Protocol Number: KB-LANRA-1001

Official Title: 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

NCT Number: NCT05028751

Document Date: 30 May 2023

TITLE PAGE

Protocol Title:

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

Short Title:

A Study to Evaluate Lanraplenib (LANRA) in Combination With Gilteritinib in Participants with FLT3-mutated Relapsed or Refractory Acute Myeloid Leukemia (AML)

Protocol Number: KB-LANRA-1001

Version Number: 7.0 Global (Amendment 6.0 Global)

Compound: Lanraplenib (LANRA)

Brief Title: Lanraplenib plus gilteritinib therapy in patients with *FLT3* mutated, R/R AML

Study Phase: 1b/2

Sponsor Name: Kronos Bio, Inc.

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Regulatory Agency Identifier Number(s):

IND:	156759
EudraCT:	2022-001279-15

Approval Date: 30 May 2023

FINAL PROTOCOL APPROVAL SHEET

Protocol title: **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**

Sponsor: Kronos Bio, Inc.

Sponsor signatory:

[redacted]

[redacted] Date

Chief Medical Officer

SIGNATURE OF INVESTIGATOR

Protocol title: **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**

Protocol identifier: KB-LANRA-1001

This protocol is a confidential communication of Kronos Bio, Inc. (Kronos Bio). I confirm that I have read this protocol, understand it, and will execute the trial according to all of its specifications. I will also adhere consistently to the ethical principles originating in the Declaration of Helsinki and that are consistent with good clinical practices and applicable laws and regulations. Acceptance of this document constitutes my agreement that no unpublished information contained herein will be published or disclosed without prior written approval of Kronos Bio.

I have read this protocol in its entirety and agree to conduct the study accordingly.

Signature of investigator and Date:

_____

Printed name of investigator:

_____

Investigator title:

_____

Name and address of study site:

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1.0 Synopsis

Protocol Title:
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

Regulatory Agency Identifier Numbers:

IND: 156759

EudraCT: 2022-001279-15

Objectives and Endpoints (Phase 1b):

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 acute myeloid leukemia (AML).	Type, incidence, severity, causality, and outcome of adverse events (AEs), including serious and Grade ≥3 AEs; dose-limiting toxicities (DLTs); maximally tolerated dose (MTD)/recommended Phase 2 dose (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 × 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 complete remission (CR) rate including CR and CR with partial hematology recovery (CRh) as defined by European LeukemiaNet (ELN) 2017 criteria (Döhner 2017). Duration of response (DOR), 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 (EFS), 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 (OS), 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. Mutational profiling in leukemic cells using standard platforms eg, NGS, for correlations with response and progression.
To explore the predictive value of potential biomarkers at baseline that correlate with clinical outcomes (eg, CR/CRh, EFS, duration of response).	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.
To characterize pharmacodynamic properties (including the extent of target engagement) of LANRA alone and in combination with gilteritinib.	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.

Objectives and Endpoints (Phase 2):

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 partial CR (CRh) as defined by ELN 2017 criteria (Döhner 2017). DOR, defined as the time from first qualifying response (CR/CRh) until relapse or death from any cause, as assessed by study investigators. EFS, 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. OS, defined as the time from enrollment until death from any cause.

Exploratory:	
To further assess the incidence of *FLT3* 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).	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.
To further characterize pharmacodynamic properties (including the extent of target engagement) of LANRA alone and in combination with gilteritinib.	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.

Overall Design:

This multicenter, Phase 1b/2 study will investigate the safety, PK, pharmacodynamics (PD), and preliminary anti-leukemic activity of the selective, 3rd generation spleen tyrosine kinase (SYK) inhibitor, LANRA, in combination with the FLT3 inhibitor, gilteritinib, in patients with *FLT3*-mutated 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, 2, 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, for evaluations of the safety, PK, PD, and efficacy of the combination.

Phase 1b: Eligible patients will enroll sequentially into one of the following dose cohorts for PK/PD evaluations and determination of the MTD/RP2D of LANRA in combination with standard dose gilteritinib:

- Cohort 1, LANRA 20 mg QD + gilteritinib 120 mg QD
- Cohort 2, LANRA 40 mg QD + gilteritinib 120 mg QD
- Cohort 3, LANRA 60 mg QD + gilteritinib 120 mg QD
- Cohort 4, LANRA 90 mg QD + gilteritinib 120 mg QD

A "3 + 3" dose escalation scheme will be employed in which 1 DLT reported 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. The starting dose of LANRA is 20 mg once daily (QD).

Phase 2: 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. For both Phase 1b and Phase 2, response assessments will be based on bone marrow and physical examinations and peripheral blood counts. Bone marrow aspirates will be performed on C2D1, C3D1 and every 3 cycles thereafter until the patient exhibits 2 consecutive bone marrow examinations indicating CR or CRh. Patients who have not achieved at least a partial response per ELN 2017 criteria after 6 months of study treatment will permanently discontinue study treatment. 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 CR or CRh, as defined by ELN response criteria (Appendix 2).

Number of Participants:

Approximately 100 patients are estimated to enroll across both parts; patients will be enrolled from multiple trial sites worldwide for Phase 1b and Phase 2. In both Phase 1b and Phase 2, patients will receive their assigned treatment regimen until progression/relapse or lack of response after 6 months of study treatment, intolerance, or withdrawal from study by the patient or study investigator.

Study Duration:

The study will be completed after all enrolled patients either relapse or die, or 5 years after the last patient enrolls (whichever is earlier) or the Sponsor terminates the trial.

Statistical Analysis:
Detailed methodology for summary and statistical analyses of the data collected in this study will be documented in a Statistical Analysis Plan (SAP).

Summary statistics and listings will be used to analyze the study data. Continuous variables will be summarized by means, standard deviations, medians, interquartile ranges, minimal and maximal values. Categorical variables will be summarized by number and percent.

Unless otherwise specified, data summaries and analyses described below will be reported by dose group and overall in Phase 1b and overall in Phase 2 using all available data. Missing data will not be imputed unless otherwise described in the SAP.

DLTs will be summarized by dose group. Descriptive summaries will be generated for all safety data including treatment-emergent adverse events (TEAEs) as well as changes from baseline in selected laboratory assessments, vital signs, physical findings and electrocardiograms (ECGs). All AEs will be graded for severity using National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI-CTCAE) v5.0 (Common Terminology Criteria for Adverse Events (CTCAE) (cancer.gov)).

