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STATISTICAL ANALYSIS PLAN

A Phase 1b/2 study of the safety, pharmacokinetics, pharmacodynamics, and preliminary efficacy of the selective SYK inhibitor lanraplenib (LANRA) in combination with the *FLT3* inhibitor, gilteritinib, in patients with *FLT3*-mutated relapsed or refractory AML

Compound:	Lanraplenib (LANRA)
Trial Phase:	1b/2
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STATISTICAL ANALYSIS PLAN REVIEW AND APPROVAL

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1.1. GLOSSARY OF ABBREVIATIONS

Abbreviation/Term	Definition
ADL	activities of daily living
AE	adverse event
ALC	absolute lymphocytes count
ALT	alanine aminotransferase
AML	acute myeloid leukemia
ANC	absolute neutrophil count
anti-HBc	hepatitis B antibody
Anti-HBs	hepatitis B antibody
Anti-HCV	hepatitis C antibody
Anti-HIV	HIV antibody
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
ATC	Anatomic Therapeutic Chemical
AUC	area under the concentration × time curve
AUC0-last	area under the concentration × time curve from time 0 until the last measurable plasma concentration
BUN	blood urea nitrogen
C1D1	Cycle 1 Day 1
cCR	composite complete remission
CI	confidence interval
Cmax	maximal plasma concentration

CPK	creatine phosphokinase
CR	complete remission
CRh	complete remission with partial hematologic recovery
CRi	complete remission with incomplete blood count recovery
DEC	Dose Escalation Committee
DLT	dose-limiting toxicity
ECG	electrocardiogram
ECHO	echocardiogram
ECOG PS	Eastern Cooperative Oncology Group Performance Status
eCRF	electronic case report form
EE	Efficacy Evaluable
EFS	Event free survival
ELN	European LeukemiaNet
FISH	fluorescence in situ hybridization
FLT3	FMS-like tyrosine kinase 3
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HOXA9	homeobox protein
HOXA9	Homeobox A9
INR	international normalized ratio
ITD	internal tandem duplication
K-M	Kaplan-Meier
LANRA	lanraplenib

LDH	Lactate dehydrogenase
LLN	lower limit of normal
MedDRA	Medical Dictionary for Regulatory Activities
MEIS1	Meis Homeobox 1
MRD	measurable residual disease
MTD	maximally tolerated dose
MUGA	Multi-gated acquisition
N	number of patients
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NGS	next-generation sequencing
NPM1	*nucleophosmin-1*
NPM1-m	*nucleophosmin-1 mutated*
PD	pharmacodynamic(s) *or* progressive disease
PK	pharmacokinetic(s)
PR	partial remission
pSYK	phosphorylated spleen tyrosine kinase
PT	prothrombin time *or* preferred term
QD	once a day
QTcF	Fridericia corrected QT interval
R/R	relapse/refractory
RP2D	recommended Phase 2 dose
RT-PCR	Reverse transcriptase polymerase chain reaction

SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	stable disease
SOC	system organ class
SOC	system organ class
ß-hCG	hormone found in blood and urine during pregnancy
STD	standard deviation
SYK	spleen tyrosine kinase
TEAE	treatment-emergent adverse event
TELT	treatment-emergent laboratory toxicity
TESAE	treatment-emergent serious adverse event
TKD	tyrosine kinase domain
Tmax	time to maximal plasma concentration
ULN	upper limit of normal
US	United States
WBC	white blood cell
WHO	World Health Organization
WOCBP	woman of child-bearing potential

2. INTRODUCTION

This document (statistical analysis plan [SAP]) describes the statistical methods and data presentations to be used in the summary and planned analysis of demographic, baseline disease characteristics, medical and cancer treatment history, prior and concomitant medications, disposition, safety, exposure, and efficacy data obtained from Phase 1b of Study KB-LANRA-1001. Background information is provided for the overall study design and objectives. The reader is referred to the study protocol and electronic case report forms (eCRFs) for details of study conduct and data collection, the pharmacokinetics (PK) analysis plan for analysis of PK data, the pharmacodynamic (PD) analysis plan for the analysis of PD data, and to the Dose Escalation Committee (DEC) charter for the roles and the responsibilities for that committee in safety monitoring and determination of the maximum tolerated dose (MTD)/recommended phase 2 dose (RP2D) for LANRA.

2.1. STUDY OVERVIEW

This multicenter, Phase 1b/2 study will investigate the safety, PK, PD and make a preliminary assessment of the anti-leukemic activity of the selective, 3rd generation *SYK* inhibitor, lanraplenib (LANRA), in combination with the selective *FLT3* inhibitor, gilteritinib, in patients with *FLT3*-mutated acute myeloid leukemia (AML), who have recurrence of leukemia or are refractory after at least 1 prior regimen. This study will be conducted in 2 parts: dose escalation (Phase 1b) and cohort expansion (Phase 2). The study will consist of a Screening Phase lasting up to 21 days during which patients will be assessed for eligibility; a Treatment Phase beginning on Cycle 1, Day 1 (C1D1) consisting of consecutive 28-day cycles; an End-of-Treatment evaluation; and a Post-Treatment Follow-up Phase. During the Treatment Phase, patients will undergo study visits on Days 1, 4, 8, 11, 15, 16 and 22 in Cycle 1, Days 1, 8, 15 and 22 in Cycle 2, and Days 1 and 15 in Cycle 3 and beyond. Approximately 100 patients are estimated to enroll across both Phase 1b and Phase 2; patients will be enrolled from multiple trial sites worldwide for Phase 1b and for Phase 2. In both Phase 1b and Phase 2, patients will receive their assigned treatment regimen until progression/relapse or lack of at least a partial remission (PR) after 6 months of study treatment, intolerance, or withdrawal from treatment by the patient or study investigator. All patients will be followed for survival.

In Phase 1b, eligible patients will be enrolled sequentially into dose cohorts listed in Table 1 for PK/PD evaluations and determination of the MTD/RP2D of LANRA in combination with gilteritinib.

Table 1: Dose-escalation Scheme (Provisional)

Dose Cohort (n):	LANRA Dose:	Gilteritinib Dose:
Cohort 1	20 mg QD	120 mg QD
Cohort 2	40 mg QD	120 mg QD
Cohort 3	60 mg QD	120 mg QD
Cohort 4	90 mg QD	120 mg QD

A "3 + 3" dose escalation scheme will be employed in which 1 dose-limiting toxicity (DLT) reported from among the first 3 evaluable patients in a dose cohort will prompt enrollment of 3 additional evaluable patients. More than 1 DLT attributed to LANRA among 6 patients evaluable for DLT would indicate an intolerable dose, thus rendering the most proximate lower dose with either 0 of 3 or 1 of 6 patients with LANRA-related DLTs the MTD in combination with gilteritinib. The starting dose of LANRA is 20 mg QD (Cohort 1, Table 1). To better understand the safety, tolerability, PK, PD, and anti-tumor activity of the study regimen, additional patients (up to a total of 20 per dose cohort) may be allocated to previously cleared dose cohort(s) that are considered safe and adequately tolerated, if there are no available patient slots in the dose level currently being evaluated. The decision to enroll additional patients at a dose level previously cleared by the DEC (ie, enrollment of a "backfill" cohort) will be based on recommendations provided by the DEC coincident with each scheduled DEC convocation. Furthermore, additional patients may be added to a previously cleared dose cohort only if at least 1 of the 3 to 6 patients initially enrolled to that cohort have achieved one of the following ELN 2017-defined response categories: CR, CRh, CRi, PR, MLFS.

