160 mmol/L	>160 mmol/L
		Hyponatremia	<LLN - 130 mmol/L	125-129 mmol/L	120-124 mmol/L	<120 mmol/L
Chemistry/ Lipid Profile	Triglycerides	Hypertriglyceridemia	150 mg/dL - 300 mg/dL	>300 mg/dL - 500 mg/dL	>500 mg/dL - 1000 mg/dL	>1000 mg/dL
Chemistry	Uric Acid	Hyperuricemia	>ULN	-	-	-

Category	Analyte Name	CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4
Chemistry	Bicarbonate or CO2	Blood bicarbonate decreased	<LLN	-	-	-
Hematology	Eosinophils	Eosinophilia	>ULN and > Baseline			
Hematology	Hemoglobin	Anemia	<LLN – 100 g/L	<100 – 80 g/L	<80 g/L	-
Hematology	Lymphocytes	Lymphocyte count decreased	<LLN - 800/mm3	<800 - 500/mm3	<500 - 200/mm3	<200/mm3
		Lymphocyte count increased	-	>4000/mm3 - 20,000/mm3	>20,000/mm3	-
Hematology	Neutrophils	Neutrophil count decreased	<LLN - 1500/mm3	<1500 - 1000/mm3	<1000 - 500/mm3	<500/mm3
Hematology	Platelets	Platelet count decreased	<LLN - 75,000/mm3	<75,000 - 50,000/mm3	<50,000 - 25,000/mm3	<25,000/mm3
Hematology	Leukocytes/ White Blood Cells	Leukocytosis	-	-	>100,000/mm3	-
		White blood cell decreased	<LLN - 3000/mm3	<3000 - 2000/mm3	<2000 - 1000/mm3	<1000/mm3

Category	Analyte Name	CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4
Coagulation	Activated partial thromboplastin time	Activated partial thromboplastin time prolonged	>ULN - 1.5 x ULN	>1.5 - 2.5 x ULN	>2.5 x ULN	-
Coagulation	Fibrinogen	Fibrinogen decreased	<1.0 - 0.75 x LLN; if abnormal, <25% decrease from baseline	<0.75 - 0.5 x LLN; if abnormal, 25 - <50% decrease from baseline	<0.5 - 0.25 x LLN; if abnormal, 50 - <75% decrease from baseline	<0.25 x LLN; if abnormal, 75% decrease from baseline; absolute value <50 mg/dL
Coagulation	International Normalized Ratio	INR increased	>1.2 - 1.5	>1.5 - 2.5	>2.5	-

Note: Values noted as 'abnormal' at baseline should be outside the normal range in the direction of the toxicity grade.
Note: In cases where the lower limit of normal (LLN) or upper limit of normal (ULN) of a given laboratory value falls in the Grade 2 or higher range of the scale, the toxicity will be graded at the higher value (i.e., a lymphocyte test has a LLN of 600/mm^3, any value of 600/mm^3 will be considered as a Grade 2 abnormality).