Plasma concentrations of LANRA and gilteritinib will be tabulated and summarized by dose level, study day, and time in Phase 1b. The PK parameters for gilteritinib and LANRA (and if possible, LANRA major metabolites, if any) will be derived from plasma concentrations using standard non-compartmental methods and actual sample times. Minimally, the following PK parameters will be calculated: C_{max}, T_{max}, $AUC_{0\text{-}last}$, accumulation ratio (R_{acc}) and if data permit, half-life ($t_{½}$), area under the concentration time curve from time 0 extrapolated to infinity ($AUC_{0\text{-}inf}$), apparent clearance (CL/F), and apparent volume of distribution at steady state (V_{ss}/F). PK parameters such as trough plasma concentration (C_{trough}) will be summarized in conjunction with sparse sampling in Phase 2. PK parameters will be summarized using descriptive statistics (N, arithmetic means, standard deviations, minimal, median and maximal values, geometric means and percent coefficient of variation).

The relationship between changes from baseline in QTc at specified time points post-dose and plasma concentrations of LANRA may be assessed. A separate plan for such analyses will be generated in accordance with principles outlined in International Council for Harmonisation (ICH) Directive E14 with results reported separately from the main clinical study report for this trial. Other exposure-response relationships (efficacy, safety and biomarkers) may be conducted, if supported by sufficient data.

Best response (CR, CRh, complete remission with incomplete blood count recovery [CRi], partial response [PR], 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 (Appendix 2). Patients with no post-baseline response assessments will be considered non-responders. The 80% confidence intervals (CIs) 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, 80% CIs for estimates of the proportion of patients with any CR (CR, CRh, CRi) will be constructed in a similar manner.

EFS is defined as the time from C1D1 until treatment failure (ie, failure to achieve CR or CRh), relapse from CR/CRh or death from any cause. DOR is defined as the time from the first documented CR/CRh until relapse or death. Kaplan-Meier (KM) methodology will be used to estimate the medians for EFS and duration of response and at specified landmark

timepoints. The 80% CIs for estimates of the medians and landmark rates for EFS and duration of response will be calculated using log-log transformation. Duration of follow-up will be estimated using the reverse KM method. Patients who do not experience the event of interest will be censored at the last assessment of response at which they were both alive and relapse-free. All summaries of EFS and those for duration of response will employ the safety and efficacy evaluable populations, respectively. OS will be estimated using KM methodology. Patients alive at last follow-up will be censored at the date of last contact.

2.0 Introduction

2.1 FLT3-mutated Acute Myeloid Leukemia – Biology, Incidence, Prognosis

FMS-like tyrosine kinase 3 (FLT3) is a transmembrane ligand-activated receptor tyrosine kinase that is normally expressed by lineage-restricted hematopoietic stem or progenitor cells and plays an important role in the early stages of both myeloid and lymphoid lineage development (Pratz and Levis, 2017). FLT ligand binds and activates FLT3, promoting cell survival, proliferation, and differentiation through various signaling pathways, including PI3K, RAS, and STAT5 (Daver et al, 2019). Mutations of the *FLT3* gene are found in approximately 30% of newly diagnosed patients with acute myeloid leukemia (AML) and occur as either in-frame, internal tandem duplications (ITDs) of between 3 and >100 amino acids in the juxtamembrane domain (in approximately 25% of cases) or point mutations in the tyrosine kinase domain (TKD), most commonly at the aspartate residue at position 835 (D835) (in 7–10% of cases) (O'Donnell et al, 2017; Nagel et al, 2017; Stone et al, 2017). Both *FLT3*-ITD and *FLT3*-TKD mutations lead to constitutive activation of FLT3 kinase activity, resulting in proliferation and survival of AML. *FLT3*-ITD is a common driver mutation that typically presents with a high leukemic burden and is associated with a poor prognosis: a meta-analysis demonstrated that the presence of *FLT3*-ITD in newly diagnosed AML patients is associated with shorter overall survival (OS) and relapse-free survival (RFS) compared with those without the mutation (hazard ratios [HRs] for death and relapse, 1.86 and 1.75, respectively) (Port et al, 2014). In a large, randomized study of newly diagnosed AML patients with *FLT3* mutations, the median event-free survival (EFS) was a mere 3.0 months (95% CIs: 1.9, 5.9) and the 4-year OS rate was 44.3% among patients treated with standard cytarabine/daunorubicin induction and high-dose cytarabine consolidation; 53.5% of patients (95% CIs: 48.2, 58.8) achieved a complete remission (CR) (Stone et al, 2017). Other factors that may influence the prognostic utility of *FLT3*-ITD include mutant-to-wild-type allelic ratio, insertion site, ITD length, karyotype, and the presence of a concurrent mutation in the *nucleophosmin-1 (NPM1)* gene (Daver et al, 2019). One potentially important aspect of FLT3 biology is that the ITD-mutated receptors are highly responsive to FLT ligand (FL) (Sato et al, 2011). Autophosphorylation of FLT3-ITD receptors, as well as their ability to stimulate growth, are both significantly augmented by the addition of FL (Zheng et al, 2011). FL is expressed by leukemia cells as well as a broad array of cell types throughout the body, and levels in plasma, normally present at barely detectable levels, rise by a fold of two- to three-logs during chemotherapy-induced aplasia (Pratz & Levis, 2017). This may help explain why allelic burden is often significantly higher among the approximately 75% of patients with newly diagnosed, *FLT3*-ITD–mutated AML who harbor the mutation at relapse (Shih et al, 2002; Krönke et al, 2013; Pratz & Levis, 2017). In contrast to the poor prognosis associated with *FLT3*-ITD-mutated AML, the prognostic impact of *FLT3*-TKD mutations is less well defined (Daver et al, 2019).

2.2 Treatment of FLT3-mutated AML:

Agents that target FLT3 are broadly classified as first-generation, multitargeted kinase inhibitors (eg, sunitinib, sorafenib, midostaurin) and next-generation potent and selective inhibitors, of which there are several currently in clinical development (quizartinib, crenolanib, gilteritinib) and one that is Food and Drug Administration (FDA)- and European Medicines Agency (EMA)-approved in the relapsed or refractory (R/R) setting (gilteritinib, marketed as XOSPATA®) (Daver et al, 2019).