Following completion of Phase 1b, an expansion cohort consisting of patients who meet all eligibility criteria will enroll in order to further assess the safety, PK, PD and anti-leukemic activity of the combination at the LANRA MTD/RP2D. Patients enrolled in phase 2 will begin combination therapy with LANRA and gilteritinib on C1D1. Enrollment in Phase 2 will follow a two-stage design for assessment of the primary efficacy endpoint, composite CR (cCR) rate, including those patients who achieve a best response of complete remission (CR) or complete remission with partial hematology recovery (CRh), as defined by European LeukemiaNet 2017 (ELN) response criteria.

2.2. SCHEDULE OF ASSESSMENTS

Table 2: Schedule of Assessments – Screening Through Cycle 2

Assessment:	Screening	Cycle 1 †								Cycle 2 †			
		C1 D1	C1 D2	C1 D4	C1 D8	C1 D11	C1 D15	C1 D16	C1 D22 ±1d **	C2 D1 ±1d	C2 D8 ±1d	C2 D15 ±1d	C2 D22 ±1d
Informed consent ††	X												
Physical examination [a]	X	X			X		X		X	X		X	
Vital signs/pulse oximetry [b]	X	X		X	X	X	X	X	X	X	X	X	X
Weight/height [c]	X	X								X			
Medical history	X												
Leukemia history [d]	X												
ECOG PS	X									X			
ECG [e]	X	X			X		X			X			
ECHO/MUGA[f]	X	As clinically indicated											
Hematology [g, t]	X	X*		X	X	X	X		X	X	X	X	X
Coagulation [h, t]	X	X*					X			X			
Clinical chemistries [i,t]	X	X*			X		X		X	X		X	
Urinalysis [j, t]	X	As clinically indicated											
Viral serologies (HBsAg, anti-HBs, anti-HBc, anti-HCV, anti-HIV)	X												

Serum pregnancy test (WOCBP) [k]	X												
Urine pregnancy test (WOCBP) [k, t]		X								X			
Bone marrow examination [m]	X									X			
Study medication dispensation [n]		X								X			
Assessment of compliance	X	X		X	X	X	X	X	X	X	X	X	X
Adverse event (AE) review [o]		X		X	X	X	X	X	X	X	X	X	X
Prior medications [p]	X												
Concomitant medication review [q]		X		X	X	X	X	X	X	X	X	X	X
Pregnancy prevention counseling [r]	X	X		X	X	X	X	X	X	X	X	X	X
PK/PD Assessments	X	X	See Table 4 and Table 5 for full descriptions of PK and PD sampling time points in **Phase 1b**. See Table 6 for a full description of PK and PD sampling time points in **Phase 2**. After Cycle 2, additional blood samples for PD assessments are requested on Day 1 Cycle 3 and every 3 cycles thereafter (ie, Cycle 6, Cycle 9, etc.) until 2 consecutive response assessments of CR/CRh are documented, and at End-of-Treatment in both **Phase 1b** and **Phase 2** (see Table 3 below).											
Bone marrow biopsy unstained slides **(Optional)**	Either archival samples or those obtained from patients at Screening or during the Treatment Phase are acceptable (see Section 11.6 of the protocol)												

Table 3: Schedule of Assessments – Cycle 3+, End-of-Treatment, Post-Treatment Follow-up

Assessment	D1 ± 1 d	D15 ± 1 d	End of Treatment [s]	Post-treatment Follow-up
Physical examination [a]	X	X	X	
Vital signs/pulse oximetry [b]	X	X	X	
Weight/height [c]	X		X	
ECOG PS	X		X	
ECG [e]	X		X	
ECHO/MUGA[f]	As clinically indicated			
Hematology [g, t]	X		X	
Coagulation [h, t]	X			
Clinical chemistries [i, t]	X		X	
Urinalysis [j, t]	As clinically indicated			
Serum pregnancy test (WOCBP) [k]	as clinically indicated (for confirmation of a positive urine pregnancy test)			
Urine pregnancy test (WOCBP) [k, t]	X		X	
Bone marrow examination [m]	X			
Study drug dispensation [n]	X			

Assessment of compliance	X	X		
Adverse event review [o]	X	X	X	
Concomitant medication review [q]	X	X	X	
Pregnancy prevention counseling [r]	X	X	X	
PD/biomarkers assessments (peripheral blood)[u]	X		X	
Assessment	D1 ± 1 d	D15 ± 1 d	End of Treatment [s]	Post-treatment Follow-up ± 1 week
Bone marrow biopsy unstained slides (**Optional**)	Either archival samples or those obtained from patients at Screening or during the Treatment Phase are acceptable (see Section 11.6 of the protocol)			
Progression/Relapse; Survival status [v]				X

Abbreviations: AML, acute myeloid leukemia; ; ECG, electrocardiogram; ECHO, echocardiogram; FISH, fluorescence in situ hybridization; MUGA, multi-gated acquisition; WOCBP, women or child-bearing potential.

[†] All cycles are 28 days.

[††] Study site personnel must obtain signed informed consent before any study-specific procedures are conducted unless these are part of the standard of care and must document the informed consent process in the patient's medical record.

*These assessments need not be performed if obtained as part of the Screening evaluation within 48 hours of Cycle 1, Day 1 (C1D1) and are consistent with eligibility requirements.

**Beginning Cycle 1, Day 22, there is a study visit scheduling window of +/- 1 day.

[a] Perform complete physical examination including neurological exam at Screening **within 14 days of C1D1**. At all other times, perform abbreviated, targeted examination. Report all treatment-emergent, clinically relevant abnormal physical findings on the adverse events eCRF.

[b] Includes resting heart rate, systolic/diastolic blood pressures, body temperature (°C); percent oxygen saturation is measured by pulse oximetry.

[c] Record both height and weight at Screening and thereafter only body weight.

[d] The following information minimally will be recorded: age and date of diagnosis; subtype of AML at diagnosis (*de novo* AML, AML with myelodysplastic features or therapy related AML); best response to last prior regimen (partial remission; stable or progressive disease; primary refractory disease after 1st line

induction or recurrence of leukemia after CR) per ELN criteria (Appendix 2 of the protocol); number of relapses (0, 1, ≥2); type of *FLT3* mutation (ITD, TKD or both) and allelic frequency (high, low) at diagnosis (if applicable) and baseline; history of hematopoietic stem cell transplant including post-transplant best response; prior exposure to a *FLT3* inhibitor (e.g. midostaurin and/or selective FLT3 inhibitor) and presence of other somatic mutations (e.g. *NPM1*, *IDH1*, *IDH2*, *DNMT3A, TP53*) at diagnosis and baseline, if known.