Both sorafenib and midostaurin exhibited relatively modest single-agent activity in patients with R/R disease (Stone et al, 2005; Borthakur et al, 2011). A randomized, placebo-controlled Phase 2 trial in newly diagnosed AML patients ≤ 60 years found that the addition of sorafenib to intensive induction and consolidation chemotherapy significantly prolonged EFS but not OS and was associated with increased toxicity (Röllig et al, 2015). In an exploratory subgroup analysis, no EFS benefit was observed in the small group of patients with *FLT3*-ITD mutations whereas patients with non-*FLT3* mutations had significantly improved EFS and RFS (Daver et al, 2019). In a Phase 1b study, midostaurin was administered to newly diagnosed AML patients as part of an intensive induction and consolidation chemotherapy regimen beginning on Days 8 through Day 21 of each chemotherapy cycle and was found to have an acceptable safety profile at a dose of 50 mg twice daily (BID) (Stone et al, 2012). In response to the encouraging activity observed in patients with *FLT3* mutations in the Phase 1b study, the Cancer and Leukemia Group B (CALGB) in collaboration with Novartis (Basel, Switzerland) conducted a multicenter, international, Phase 3 trial comparing outcomes among 717 patients with newly diagnosed *FLT3*-mutated AML randomly assigned to treatment with midostaurin or placebo in combination with intensive induction and consolidation chemotherapy (the RATIFY study); the primary endpoint was OS. Both EFS and OS were significantly longer among patients treated with midostaurin (HR for both EFS and OS, 0.78; p=0.002 and 0.009 [1-sided], respectively). Subgroup analysis of patients with ITD (with high and low allelic ratio) and TKD mutations demonstrated clinical benefit from the addition of midostaurin and in an exploratory analysis of OS with censoring at the time of allogeneic stem cell transplantation, the OS benefit was maintained. Results from the RATIFY trial were the basis for FDA and EMA approval of midostaurin for treatment of *FLT3*-mutated AML in the front-line setting.

Next-generation FLT3 inhibitors have greater specificity for FLT3 and significantly higher potency than 1st generation multikinase inhibitors. Gilteritinib and crenolanib are type I inhibitors that target both the inactive and active conformational states of the FLT3 kinase domain, whereas quizartinib is a type II inhibitor that is specific for the inactive conformation. Unlike the 1st generation compounds, these have shown promising single-agent activity in the R/R setting (Daver et al, 2019).

2.2.1 Gilteritinib:

Gilteritinib is a small-molecule, oral FLT3 inhibitor with highly specific and potent inhibition of FLT3 receptors with both ITD and D835 mutations (either alone or in combination) (Mori et al, 2017; Lee et al, 2017). *In vivo*, gilteritinib inhibited tumor growth and induced tumor regressions in mice xenografted with MV4-11 AML cells (Mori et al,

2017). A Phase 1/2 dose-escalation/expansion study (the CHRYSALIS study) evaluated the safety/tolerability, pharmacokinetic (PK), and antileukemic activity of once-daily gilteritinib as a single agent at doses of 20–450 mg in patients with R/R, *FLT3*-wild type (n=58) or *FLT3*-mutated AML (n=194) (James et al, 2020; Perl et al, 2017). Gilteritinib was well tolerated with a maximally tolerated dose (MTD) of 300 mg QD. Potent FLT3 inhibition and dose-proportional PK were observed across all doses. Doses ≥ 80 mg/day were associated with > 90% FLT3 inhibition and an overall response rate of 52% (including 41% with CR, CRi [CR with incomplete blood count recovery] or CRp [CR with partial platelet count recovery]) among patients with *FLT3*-mutated disease (Perl et al, 2017) and a median OS of 31 weeks. The Phase 3 ADMIRAL trial compared the efficacy and safety of gilteritinib as a QD dose of 120 mg with standard, either high or low intensity, salvage chemotherapy in patients with *FLT3*-mutated, R/R AML. The median OS in the gilteritinib treated group was 9.3 months vs. 5.6 months for the chemotherapy-treated group (HR, 0.64; 95% CI, 0.49 to 0.83; P<0.001) (Perl et al, 2019). Thirty-four percent of patients achieved CR with full or partial hematologic recovery in the gilteritinib group compared with 15.3% in the chemotherapy group; the percentages of patients achieving CR were 21.1% and 10.5%, respectively. Grade ≥3 adverse events (AEs) and serious adverse events (SAEs) occurred less frequently in the gilteritinib group than in the chemotherapy groups when adjusted for therapy duration. The most common Grade ≥3 AEs in the gilteritinib group were febrile neutropenia (45.9%), anemia (40.7%), and thrombocytopenia (22.8%) (Perl et al, 2019). Results from the CHRYSALIS and ADMIRAL studies were the basis for the recent FDA and EMA approval of gilteritinib in patients with R/R, *FLT3*-mutated AML.

2.3 SYK Inhibition as a Therapeutic Strategy in *FLT3*-mutated AML

Spleen tyrosine kinase (SYK) is a non-receptor tyrosine kinase involved in cellular proliferation, differentiation and survival that is broadly expressed in most hematopoietic cells. The loss of SYK expression in AML cell lines is associated with morphologic evidence of differentiation and expression of mature myeloid cell surface markers, suggesting that SYK plays a role in counteracting differentiation in leukemic cells (Hahn 2009). SYK protein expression and activity appear to be modulated by HOXA9 and MEIS1, homeodomain-containing transcription factors that are overexpressed in approximately 30-40% of AML patients and correlate with a poor prognosis (Drabkin 2002; Gao et al, 2016; Heuser 2009; Zangenberg et al, 2009). Recent data have shown that overexpression of *HOXA9* and *MEIS*1 leads to an upregulation of SYK protein and increased SYK activity. Furthermore, transformation of myeloid progenitors with *HOXA*9 and *MEIS*1 in preclinical models induced addiction to SYK signaling. Accordingly, pharmacologic inhibition or knock-down of SYK significantly reduced tumor burden and prolonged survival in AML mouse models (Mohr et al, 2017). In AML, SYK signaling occurs via stimulation of ß-integrin and Fc-ɤ receptors resulting in activation of STAT3 and STAT5 and promotion of leukemic cell proliferation (Oellerich 2015).

Importantly, activation and direct phosphorylation of the FLT3 receptor by SYK has also been reported. SYK has been shown to cooperate with FLT3 ITD to drive leukemogenesis. Combined pharmacologic inhibition of SYK and FLT3 results in robust anti-leukemic effects in murine models of *FLT3* ITD-driven AML (Puissant et al, 2014).

2.4 Preclinical and Clinical Rationale for the Evaluation of Lanraplenib in Combination with Gilteritinib in *FLT3*-mutated AML

2.4.1 Preclinical Rationale

Lanraplenib (LANRA; formerly GS-9876) is a 3rd generation ATP-competitive inhibitor of SYK with a half-maximal inhibitory concentration (IC_{50}) of 9.5 nM against the purified SYK enzyme and is > 15-fold more selective for SYK compared with a panel of > 359 non-mutant kinases, except for ZAP70 (7-fold), JAK2 (13-fold), and SRC (15-fold more selective).

The activities of LANRA and its predecessor, entospletinib (ENTO), were evaluated for effects on the viability of AML patient samples in ex vivo cultures (Figure 1). Both LANRA and ENTO exhibited dose-dependent reductions in viability of leukapheresis-derived AML cells from 15 patients and in 11, the calculated IC_{50} values were within 2-fold of each other.

Figure 1: Ex vivo Evaluation of the Dose-Response Relationship for LANRA and ENTO in Leukapheresis-derived Primary AML Isolates

	IC50	R squared	LogIC50
Entospletinib	2033	0.9483	3.308
Lanraplenib	2706	0.9902	3.432

Fig 1: Primary leukapheresis-derived AML cells were cultured for 6 days in the presence of vehicle (0.1% dimethyl sulfoxide [DMSO]) and either LANRA or ENTO across a range of dilutions. Five micromolar cytarabine was used as a positive control in the assay. On day 6, cell viability was measured by addition of CellTiter Glo reagent and relative luminescence units (RLUs) were recorded on a plate reader. Cell viability (Y-axis) was plotted against drug concentrations (X-axis); IC_{50} and coefficient of determination (R^2) values were calculated and included in the table. A) A representative example of the comparable, concentration-dependent effects of ENTO and LANRA on viability of *NPM1*m leukemic cell a specific patient (CTC-2232) B) Average half-maximal effective concentration (EC_{50}) values for LANRA in *NPM1* mutated, *NPM1/FTL3*-ITD co-mutated and mutation negative samples.

LANRA and ENTO also demonstrated comparable reductions in viability in a panel of AML and lymphoma cell lines. The inhibitory activities of LANRA and ENTO were evident in cell line cultures with differing mutational backgrounds, including those with *FLT3* mutations (MOLM-13, MV-4-11) (Figure 2).

Figure 2: LANRA and ENTO Show Comparable Activity Across a Panel of AML and Lymphoma Cell Lines

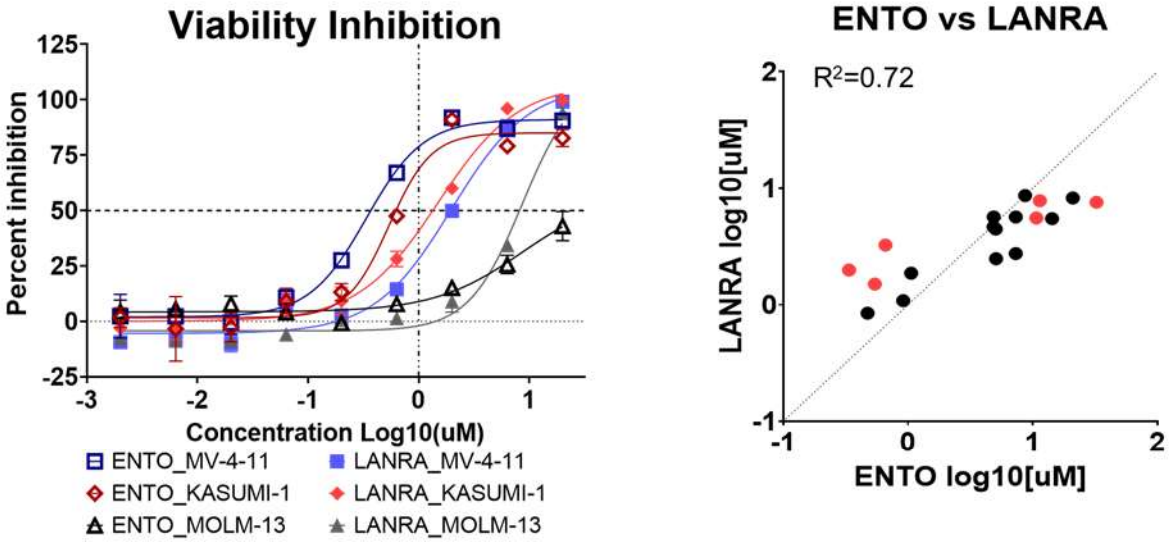

Fig. 2: ENTO and LANRA show comparable, concentration-dependent effects on cell viability in a panel of AML cell lines, as assessed with CellTiter Glo® (left). A subset of AML (red) and lymphoma (black) cell lines showed low µM to nM sensitivity to both agents (right).

The ability of LANRA and ENTO to induce additive or synergistic effects when combined with other active agents used in the treatment of AML was assessed (Figure 3). Two of the most potent combinations were with the selective FLT3 inhibitor, gilteritinib, and the BCL-2 inhibitor, venetoclax. LANRA showed a broad and robust synergistic effect in combination with both gilteritinib or venetoclax exceeding a Loewe synergy score of 10 at multiple doses.

Figure 3: Synergistic Effects of LANRA in Combination with the FLT3 Inhibitor, Gilteritinib or the BCL2 Inhibitor Venetoclax in NPM1m, FLT3-ITD AML Models