[e] Obtain triplicate measurements, each separated by approximately 2 minutes with patient in semi-recumbent position at the following timepoints in **Phase 1b**: Screening, C1D1 (pre-dose and paired with PK blood samples at 1, 2, 4, & 6 hours post-LANRA dose), C1D8 (pre- or post-dose), C1D15 (pre-dose and paired with PK blood samples at 1, 2, 4, & 6 hours post LANRA and gilteritinib dosing), C2D1, C3D1 (both pre- or post-dose), and as clinically indicated thereafter. **NOTE:** Pre-dose is considered 0-2 hours before LANRA dosing on C1D1 and LANRA/gilteritinib dosing on C1D15. See Table 4 below for C1D1 paired PK sampling timepoints and Table 5 for C1D15 paired PK sampling time points. In **Phase 2**, obtain triplicate ECG measurements at Screening, C1D8, C1D15, C2D1, and C3D1 (all pre- or post-dose).

[f] Record left ventricular ejection fraction and any other clinically relevant findings at Screening. Thereafter, repeat ECHO/MUGA as clinically indicated.

[g] Includes hemoglobin, hematocrit, white blood cell (WBC) count, platelet count and WBC differential (neutrophils, bands, lymphocytes, monocytes, eosinophils, basophils, blasts).

[h] Includes prothrombin time (PT), activated partial thromboplastin time (aPTT), international normalized ratio (INR), fibrinogen and D-dimer levels. After Screening, monitor coagulation parameters on Days 1 and 15 of Cycle 1, Day 1 of Cycles 2 and 3 and as clinically indicated thereafter.

[i] Includes electrolytes (sodium, potassium, chloride, total CO_2 and/or bicarbonate, calcium, phosphate, magnesium), liver function studies (aspartate aminotransferase [AST], alanine aminotransferase [ALT], total and direct bilirubin), albumin, lactate dehydrogenase (LDH), alkaline phosphatase, blood urea nitrogen or serum/plasma urea, creatinine, uric acid, glucose, creatine phosphokinase (CPK), amylase and lipase. Monitor electrolytes, liver function tests, blood urea nitrogen (BUN), creatinine, uric acid, and phosphate in accordance with institutional care standards until the risk of tumor lysis syndrome has abated. For patients receiving nephrotoxic antimicrobial agents, closer monitoring of renal function is recommended, consistent with institutional standards of care.

[j] Includes dipstick evaluation for pH, glucose, protein, blood, and leukocyte esterase; conduct microscopic evaluation for red and white blood cells only if dipstick is abnormal. Perform urinalysis at Screening, and as clinically indicated during study treatment and thereafter if urine dipstick is abnormal.

[k] Perform serum pregnancy test in WOCBP during Screening **within 7 days of C1D1**. Thereafter, perform urine ß-hCG test at the beginning of each new cycle of study treatment and at End-of-Treatment. Repeat serum pregnancy test for confirmation of a positive urine ß-hCG test result.

[m] Perform bone marrow aspiration at Screening for morphology, karyotyping/FISH and biomarker assessments. A trephine bone marrow biopsy is required for patients in whom a satisfactory aspirate cannot be obtained (eg. due to dry tap, hypocellular or hemodiluted sample). Perform bone marrow aspiration (or biopsy) for response and biomarker assessments on Day 1 of Cycle 2 and Cycle 3 and every 3 cycles thereafter (ie.. Cycle 6, Cycle 9, etc.) until CR/CRh is documented on 2 consecutive bone marrow examinations. At other times, perform bone marrow examination for confirmation of suspected progression/relapse. Measurable residual disease will be assessed retrospectively in bone marrow aspirate (and peripheral blood concurrently) as an exploratory efficacy endpoint in patients who achieve CR or CRh. MRD assessments will be performed in a central testing facility designated by the Sponsor beginning with the 1st documented CR or CRh.

[n] LANRA will be dispensed by study center personnel at the beginning of each 28-day cycle to ensure adequate drug supply for home administration throughout the treatment phase in accordance with details outlined in the Pharmacy Manual. Instructions will be provided to patients for dosing, storage and disposition of unused study drug. In Phase 1b, patients will receive LANRA *only* on C1D1 under medical supervision after predose PK/PD blood samples are obtained.

Beginning on C1D2, patients will begin combination therapy with LANRA and gilteritinib, after the C1D2 (Hour 24) PK/PD blood samples are obtained (see Table 4). In Phase 2, patients will begin combination therapy with LANRA and gilteritinib on C1D1.

[o] Record all treatment-emergent adverse events including clinically relevant laboratory abnormalities on the adverse event eCRF. Treatment-emergent events are those that either begin or increase in intensity on C1D1 through the End-of-Treatment Evaluation. Record only serious adverse events that occur during the Screening evaluation. Events that meet the criteria for seriousness must be reported immediately, without undue delay, and within 24 hours to Kronos Bio Drug Safety (or designee). All adverse events are graded for severity using NCI-CTC AE, v. 5.0. **See Section 16.0 of the protocol for further details on AE reporting**.

[p] Record all medications (including over-the-counter medications) patient is taking from the time of informed consent until C1D1.

[q] Record all new or continuing medications patient is taking from C1D1 until the End-of-Treatment Visit.

[r] All male patients capable of fathering a child and WOCBP should be counseled regarding the need for pregnancy prevention in accordance with guidelines outlined in Appendix 6 of the protocol.

[s] The End-of-Treatment Study Visit must occur 30 ± 7 days after the last dose of either gilteritinib or LANRA (whichever is later) or prior to initiation of new anticancer therapy.

[t] During the treatment phase, these assessments may be performed at a licensed facility other than the trial site up to 1 day prior to a scheduled study visit.

[u] After Cycle 2, additional blood samples for PD assessments are requested on Day 1 of Cycle 3 and every 3 cycles thereafter (ie, Cycle 6, Cycle 9, etc.) until 2 consecutive response assessments of CR/CRh are documented, and at End-of-Treatment. Blood samples for PD assessments on Day 1 of Cycle 3 and every 3 cycles thereafter should be collected pre-dose.

[v] Patients who discontinue study treatment for reasons other than progression/relapse will be followed monthly until progression/relapse at the discretion of the investigator and in the absence of intervening anti-leukemic therapy. Following progression/relapse, patients will be followed for survival every 3 months. Acceptable windows for post-treatment follow-up visits are ± 1 week.

Table 4: Schedule of PK and PD Assessments – Phase 1b, Cycle 1, Day 1 (C1D1) to Cycle 1, Day 8 (C1D8)

Cycle, Day	C1D1								C1D2	C1D8
Hour	-2 to 0 (predose)	0.5 ± 5 min (postdose)	1.0 ± 5 min	2.0 ± 10 min	3.0 ± 10 min	4.0 ± 30 min	6.0 ± 30 min	8.0 ± 30 min	24 ± 2 (predose)	24 ± 2 (predose)
PK (plasma)	X	X	X	X	X	X	X	X	X	X
PD (whole blood)	X			X		X		X	X	X

Table 5: Schedule of PK and PD Assessments – Phase 1b, Cycle 1, Day 15 (C1D15) to Cycle 2, Day 1 (C2D1)

Cycle, Day	C1D15								C1D16	C1D22	C2D1
Hour	-2 to 0 (predose)	0.5 ± 5 min (postdose)	1.0 ± 5 min	2.0 ± 10 min	3.0 ± 10 min	4.0 ± 30 min	6.0 ± 30 min	8.0 ± 30 min	24 ± 2 (predose)	24 ± 2 (predose)	24 ± 2 (predose)
PK (plasma)	X	X	X	X	X	X	X	X	X	X	
PD (whole blood)	X			X		X		X	X	X	X

Table 6: Schedule of PK and PD Assessments – Phase 2, Cycle 1, Day 1 (C1D1) to Cycle 2, Day 1 (C2D1)

Cycle, Day	C1D1			C1D15			C1D22	C2D1
Hour	-2 to 0 (predose)	2.0 ± 10 min	4.0 ± 30 min	0 to -2 (predose)	2.0 ± 10 min	4.0 ± 30 min	0 to -2 (predose)	24 ± 2 (predose)
PK (plasma)	X	X	X	X	X	X	X	
PD (whole blood)	X	X	X	X	X	X	X	X

Abbreviations: PD, pharmacodynamic(s); PK, pharmacokinetic(s).