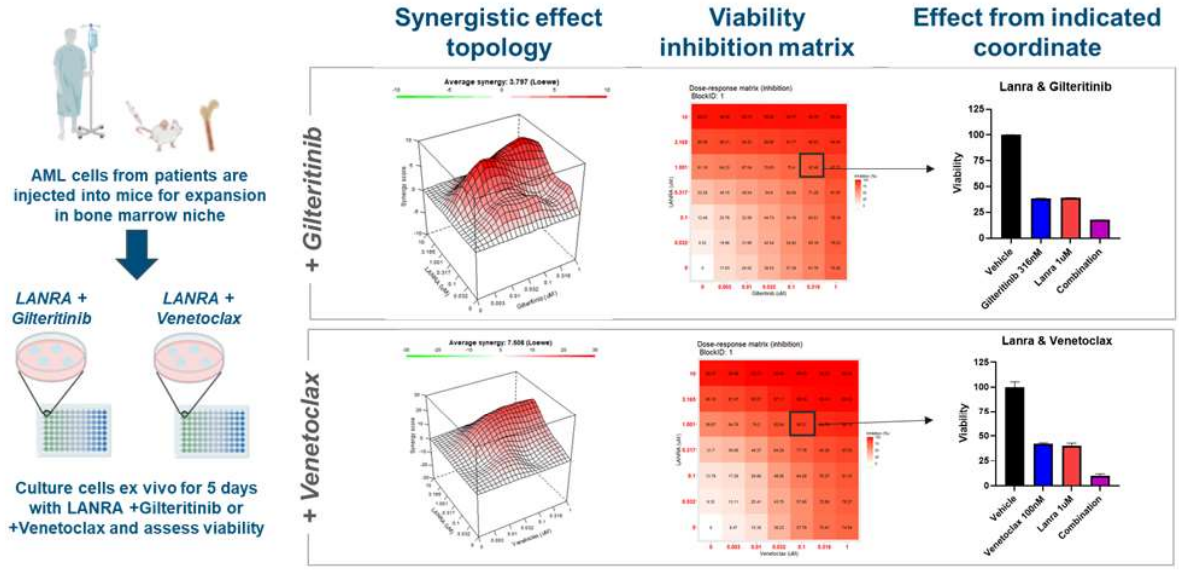

Fig 3: An *NPM1*m/*FLT3*-ITD AML patient isolate was grown under semisolid colony forming conditions for 5 days with LANRA and either gilteritinib or venetoclax to assess effects of these combinations on cell viability. The antileukemic effects of the combination were assessed using CellTiterGlo® as readout for cell viability.

This ex vivo study was followed by a patient derived xenograft study of the same AML isolate in which animals were treated with the combination of LANRA and gilteritinib for 28 days (Figure 4). Leukemic burden was assessed as a percent of human CD45 positive cells in peripheral blood by flow cytometry. The combination of LANRA and gilteritinib showed meaningful improvements in tumor burden reduction and overall survival compared with either single agent alone.

Figure 4: LANRA in Combination with Gilteritinib Shows Improved Clearance of Leukemic Cells and Extends Overall Survival in a FLT3-ITD AML Patient derived Xenograft Model

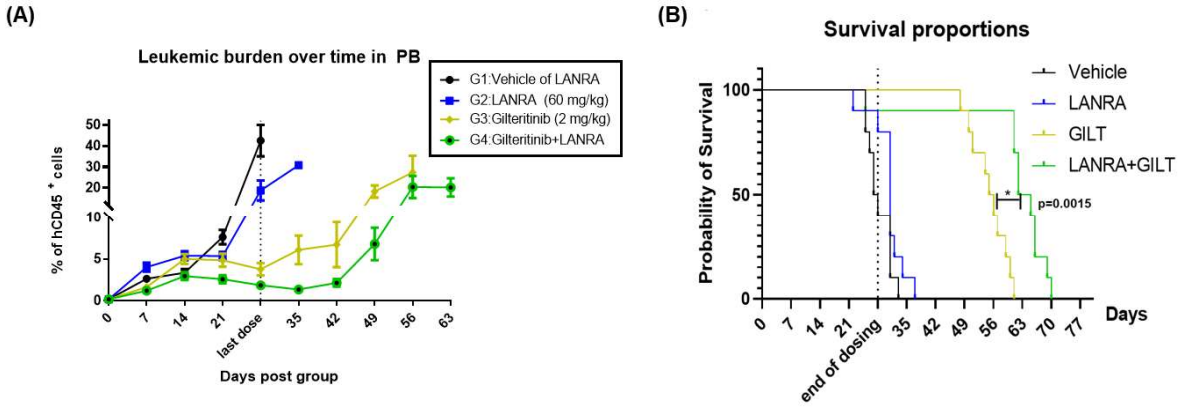

Fig 4. LANRA was studied alone and in combination with gilteritinib in an *FLT3*-ITD/*NPM1*m patient-derived xenograft model (PDX). Mice were treated with **60 mg/kg** LANRA via sub-cutaneous injection, twice daily, or with **2 mg/kg** gilteritinib via oral gavage, once daily, as single agents, or in combination. **(A)** Leukemic burden was assessed by flow cytometry measuring human CD45 in peripheral blood (PB) obtained from serial bleeds over time.
(B) Kaplan-Meier survival curve showing the probability of survival following treatment with each single agent or the combination.

2.4.2 Clinical Rationale – Results from a Phase 1b/2 Study of ENTO in Newly Diagnosed AML (including patients with *FLT3*-ITD AML)

In a Phase 1b/2 study of 53 previously untreated AML patients, ENTO was evaluated at doses of 200 or 400 mg BID plus 1-2 cycles of intensive induction therapy (continuous infusion cytarabine x 7 days, bolus daunorubicin x 3 days; "7+3") followed by high-dose cytarabine consolidation. In this study, 70% of patients achieved a CR or CRi including 5 (83%) of 6 patients with *FLT3*-ITD AML. The combination of ENTO with 7+3 induction and high dose cytarabine consolidation was generally well-tolerated with skin rash, transaminase elevations and indirect hyperbilirubinemia being the mostly commonly reported, treatment-related toxicities (Walker et al, 2020).

Unlike ENTO, LANRA can be administered QD in either the fed or fasted state and with concurrent administration of gastric acid-reducing agents, specifically, proton pump inhibitors.

This study will evaluate the safety, PK, PD, and preliminary efficacy of LANRA in combination with the selective FLT3 inhibitor gilteritinib, in previously treated, *FLT3*-mutated AML patients.

2.5 Risk Benefit Assessment

2.5.1 Gilteritinib-associated Toxicities:

The safety profile for gilteritinib is based on data from 319 patients with R/R AML treated with gilteritinib 120 mg daily, who were enrolled to three clinical trials. The median duration

of exposure was 3.6 months (range 0.1 to 43.4 months). The most frequent adverse reactions following treatment with gilteritinib were increased alanine aminotransferase (ALT) (82%), increased aspartate aminotransferase (AST) (81%), increased blood alkaline phosphatase (69%), increased blood creatine phosphokinase (54%), diarrhea (35%), fatigue (30%), nausea (30%), constipation (28%), cough (28%), peripheral oedema (24%), dyspnea (24%), dizziness (20%), hypotension (17%), pain in extremity (15%), asthenia (14%), arthralgia (13%), and myalgia (13%). The most frequent serious adverse reactions were acute kidney injury (7%), diarrhea (5%), increased ALT (4%), dyspnea (3%), increased AST (3%) and hypotension (3%) (XOSPATA [gilteritinib] Summary of Product Characteristics 2021). Twenty-two (7%) patients permanently discontinued gilteritinib due to an adverse reaction, most commonly increased AST (2%) and ALT (2%) (XOSPATA [gilteritinib] U.S. Prescribing Information, 2022).