In both Phase 1b and Phase 2, plasma samples for LANRA and gilteritinib concentrations should be obtained at the following additional unscheduled time points:

1. As part of the diagnostic evaluation of AEs attributed to LANRA and/or gilteritinib (if possible).
2. Coincident with an increase in ECG QTc interval of >500 msec or >60 msec above baseline, based on 2 consecutive measurements (see Section 11.7.3 of the protocol).

3. OBJECTIVES AND ENDPOINTS

Phase 1b: Dose Escalation

Objectives:	Endpoints:
Primary:	
To evaluate the safety of lanraplenib (LANRA) in combination with the FMS-like tyrosine kinase 3 (FLT3) inhibitor gilteritinib, in patients with relapsed/refractory (R/R) *FLT3*-mutated AML.	Type, incidence, severity, causality, and outcome of adverse events (AEs), including serious and Grade ≥3 AEs; DLTs; MTD/RP2D of LANRA in combination with standard doses of gilteritinib.
Secondary:	
To characterize the pharmacokinetics (PK) of LANRA alone and in combination with gilteritinib. To characterize the PK of gilteritinib when administered in combination with LANRA.	Standard PK parameters including (but not limited to) maximal plasma concentration (C_{max}), time to maximal plasma concentration (T_{max}) and area under the plasma concentration x time curve from hour 0 to the last measurable time point ($AUC_{0\text{-last}}$).
To evaluate preliminary antileukemic activity of the combination in patients with R/R *FLT3*-mutated AML.	Composite CR rate including CR and CRh as defined by ELN 2017 criteria (Döhner 2017). Duration of response, defined as the time from first qualifying response (CR/CRh) until relapse or death from any cause, as assessed by study investigators. Event free survival, defined at the time from treatment onset until treatment failure (i.e., failure to achieve CR/CRh), relapse from CR/CRh, or death from any cause. Overall survival defined as the time from enrollment until death from any cause.
Exploratory:	

To assess the incidence of *FLT3* measurable residual disease (MRD) negativity (if any) in bone marrow and peripheral blood among patients who achieve CR/CRh.	Assessment of MRD in bone marrow and peripheral blood beginning with the 1st bone marrow examination indicating CR/CRh using a molecular characterization platform (eg, reverse transcriptase polymerase chain reaction [RT-PCR]; next generation sequencing [NGS]). Level of concordance for MRD in bone marrow aspirate and peripheral blood in patients with CR/CRh.
To explore the predictive value of potential biomarkers at baseline that correlate with clinical outcomes (eg, CR/CRh, EFS, duration of response). To characterize pharmacodynamic properties (including the extent of target engagement) of LANRA alone and in combination with gilteritinib.	Mutational profiling in leukemic cells using standard platforms eg, NGS, for correlations with response and progression. Baseline and longitudinal gene expression levels (eg *HOXA9/MEIS1*) in leukemic cells from peripheral blood and bone marrow aspirate using standard expression profiling platforms (eg, Nanostring® or NGS) for correlations with response and progression. Baseline and longitudinal targeted protein/phosphoprotein profiling (eg phosphorylated spleen tyrosine kinase [pSYK] expression)/expression of other relevant genes in leukemic cells for correlations with response and progression.
To assess the metabolite profile of LANRA in plasma.	Type(s) of prominent LANRA metabolites in plasma.

Phase 2: Cohort Expansion

Objectives:	Endpoints:
Primary:	
To further evaluate the safety of LANRA at its RP2D in combination with gilteritinib in patients with *FLT3*-mutated AML.	Type, incidence, severity, causality, and outcome of AEs, including serious and Grade ≥3 AEs; DLTs for LANRA at its RP2D in combination with standard doses of gilteritinib

Secondary:	
To further evaluate preliminary antileukemic activity of the combination in patients with R/R *FLT3*-mutated AML.	Composite CR rate including CR and CRh as defined by European LeukemiaNet 2017 criteria (Döhner 2017). Duration of response, defined as the time from first qualifying response (CR/CRh) until relapse or death from any cause, as assessed by study investigators. Event free survival, defined at the time from treatment onset until treatment failure (ie. failure to achieve CR/CRh), relapse from CR/CRh or death from any cause. Overall survival defined as the time from enrollment until death from any cause.
Exploratory:	
To further assess the incidence of *FLT3* measurable residual disease (MRD) negativity (if any) in bone marrow and peripheral blood among patients who achieve CR/CRh.	Assessment of MRD in bone marrow and peripheral blood beginning with the 1st bone marrow examination indicating CR/CRh using a molecular characterization platform (eg, RT-PCR, NGS). Level of concordance for MRD in bone marrow aspirate and peripheral blood in patients with CR/CRh.
To further explore the predictive value of potential biomarkers at baseline that correlate with clinical outcomes eg, CR/CRh, EFS, duration of response). To further characterize pharmacodynamic properties (including the extent of target engagement) of LANRA alone and in combination with gilteritinib.	Mutational profiling in leukemic cells using standard platforms (eg, NGS), for correlations with response and progression. Baseline and longitudinal gene expression levels (eg, *HOXA9/MEIS1*) in leukemic cells from peripheral blood and bone marrow aspirate using standard expression profiling platforms (eg Nanostring® or NGS) for correlations with response and progression. Baseline and longitudinal targeted protein/phosphoprotein profiling (eg, pSYK expression)/expression of other relevant genes in leukemic cells for correlations with response and progression.
To further assess the PK of LANRA in combination with gilteritinib.	Sparse PK sampling for LANRA and gilteritinib plasma concentrations.

4. GENERAL STATISTICAL CONSIDERATIONS

4.1. STATISTICAL HYPOTHESIS

There is no formal statistical hypothesis to be evaluated in this study; all statistical testing will be descriptive in nature.