Potentially fatal or life-threatening toxicities associated with gilteritinib included Differentiation Syndrome (DS; a syndrome associated with rapid proliferation and differentiation of myeloid progenitors/precursors), reported in 2% of patients; Posterior Reversible Encephalopathy Syndrome (PRES) presenting with symptoms including seizures and altered mental status, reported in <1% of patients; pancreatitis reported in 4% of patients; and treatment-emergent QT interval prolongation in 9% of patients (XOSPATA [gilteritinib] U.S. Prescribing Information, 2022; XOSPATA [gilteritinib] Summary of Product Characteristics 2021). Guidelines for the management of these uncommon but potentially serious adverse reactions are provided in Section 8.1. In order to monitor for the occurrence of QT interval prolongation, electrocardiograms (ECGs) will be assessed at Screening, in Cycle 1 on Days 8 and 15, on Day 1 of Cycles 2 and 3, and thereafter, as clinically indicated in accordance with the gilteritinib prescribing information (XOSPATA [gilteritinib] U.S. Prescribing Information, 2022; XOSPATA [gilteritinib] Summary of Product Characteristics 2021).

2.5.2 Lanraplenib-associated Toxicities

2.5.2.1 Non-clinical data:

Findings associated with administration of LANRA to Sprague-Dawley rats at daily doses up to 100 mg/kg for up to 26 weeks consisted primarily of lymphodepletion in primary and secondary lymphoid organs (thymus, spleen, lymph nodes, bone marrow) accompanied by multifocal bacterial infections, consistent with LANRA's immunomodulatory mechanism of action. Additionally, findings indicative of low-grade hemolysis of uncertain origin in animals treated at the 100 mg/kg dose level were observed.

In addition to lymphodepletion, notable observations associated with administration of LANRA to cynomolgus monkeys at total daily doses ≥ 20 mg/kg for 2 weeks or up to 20 mg/kg for 4 weeks included clinical and histopathologic findings consistent with a coagulopathy (ie, ecchymoses, visceral hemorrhage/ulceration and associated inflammatory cell infiltrates). These findings were not replicated in a study of LANRA administered to monkeys for up to 39 weeks at daily doses up to 15 mg/kg and have not been observed in human patients treated with total daily doses up to 50 mg for 7 days or 30 mg for up to

49.4 weeks (see below). Consult the LANRA Investigator's Brochure (IB; Section 3.3) for additional details on non-clinical safety and PK findings associated with LANRA.

In light of the above-described coagulopathy observed in the 2- and 4-week monkey studies, this study will monitor coagulation parameters including fibrinogen and D-dimer levels, on Days 1 and 15 of Cycle 1, Day 1 of Cycle 2 and Cycle 3 and as clinically indicated thereafter.

2.5.2.2 Clinical data:

Clinical data are derived from 233 patients enrolled to 7 studies of LANRA, including the following:

- a Phase 1, ascending single dose, PK and safety study in which healthy volunteers received LANRA doses up to 50 mg (n=60);
- a Phase 1, ascending multiple dose PK and safety study in healthy volunteers treated with LANRA for 7 days at doses up to 50 mg/day (n=24);
- a Phase 1, single-dose (20 mg) PK and safety study in patients with moderate (n=10) or severe (n=9) renal functional impairment, including 16 healthy volunteers;
- a Phase 2, safety and efficacy study in patients with rheumatoid arthritis (RA) treated at doses of 10 (n=20) or 30 mg/day (n=20) for 12 weeks;
- a Phase 2, safety and efficacy study in patients with moderately to severely active cutaneous lupus erythematosus (CLE; n=23) treated at daily doses of 30 mg for up to 48 weeks;
- a Phase 2, safety and efficacy study in patients with lupus membranous nephritis (LMN; n=4) treated at daily doses of 30 mg for up to 16 weeks; and
- a Phase 2, safety and efficacy study in patients with active Sjögren's Syndrome (n=47) treated at daily doses of 30 mg for up to 49.4 weeks.

In clinical studies of LANRA in healthy volunteers, no safety signals were identified and no Grade 3 or 4 AEs were reported. There were no clinically significant changes in vital signs, physical findings, laboratory parameters, or ECGs.

The mean (SD) duration of exposure to LANRA in the RA study was 12.0 (0.67) weeks and the maximal exposure duration was 12.3 weeks. LANRA was generally well-tolerated; all patients in the 30-mg QD cohort completed protocol-specified treatment and 19 of 20 patients completed study treatment in the 10 mg QD cohort (1 patient discontinued due to investigator discretion). Seven (30%) and 8 (40%) patients in the 30- and 10-mg LANRA cohorts, respectively, reported at least 1 non-serious AE. AEs reported in more than 1 patient in the 30 mg LANRA cohort were hypothyroidism (n=2), and in the 10 mg LANRA cohort, "condition aggravated" (n=2). One patient in the 30 mg LANRA cohort reported Grade ≥3 increased blood pressure assessed by the investigator as not related to study treatment. No SAEs or deaths were reported. In the CLE study, 2 patients experienced SAEs (coronary artery occlusion; drug hypersensitivity); there were no deaths. Twenty (87%) LANRA-treated patients reported at least 1 AE. AEs reported in >1 patient included: upper

respiratory tract infection (URI; n=4), urinary tract infection (UTI; n=3), diarrhea, nausea, bronchitis, nasopharyngitis, extremity pain and headache (each n=2). The Sponsor (Gilead Sciences) terminated the study of LANRA in LMN prematurely due to very low enrollment over a period of 16 months and in the absence of safety concerns. One patient reported 2 SAEs (systemic lupus erythematosus [SLE], acute kidney injury); there were no deaths. All patients reported at least 1 non-serious AE: bronchitis (n=2), amaurosis fugax, vitreous floaters, peripheral edema, sinusitis, URI, decreased lymphocyte count, hypoalbuminemia, SLE and anxiety (n=1 each). In the Sjögren's Syndrome study, 3 patients reported SAEs (acute coronary syndrome, acute pancreatitis, and suicidal ideation). Forty (85.1%) patients reported at least 1 non-serious AE. Non-serious AEs reported in > 1 patient were fatigue (n=6), viral gastroenteritis (n=5), URI, nasopharyngitis, ALT increased, AST increased (n=4 each), diarrhea, pyrexia, sinusitis, UTI (n=3 each), lymphadenopathy, neutropenia, dental caries, nausea, vomiting, bronchitis, laryngitis, lower respiratory tract infection, and oral herpes (n=2 each).