4.2. SAMPLE SIZE

Approximately 100 patients in total are planned for enrollment in the study. Up to 69 patients will be enrolled to phase 1b with the actual number determined by the number of dose cohorts and number of patients in each cohort evaluated for determination of LANRA MTD/RP2D. Approximately 31 patients are planned for enrollment in Phase 2. The optimal two-stage design to test the null hypothesis that the composite CR rate (CR/CRh) is ≤23% (XOSPATA® [gilteritinib] US Prescribing Information, 2022) versus the alternative hypothesis, that CR/CRh is ≥23% has an expected (average) sample size of 19.26 and a probability of early termination of 0.710. If the study regimen is not effective, there is a 0.025 probability of concluding that it is (the target for this value was 0.025 one-sided). If the study regimen is effective, as defined by CR/CRh = 46%, there is a 0.806 probability of concluding that it is (the target for this value was 0.800). (Calculations made using PASS 2020). After testing the treatment regimen on 12 patients in the first stage (including those treated at the MTD/RP2D in Phase 1b), the trial will be terminated if 3 or fewer patients respond. If the trial enrolls the second stage, additional patients will be enrolled to obtain at least 37 patients treated on the RP2D dose (including at least 6 patients enrolled to Phase 1b and treated at the RP2D). If the total number of patients enrolled to stage 1 and stage 2 who achieve a CR/CRh is ≤13, the study regimen is rejected.

4.3. RANDOMIZATION AND MASKING

This is an open-label study. Patients who satisfy all inclusion and exclusion criteria will be enrolled into the next available patient slot.

4.4. HANDLING OF DATA

4.4.1. Strata and Covariates

There are no planned adjustments for covariates.

4.4.2. Examination of Patient Subsets

There are no planned subsets.

4.4.3. Multiple Testing and Comparisons

All analyses will be conducted without adjustments for multiple testing or comparisons.

4.4.4. Definitions and Data Derivations

Age
The age of a patient is defined as (Date of Day Informed Consent Signed – Date of Birth + 1)/365.25.

Cycle 1 Day 1
Cycle 1 Day 1 (C1D1) is defined as the earliest day that either study drug is administered.

Baseline Value
Baseline value is defined as the last observation of an assessment prior to the first dose of either study drug. For ECG assessments, the baseline value is the average of the predose triplicate measures taken on C1D1.

Study Day
Defined as the day relative to the administration of the first dose of either study drug (i.e., Cycle 1 Day 1). 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 either study drug 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 predose/screening assessments (e.g., an assessment taken on C1D1 where no time was recorded but was not designated as a predose assessment will be considered a post-baseline assessment and an assessment on C1D1 without a time but designated as a predose 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

Months since Initial Diagnosis
Months since initial diagnosis will be calculated as the actual number of calendar months between the date of initial diagnosis and C1D1.

Overall Duration of Exposure

The latest Date of either study drug – C1D1 + 1. Dates of last dose are captured on the End of Treatment eCRFs.

Duration of Exposure to LANRA
Duration of exposure to LANRA will be defined as the Date of Last Dose of LANRA – Date of First Dose of LANRA + 1. The date of last dose is captured on the End of Treatment eCRF.

Duration of Exposure to Gilteritinib
Duration of exposure to Gilteritinib will be defined as the Date of Last Dose of Gilteritinib – Date of First Dose of Gilteritinib + 1. The date of last dose is captured on the End of Treatment eCRF.

Last Study Drug
The study drug with the latest date of exposure.

Cumulative Dose of LANRA
The sum of the LANRA doses administered to a patient measured in milligrams (mg)

Cumulative Dose of Gilteritinib
The sum of the gilteritinib doses administered to a patient measured in milligrams (mg)

Actual Dose Intensity of LANRA (mg/cycle)
Defined as the cumulative dose of LANRA / (duration of exposure / 28)

Actual Dose Intensity of Gilteritinib (mg/cycle)
Defined as the cumulative dose of gilteritinib / (duration of exposure / 28)

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

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

Treatment Interruptions
Treatment Interruptions will be defined as doses that are missed for any reason and will be calculated using the Dosing Log eCRF page by obtaining the number of missed doses over the duration of treatment.

Dose Reductions
Dose reductions will be defined as a planned reduction in dose level for AE management. These will be managed as noted in Table 2 (for gilteritinib) and Table 3 (for LANRA) of the protocol and identified by comparing the dose received as recorded in the Dosing Log eCRF page versus the dose assigned.

Duration of Follow-up

Duration of follow-up will be defined as the End of Study date – C1D1 + 1. End of study date is collected on the End of Study eCRF. Patients who are lost to follow-up will be censored at their date of last contact.

Measurable Residual Disease (MRD)
Presence of leukemia cells using a molecular characterization platform (eg. RT-PCR, NGS)

MRD Negative
A patient is considered MRD Negative if he/she has exhibits MRD negativity (<0.01%) in bone marrow as measured by a molecular assay for *FLT3* mutation (e.g., by next generation sequencing) in a central laboratory in the setting of a CR or CRh .

Overall Survival
The time from enrolment until death from any cause.

Complete Remission (CR)
Complete remission requires all of the following:

- Bone marrow blasts <5%
- Absence of circulating blasts and blasts with Auer rods
- Absence of extramedullary disease (ie. leukemia outside of bone marrow confirmed by biopsy)
- Absolute neutrophil count > 1.0 x 10^9/L (1,000/μL)
- Platelet count > 100 x 10^9/L (100,000/μL)

Complete Remission with partial hematologic recovery (CRh)
Complete remission with partial hematologic recovery requires all aforementioned 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 Remission with incomplete blood count recovery (CRi)*
Complete remission with incomplete blood count recovery requires all aforementioned CR criteria except for residual neutropenia or thrombocytopenia and is defined as

- Bone marrow blasts < 5%
- Absence of circulating blasts and blasts with Auer rods

- Absence of extramedullary disease
- Absolute neutrophil count > 1.0 x 10^9/L (1,000/μL) or platelet count > 100 x 10^9/L (100,000/μL)

*If patients meet criteria for both CRh and CRi, they should be classified as CRh

Morphological Leukemia Free State (MLFS)**

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

** 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 Remission (PR)
PR meets all hematologic criteria of CR:

- Absolute neutrophil count ≥ 1.0 x 10^9/L (1,000/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 pre-treatment

Stable Disease
Absence of 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 count 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)
- Persistent bone marrow blast percentage > 70% over ≥ 3 months without at least a 100% improvement in absolute neutrophil counts (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
- > 50% increase in circulating blasts to > 25 x 10^9/L (>25,000/μL) in the absence of Differentiation Syndrome***
- New Extramedullary disease

*** Certain targeted therapies, for example, those inhibiting mutant IDH proteins, other kinases or targets may cause a Differentiation Syndrome, i.e., a transient increase in the percentage of bone marrow blasts accompanied by an increase in circulating blasts. 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.

Composite Complete Remission (cCR)
Achieving either complete remission or complete remission with partial hematologic recovery.

Duration of Response
Duration of response is defined as the time from first qualifying CR (CR or CRh) until relapse or death from any cause, as assessed by study investigators.

Event-free survival (EFS)
Event-free survival (EFS) is defined as the time from C1D1 until treatment failure (i.e., failure to achieve CR or CRh), relapse from CR/CRh or death from any cause.