Consult the LANRA IB (Section 4.0) for additional safety and PK findings from LANRA clinical studies collected to date.

2.5.3 Potential for Overlapping Toxicities Resulting from the Combination of LANRA and Gilteritinib

In the reference safety information for LANRA, liver transaminase elevations are listed as potential adverse drug reactions, based on clinical trial experience to date. Transaminase elevations were infrequent and reversible upon discontinuation of LANRA. A review of the respective toxicity profiles for LANRA and gilteritinib reveals that the most likely overlapping and potentially treatment-limiting toxicity resulting from the combination is liver toxicity (ie, transaminase elevations). Other potential overlapping toxicities include (but are not limited to) rash, constitutional symptoms (fatigue/malaise, myalgia/arthralgia, fever, headache) and gastrointestinal signs/symptoms (nausea, vomiting, diarrhea, abdominal pain, constipation). These can be monitored by close surveillance and conventional safety assessments as described in Section 11; all are potentially manageable with supportive care interventions and study treatment modifications (Section 8).

Co-administration with gilteritinib is not expected to impact LANRA plasma exposures. An evaluation of PK parameters for LANRA alone and in combination with gilteritinib will be conducted in this study to investigate the potential for meaningful PK interaction between the two.

In consideration of the above, the Sponsor has concluded that the potential benefits of the proposed study outweigh the risks for the following reasons:

- the prognosis for patients with R/R *FLT3*-mutated AML is dismal,
- there are limited effective treatment options available for this subgroup of patients,
- there is significant room for improvement when considering outcomes for patients treated with gilteritinib monotherapy in this clinical setting (Section 2.2.1),

- there is compelling evidence from non-clinical pharmacologic studies (Puissant 2014), as well as ex vivo pharmacodynamic studies of leukemic isolates from AML patients to suggest that incremental clinical benefit could be achieved from concurrent inhibition of SYK and FLT3,
- there is preliminary clinical evidence that the SYK inhibitor ENTO (the predecessor to LANRA) may improve CR rates when combined with standard "7 + 3" induction chemotherapy in newly diagnosed patients with *FLT3*-mutatated AML (Walker 2020) and,
- the safety profile for LANRA based on clinical studies conducted to date along with the ability to closely monitor patients with frequent safety assessments as well as the use of appropriate guidelines for treatment modification suggest that the combination can be tested with an adequate margin of safety.

2.5.4 COVID-19 Considerations

Patients undergoing systemic chemotherapy for cancer and leukemia have an increased risk of severe complications, some leading to death, following coronavirus disease 2019 (COVID-19). This includes patients who have been fully vaccinated against the virus. The extent to which LANRA may increase the magnitude of risk when administered concurrently with gilteritinib (if any) is currently unknown. Prospective trial participants, including those who have been vaccinated against COVID-19, should be counseled to employ social distancing measures including the regular use of face coverings and avoidance of indoor congregant environments, especially those that include others for whom the vaccination and/or COVID-19 infection status are unknown.

Consult Appendix 5 for additional risk mitigation procedures potentially associated with clinical trial conduct in the COVID-19 pandemic era.

2.6 Rationale for Starting Dose of LANRA and Selection of Recommended Phase 2 Dose (RP2D)

To date, 233 patients have received LANRA monotherapy. As noted, doses of LANRA up to 50 mg/day for 7 days in healthy volunteers and up to 30 mg/day for up to 49.4 weeks in patients with autoimmune diseases have been safe and adequately tolerated. In light of the potential for overlapping toxicities with the combination of LANRA plus gilteritinib (Section 2.5.3), the proposed starting dose for LANRA in the Phase 1b (dose escalation) component of this study will be 20 mg QD, which should allow for an acceptable safety margin when combined with the standard dose of gilteritinib (120 mg QD). Consistent with global regulatory guidance and the need to identify a safe dose that can induce durable responses, the dose will be escalated following a "3 + 3" dose escalation scheme to a maximal dose of 90 mg in combination with the standard dose gilteritinib, or until a MTD/RP2D (recommended Phase 2 dose) is defined.

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 a dose

cohort previously cleared for safety and tolerability by the Dose Escalation Committee (DEC), if there are no available patient slots in the dose cohort 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 agreement 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 European LeukemiaNet (ELN) 2017-defined response categories (Appendix 2): CR, CR with partial hematologic recovery (CRh), CRi, partial response (PR), morphologic leukemia-free state (MLFS). The 3+3 dose escalation rule will continue to be followed for each successively higher dose cohort however, should dose-limiting toxicities (DLT[s]) occur in 1 or more patients enrolled to a backfill cohort(s), these will be taken into account for purposes of future dose escalation decisions. Specifically, if a DLT occurs in a patient allocated to a backfill cohort, the DLT rate will be re-calculated for that cohort. If the updated DLT rate exceeds 20% with 80% probability, the updated DLT rate will be taken into consideration by the DEC when deciding whether to stop or continue dose escalation to the next higher dose level.

The dose of LANRA that will be selected as the RP2D will be the dose that most closely approximates the magnitude and duration of SYK inhibition achieved by the active dose of ENTO while maintaining a manageable safety profile. Specifically, the 400 mg BID dose of ENTO achieves responses in AML patients both as monotherapy and in combination with cytarabine/daunorubicin (7+3) induction (Walker et al, 2020). Plasma exposures at this dose of ENTO led to sustained, > 50% inhibition of SYK (as measured in ex vivo assays) (Ramanathan et al, 2017). We hypothesize that LANRA will need to achieve or exceed this threshold of SYK inhibition for efficacy. In addition to PK, safety and efficacy data, reductions in pSYK in peripheral blood mononuclear cells (PBMCs), and/or changes in a SYK dependent gene expression signature will be assessed in patients at each dose level to identify a dose of LANRA at or below the MTD that consistently achieves sustained, >50% SYK inhibition.

2.7 Study Conduct

This study will be conducted in compliance with the protocol approved by the Institutional Review Board (IRB) or Independent Ethics Committee (IEC) and in accordance with Good Clinical Practice (GCP) standards, EU Regulation 536/2014, and other country-specific requirements, as applicable.