Dose Limiting Toxicity
A DLT is defined as any of the following toxicities occurring within the DLT assessment period *unless it can be unequivocally determined to be unrelated to LANRA*:

- A nonhematologic toxicity of Grade ≥3 that is at least possibly related to LANRA with the exception of:
    - nausea, and vomiting controlled with antiemetic therapy,
      (Note: Grade 3 nausea or vomiting that requires tube feeding, total parenteral nutrition and/or initial or prolonged hospitalization for management will constitute a DLT. Grade 4 nausea or vomiting will always constitute a DLT regardless of management.)
    - infection or infection-related toxicities such as fever/sepsis, febrile neutropenia*,
    - fatigue, alopecia,
    - isolated electrolyte abnormalities (ie. those without clinical consequences) correctable to Grade ≤1 within 72 hours with or without supplementation,
    - Grade 3 or 4 Differentiation Syndrome successfully managed with high-dose steroids plus supportive care interventions with resolution within 7 days and without resulting end-organ damage.
- Any toxicity resulting in administration of <80% of the cumulative, Cycle 1 dose for either LANRA or gilteritinib.
    - Note: Administration of <80% of the cumulative Cycle 1 dose for LANRA or gilteritinib for reasons other than toxicity (eg, non-compliance or administrative reasons) will not be considered a DLT but will make the subject unevaluable for purposes of MTD determination and require the subject to be replaced.
- Grade 4 neutropenia or thrombocytopenia lasting >28 days after treatment onset that is not attributed to active AML and at least possibly related to LANRA.

- Any toxicity resulting in reduction in the dose of LANRA in Cycle 1.

*In general, infection will not constitute a DLT unless it is assessed as having resulted from unexpectedly prolonged myelosuppression in the setting of < 5% blasts in the bone marrow, absence of myelodysplastic changes, and/or absence of AML by flow cytometry in the bone marrow.

Adverse Event
An AE is defined as any unfavorable or unintended sign, symptom, laboratory abnormality or disease (new or exacerbated) temporally associated with the use of a study drug, whether considered causally related to the study drug or not.

All AEs defined as reportable in Section 16.6 of the protocol will be recorded on the ADVERSE EVENTS CRF.

Treatment-emergent Adverse Event (TEAE)
Any adverse event that occurs on or after C1D1 and up to the End-of-Treatment visit following discontinuation of the last study drug is considered treatment-emergent.

Events that occur after the initiation of non-protocol anti-leukemic therapy will be considered as non-treatment emergent even if they occur before the End-of-Treatment visit.

Treatment-emergent Laboratory Toxicity (TELT)

A TELT is identified based on the laboratory data recorded in the eCRF and is defined as a National Cancer Institute - Common Toxicity Criteria for Adverse Events (NCI-CTCAE) v5.0 (NCI 2017) grade 1 or higher abnormality, which occurs on or after C1D1 and up to the End-of-Treatment visit and exhibits at least 1 grade shift from the baseline value.

Events that occur after the initiation of non-protocol anti-leukemic therapy will be considered as non-treatment emergent even if they occur before the End-of-Treatment visit.

Concomitant Medications
Concomitant medications are those medications taken on or after C1D1. This includes medications started prior to C1D1 and continued after C1D1. These medications will be recorded in the PRIOR/CONCOMITANT MEDICATION eCRF.

Prior Medications
Prior medications are those medications taken from the time of informed consent until C1D1. These medications will be recorded in the PRIOR/CONCOMITANT MEDICATION eCRF.

End of Study
After all enrolled patients either relapse or die or 5 years after the last patient enrolls (whichever is earlier) or if the sponsor decides to terminate the trial.

4.4.4.1. Presentations by Study Visits

All study visits should be scheduled relative to C1D1 regardless of any treatment interruptions. Visits will be presented according to the visit designation (eg, Cycle 1, Day 4) as recorded on the eCRF. If the same assessment(s) are collected multiple times within a given visit, the last non-missing value will be used for summary presentations. There are no windows for study visits from C1D1 through C1D16. Acceptable windows for study visits beginning on Cycle 1, Day 22 are ± 1 day. Unscheduled visits will not be included in by-visit data presentations but will be included in all tables of treatment-emergent laboratory toxicities. All data will be presented in data listings.

4.4.4.2. Missing Data

Every effort will be made to obtain required data at each scheduled evaluation from all enrolled patients. See Section 4.4.4.4 for details of imputing missing dates. 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.

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

4.4.4.3. Imputation for Alphanumeric Data

Should there be instances where a clinical laboratory parameter is reported with imbedded non-numeric characters, 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".

4.4.4.4. 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 (eg, if an adverse 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 C1D1, then the start day of the event will be assigned to the date corresponding to C1D1. For example, if an AE occurred in December 2021, and C1D1 was on 8 December 2021, 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 event occurs in the same year as C1D1, then the start date of the event will be assigned to the C1D1 date. Following this rule, in the event a patient started 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 2023 and initiation of LANRA in 2021, the AE start date would be 01 January 2023.

- 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 data listings, start and stop dates of events will be displayed as reported on the eCRF (i.e., imputed values will not be listed).

4.5. TIMING OF ANALYSES

There will be no interim analyses in Phase 1b other than those associated with decisions pertaining to dose escalation and final determination of the MTD/RP2D.

The final analysis will occur at the End of Study as defined in section 4.4.4, where the clinical database has been cleaned, quality checked, and the database has been locked.

5. ANALYSIS POPULATIONS

The following analysis populations will be defined for this study: DLT Evaluable, Safety, Pharmacokinetic, Pharmacodynamic, and Efficacy Evaluable.

5.1. DLT EVALUABLE POPULATION

Patients will be evaluable for DLT in Part 1 if they meet the following criteria:

- They experience a DLT (as defined in Appendix 1 of the study protocol) after receiving ≥1 dose of LANRA during the DLT assessment period (Cycle 1, Day 1 until Cycle 2, Day 1).
- They receive at least 80% of the intended cumulative doses of LANRA and gilteritinib during the DLT assessment period without the occurrence of a DLT.

The DLT Evaluable Population will be used for all DLT data summaries.

5.2. SAFETY POPULATION

The Safety Population consists of all patients who receive ≥ 1 dose of either study drug and have at least 1 on-treatment safety-related observation, where a safety-related observation is defined as a reported AE or post-baseline assessment of vital signs, ECGs or safety laboratory assessments.

Patients will be analyzed according to their assigned dose level. The safety population will be used for all summaries of Safety data.

5.3. PHARMACOKINETIC POPULATION

The PK population consists of all patients with at least 1 post-dose LANRA plasma concentration.

Patients will be analyzed according to the dose level received at time of assessment. The PK population will be used for all summaries of PK data.

5.4. PHARMACODYNAMIC POPULATION

The PD population consists of all patients with baseline, and at least 1 post-dose pharmacodynamic assessment.

Patients will be analyzed according to the dose level received at the time of assessment. The PD population will be used for all summaries of PD data.

5.5. EFFICACY EVALUABLE POPULATION

The Efficacy Evaluable (EE) population will include all patients who receive ≥1 dose of either study drug and complete the first protocol-specified response assessment or have discontinued study treatment for toxicity or die prior to the first response assessment.

Patients in the EE population will be analyzed according to their assigned dose level. The EE population will be used for all summaries of efficacy data unless otherwise stated.

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 patients (n), mean, medians, interquartile ranges, standard deviation (STD), minimum, and maximum for continuous data and frequencies and percentages for categorical data. The term "treatment group" or "dose group" refers to the dose level of LANRA. Unless otherwise specified, data summaries and analyses described below will be reported by dose group and overall, in Phase 1b. Select data collected during the study will be included in data listings. Unless otherwise noted, the data will be sorted first by dose level/cohort, patient number, and then by date within each patient number.

6.1. PATIENT DISPOSITION, DEMOGRAPHIC, AND BASELINE CHARACTERISTICS

The number of patients screened, enrolled, treated, and discontinued from study treatment and follow-up will be summarized. The primary reason for study treatment discontinuation and follow-up will be summarized for Phase 1b.. The number of patients in each analysis population will be presented by treatment group.

Demographic data including age (years), sex, race, and ECOG PS will be summarized for the safety population in Phase 1b using descriptive statistics.

6.2. MEDICAL HISTORY

All clinically relevant prior or concurrent medical conditions will be mapped to a system organ class (SOC) and PT using the version of the Medical Dictionary for Regulatory Activities (MedDRA) in effect at the time of database lock. Medical history will be listed.

6.3. LEUKEMIA HISTORY

The following baseline characteristics will be summarized using descriptive statistics for patients in Phase 1b: age; months since initial diagnosis; subtype of AML at diagnosis (*de novo* AML, AML with myelodysplastic features or therapy-related AML); best response to last prior regimen (partial remission, stable or progressive disease, primary refractory disease after 1st line induction or recurrence of leukemia after CR) per ELN criteria; number of relapses (0, 1, ≥2); type of *FLT3* mutation (ITD, TKD or both) and allelic frequency (high, low); history of hematopoietic stem cell

transplant including post-transplant best response (if known); prior exposure to a *FLT3* inhibitor (e.g. midostaurin) and presence of other somatic mutations (e.g. *NPM1*, *IDH1*, *IDH2*, *DNMT3A, TP53*) at diagnosis and baseline, if known.

The number of prior systemic antileukemic regimens will be summarized. By-patient listings of systemic leukemia treatment regimens, including start and stop dates for each regimen component, will be generated for Phase 1b. Anti-neoplastic agents will be classified using 11-digit, World Health Organization (WHO) Drug Dictionary codes preferred name and the Anatomic Therapeutic Chemical (ATC) Classification for pharmacologic properties and summarized by frequency distributions for Phase 1b.

6.4. EXPOSURE TO TREATMENT

Duration of exposure, cumulative dose, actual and relative dose intensities will be summarized for LANRA and gilteritinib. Treatment interruptions, dose reductions and reasons for discontinuation of gilteritinib/LANRA will be summarized by frequency distributions and percentages.

6.5. EFFICACY ANALYSIS

Best response (CR, CRh, CRi, PR, MFLS, stable disease [SD], and progressive disease [PD]) will be summarized for the efficacy-evaluable population by frequency distributions and percentages in accordance with ELN 2017 criteria. Patients with no post-baseline response assessments will be considered non-responders. The 95% confidence interval (CI) for estimates of the proportion of patients with CR/CRh will be constructed with exact methods for the binomial distribution (eg Clopper-Pearson intervals). Additionally, 95% CIs for the estimates of the proportion of patients with any CR (CR, CRh or CRi) will be constructed in a similar manner.

Overall survival will be estimated using K-M methodology, including 95% CIs for quartiles Minimal and maximal survival times will be computed by dose level. Patients alive at last follow-up will be censored at the date of last contact.

6.6. SAFETY ANALYSIS

Descriptive summaries will be generated for select safety data including treatment-emergent adverse events, changes from baseline in selected laboratory assessments, and worst QTcF interval. All adverse events will be graded for severity using NCI-CTCAE v5.0. Toxicities that are not specified in the NCI-CTCAE will be graded for severity 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

6.6.1. Adverse Events

Adverse events will be mapped to the MedDRA version in effect at the time of database lock.

TEAEs will be reported by dose level and overall. .

If a patient 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. Patients with events mapping to multiple preferred terms within the same system organ class will be counted once at the system organ class level.

TEAEs will be summarized by treatment group using PT and SOC. Separate summaries of Grade 3 and 4 treatment-emergent adverse events, treatment-emergent serious adverse events (TESAEs), TEAEs related to LANRA, and events leading to treatment interruption, dose reduction, treatment discontinuation or death will be generated. All adverse events reported will be listed for individual patients showing both verbatim and preferred terms.

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

6.6.2. Dose Limiting Toxicities

DLTs will be summarized for Phase 1b. DLTs will be summarized using descriptive statistics. Frequency counts for each unique DLT will also be presented.

6.6.3. Clinical Laboratory Assessments

Laboratory toxicities will be graded for severity using NCI-CTCAE Version 5.0 (see Appendix B for more details about laboratory grading). Frequencies and percentages of patients experiencing treatment-emergent grade 3 and 4 toxicities will be summarized.

Descriptive summaries of select quantitative clinical laboratory results (hemoglobin, white blood cells [WBC], absolute neutrophil count [ANC], platelets, blasts count, AST, ALT, alkaline phosphatase, amylase, lipase, total bilirubin, direct bilirubin, serum creatinine, urea nitrogen) and their changes from baseline will be presented by study visit.

6.6.4. Prior and Concomitant Medications

Both prior and concomitant medications will be classified using WHO Drug Dictionary codes preferred name and ATC Classification for therapeutic indication. Prior medications (defined as all medications administered from signing of informed consent until C1D1) and concomitant medications (defined as all new or ongoing medications administered from C1D1 until the End-of-Treatment Evaluation) will be listed.

6.6.5. Vital Signs, Oxygen Saturation

Vital signs include resting heart rate, seated systolic and diastolic blood pressures and body temperature (ºC). Percent oxygen saturation as measured by pulse oximetry will be recorded. Vital signs/percent oxygen saturation will be listed.

6.6.6. Electrocardiograms

The number and proportion of patients having a worst post-baseline average Fridericia corrected QT interval (QTcF) value from > 450 msec to 480 msec, > 480 msec to 500 msec, and > 500 msec will be summarized. In addition, patients with an increase from baseline of > 30 msec to 60 msec and > 60 msec will be summarized.

ECG results will be listed.

6.6.7. Physical Examinations

Physical examination will include body weight, height (at screening only), and a full neurological examination; results will be listed Clinically relevant abnormal physical findings that are treatment-emergent will be reported as TEAEs.

7. CHANGES IN THE PLANNED ANALYSES

The estimated total number of patients was increased from 35 to 100 to accommodate a potential 4th dose cohort in Phase 1b, to increase precision of the type 1 error to 0.025 (1-sided) in Phase 2 for the composite CR endpoint, and to allow for backfill patient enrollment. Eighty percent (80%) CIs for proportions of patients with CR/CRh, those with any CR (CR, CRh or CRi), medians and landmark rates for EFS and duration of response were increased to 95% to reflect the increase in estimated total number of patients.

In light of the Sponsor's decision to terminate the trial at completion of Phase 1b, all analyses, data summaries and listings will be restricted to results from Phase 1b patients only. Phase 2 was not be enrolled.

Following the completion of the protocol specified analyses as specified in this SAP, the sponsor may choose to conduct additional exploratory analyses. Such analyses will be detailed in a separate document.

8. REVISION HISTORY

Date	Revision	Rationale
15MAR2024	Removed Phase 2 analysis	Align with new protocol amendments and analysis reduction due to study termination

9. REFERENCES

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Kalbfleisch JD, Prentice RI. The Statistical Analysis of Failure Time Data. New York, NY: John Wiley & Sons, Inc; 1980.

Lee JJ, Kuo Y-W, Liu D, Chen N. Bayesian Toxicity Monitoring. MD Anderson Cancer Center, Houston, TX. v2.2.3.0; last updated April 22, 2021.

10. PROPOSED TABLES, LISTINGS, AND FIGURES

Tables	
14.1.1	Subject Disposition and Discontinuation Summary, All Patients Enrolled: Phase 1b
14.1.2.1	Demographics, Safety Population : Phase 1b
14.1.2.2	Baseline Disease Characteristics, Safety Population : Phase 1b
14.1.4.1	Summary of Exposure, Safety Population: Phase 1b
14.1.4.2	Summary of Prior Antileukemic Regimens, Safety Population: Phase 1b
14.2.1	Summary of Best Response by ELN 2017 response criteria, Efficacy Evaluable Population: Phase 1b
14.2.2	Overall Survival, Safety Population: Phase 1b
14.3.1.1	Overview of Treatment Emergent Adverse Events, Safety Population: Phase 1b
14.3.1.2	Treatment-Emergent Adverse Events by System Organ Class, Preferred Term (All Cycles), Safety Population: Phase 1b
14.3.1.3	Treatment-Emergent Non-Serious Adverse Events by System Organ Class, Preferred Term (All Cycles), Safety Population: Phase 1b
14.3.1.4	Grade 3 or 4 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Greatest Severity (All Cycles), Safety Population: Phase 1b
14.3.1.5	Treatment-Emergent Serious Adverse Events by System Organ Class, Preferred Term (All Cycles), Safety Population: Phase 1b
14.3.1.6	Treatment Related Adverse Events by System Organ Class, Preferred Term (All Cycles), Safety Population: Phase 1b

14.3.1.7	Treatment Emergent Adverse Events Leading to Dose Reduction by System Organ Class, Preferred Term (All Cycles), Safety Population: Phase 1b
14.3.1.8	Treatment Emergent Adverse Events Leading to Treatment Discontinuation by System Organ Class, Preferred Term (All Cycles), Safety Population: Phase 1b
14.3.1.9	Treatment Emergent Adverse Events Leading to Death by System Organ Class, Preferred Term (All Cycles), Safety Population: Phase 1b
14.3.2	Select Grade 3 or 4 Treatment-Emergent Laboratory Toxicities, All Cycles, Safety Population: Phase 1b
14.3.3	Electrocardiogram by Worst QTcF Results: Phase 1b
Listings	
16.2.1	Subject Disposition, All Patients Enrolled: Phase 1b
16.2.2.1	Informed Consent, All Patients Enrolled: Phase 1b
16.2.2.2	Subject Eligibility, All Patients Enrolled: Phase 1b
16.2.3	Analysis Populations, All Patients Enrolled: Phase 1b
16.2.4.1	Demographics, All Patients Enrolled: Phase 1b
16.2.4.2	General Medical History, All Patients Enrolled: Phase 1b
16.2.4.3	AML Diagnosis, All Patients Enrolled: Phase 1b
16.2.4.4	Additional AML Details, All Patients Enrolled: Phase 1b
16.2.4.5	Prior Systemic Anti-Leukemia Regimens, All Patients Enrolled: Phase 1b
16.2.5.1	Drug Accountability, All Patients Enrolled: Phase 1b
16.2.5.2	Exposure Dosing Log, All Patients Enrolled: Phase 1b
16.2.5.3	Cycle Day 1 Dose, All Patients Enrolled: Phase 1b
16.2.5.4	Pharmacokinetic Sampling, All Patients Enrolled: Phase 1b
16.2.5.5	Prior and Concomitant Medications, All Patients Enrolled: Phase 1b
16.2.5.6	Bone Marrow Transplant Post-Study Treatment, All Patients Enrolled: Phase 1b
16.2.6.1	Response Assessment, All Patients Enrolled: Phase 1b
16.2.6.2	Bone Marrow Examination, All Patients Enrolled: Phase 1b
16.2.6.3	Relapse/Progression Assessment, All Patients Enrolled: Phase 1b
16.2.6.4	Relapse Assessment Continued, All Patients Enrolled: Phase 1b
16.2.6.5	Survival Status, All Patients Enrolled: Phase 1b
16.2.7.1	Adverse Events, All Patients Enrolled: Phase 1b
16.2.7.2	Serious Adverse Events, All Patients Enrolled: Phase 1b
16.2.7.3	Deaths, All Patients Enrolled: Phase 1b
16.2.8.1	Laboratory Toxicities – Select Hematology Analytes, All Patients Enrolled: Phase 1b
16.2.8.2	Laboratory Toxicities – Select Serum Chemistry Analytes, All Patients Enrolled: Phase 1b
16.2.8.3	Vital Signs, Height, and Weight, All Patients Enrolled: Phase 1b
16.2.8.4	Physical Examinations – Abnormal Findings, All Patients Enrolled: Phase 1b
16.2.8.5	ECG Central Reading – Triplicate, All Patients Enrolled: Phase 1b
16.2.8.6	Echocardiogram/MUGA, All Patients Enrolled: Phase 1b

16.2.8.7	ECOG Performance Status, All Patients Enrolled: Phase 1b

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 patients 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 patients actually summarized within any given summary module; some patients 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 patients actually contributing to the summary statistics presented in any given summary module. As mentioned above, this may be less than the number of patients 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 eCRFs.
  - ♦ Standard deviations will be reported to two decimal place 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 in the original parameter 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	<lower limit of normal (LLN) - 3 g/dL	<3 - 2 g/dL	<2 g/dL	-
Chemistry	Amylase	Serum amylase increased	>upper limit of normal (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	>3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline	>20.0 x ULN if baseline was normal; >20.0 x baseline if

Category	Analyte Name	CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4
			baseline was abnormal	if baseline was abnormal	if baseline was abnormal	baseline was abnormal
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

Category	Analyte Name	CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4
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
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
	Sodium	Hypernatremia	>ULN - 150 mmol/L	>150 - 155 mmol/L;	>155 - 160 mmol/L	>160 mmol/L

Category	Analyte Name	CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4
Chemistry		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	-	-	-
Chemistry	Bicarbonate or CO2	Blood bicarbonate decreased	< LLN	-	-	-
Chemistry	Serum pH	Acidosis	pH <normal, but >=7.3	-	pH <7.3	-
		Alkalosis	pH >normal, but <=7.5	-	pH >7.5	-
Hematology	Hemoglobin	Anemia	<LLN - 10.0 g/dL; <LLN - 6.2 mmol/L; <LLN - 100 g/L	Hgb <10.0 - 8.0 g/dL; <6.2 - 4.9 mmol/L; <100 - 80g/L	Hgb <8.0 g/dL; <4.9 mmol/L; <80 g/L;	

Category	Analyte Name	CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4
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	-
Hematology	Leukocytes/White Blood Cells Urine Glucose	White blood cell decreased	<LLN - 3000/mm3	<3000 - 2000/mm3	<2000 - 1000/mm3	<1000/mm3
Urinalysis		Glucosuria	Present	-	-	-
Urinalysis	Urine Protein	Proteinuria	1+ proteinuria	2+ and 3+ proteinuria	4+ proteinuria	-

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	-