3.0 Objectives & Endpoints:

3.1 Phase 1b

Objectives:	Endpoints:
Primary:	
To evaluate the safety of LANRA in combination with the FLT3 inhibitor gilteritinib, in patients with R/R *FLT3*-mutated AML.	Type, incidence, severity, causality, and outcome of AEs, including serious and Grade ≥3 AEs; dose-limiting toxicities (DLTs); MTD/RP2D of LANRA in combination with standard doses of gilteritinib.
Secondary:	
To characterize the 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 × 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 complete response (CR) rate including CR and CR with partial hematologic recovery (CRh) as defined by European LeukemiaNet (ELN) 2017 criteria (Döhner 2017). Duration of response (DOR), defined as the time from first qualifying response (CR/CRh) until relapse or death from any cause, as assessed by study investigators. EFS, 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. OS, 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).	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.
To characterize pharmacodynamic properties (including the extent of target engagement) of LANRA alone and in combination with gilteritinib.	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 assess the metabolite profile of LANRA in plasma.	Type(s) of prominent LANRA metabolites in plasma.

3.2 Phase 2

Objectives:	Endpoints:
Primary:	
To further evaluate the safety of LANRA at the 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 partial CR (CRh) as defined by ELN 2017 criteria (Döhner 2017). DOR, defined as the time from first qualifying response (CR/CRh) until relapse or death from any cause, as assessed by study investigators. EFS, 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. OS, defined as the time from enrollment until death from any cause.
Exploratory:	
To further assess the incidence of *FLT3* 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).	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.
To further characterize pharmacodynamic properties (including the extent of target engagement) of LANRA alone and in combination with gilteritinib.	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 concentration.

4.0 Summary of Study Design

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, LANRA, in combination with the selective FLT3 inhibitor, gilteritinib, in patients with *FLT3*-mutated 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, 2, 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. In both Phase 1b and Phase 2, patients will receive their assigned treatment regimen until progression/relapse or lack of at least a PR after 6 months of study treatment, intolerance, or withdrawal from study treatment by the patient or study investigator. All patients will be followed for survival.

4.1 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 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. Dose-limiting toxicities are defined in Appendix 1. The starting dose of LANRA is 20 mg QD (Cohort 1, Table 1). Enrollment will be staggered such that the first patient to enroll in a dose cohort will begin combination therapy on C1D2 (see below) and at least 24 hours before subsequent patients are enrolled to that cohort. All patients within a cohort (except those who discontinue in Cycle 1 due to DLT) must complete the DLT assessment period before a decision to begin testing the next higher dose. Enrollment of the next higher dose cohort will not proceed until a safety review has been completed for the preceding cohort(s) by a DEC consisting of

investigators with enrolled patients and sponsor representatives including (but not limited to) the medical monitor, safety officer, PK, and translational science leads. All decisions regarding dose escalation including declaration of the MTD/RP2D will be made by the DEC. The determination of whether or not to enroll the next higher dose cohort, enroll a lower dose cohort/add additional patients to a cohort previously cleared for safety/tolerability by the DEC or declare the MTD/RP2D will be based on available safety, PK, and PD data from all dose cohorts. If no protocol-defined MTD is identified for LANRA, the lowest dose that shows consistent evidence of adequate SYK inhibition based on PD assays will be deemed the RP2D (Section 2.6).

Patients will be evaluated for DLTs beginning on C1D1 up to and including safety assessments collected on Cycle 2, Day 1 for determination of LANRA MTD in combination with standard-dose gilteritinib. Patients will be evaluable for DLT in Phase 1b if one of the following occurs:

- They experience a DLT after receiving ≥1 dose of LANRA during the DLT assessment period.
- They receive at least 80% of the intended cumulative dose of LANRA and gilteritinib during the DLT assessment period without the occurrence of a DLT.

Should patients discontinue study treatment prior to completing the DLT assessment period for reasons other than a DLT, additional patients will be enrolled to ensure the required number of DLT-evaluable patients is achieved. 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 (Appendix 2): CR, CRh, CRi, PR, MLFS. The 3+3 dose escalation rule will continue to be followed for each successively higher dose cohorts however, DLTs occurring in patients enrolled to backfill cohorts will be taken into account by the DEC for purposes of future dose escalation-making decisions, per guidelines outlined in Section 2.6.

PK and PD evaluations of LANRA monotherapy will begin at Hour 0 (predose) on C1D1 through Hour 24 (C1D2) after which, all patients will initiate combination therapy on C1D2. PK evaluations for concurrently administered LANRA and gilteritinib will begin at Hour 0 (predose), C1D15 through Hour 24 (C1D16) (see Table 8 and Table 9).

Patients who discontinue LANRA for intolerance may continue gilteritinib at the investigator’s discretion (in which case, no additional sampling for LANRA PK assessments will be required). Patients who discontinue gilteritinib for intolerance may continue LANRA at the investigator’s discretion for as long as they are deriving clinical benefit. An

End-of-Treatment evaluation will take place 30 (± 7) days after permanent discontinuation of both study drugs or prior to initiation of new anti-leukemic therapy, if sooner. Patients who discontinue study treatment for reasons other than progression/relapse may be followed until progression in the absence of intervening antileukemic therapy, at the discretion of the investigator.

4.2 Phase 2

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 (Table 10), and anti-leukemic activity of the combination at the LANRA MTD/RP2D. Patients enrolled to Phase 2 will begin combination therapy with LANRA and gilteritinib on C1D1.

For both Phase 1b and Phase 2, response assessments will be based on bone marrow, physical examinations, as well as peripheral blood counts. Bone marrow aspirates will be performed on C2D1, C3D1 and every 3 cycles thereafter until the patient exhibits 2 consecutive assessments indicating CR or CRh. Patients who have not achieved at least a partial response per ELN 2017 criteria after 6 months of study treatment will permanently discontinue study treatment.

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 CR or CRh, as defined by ELN 2017 response criteria (Appendix 2). Section 15.0 [Statistical Considerations] describes the specifications for enrollment in Stage 1 and Stage 2 based upon the hypothesized improvement in cCR rate resulting from the addition of LANRA to gilteritinib.

As in Phase 1b, the frequency of DLTs will be assessed coincident with the first cycle of treatment during Phase 2, initially after the first 6 patients and every patient thereafter, until enrollment completion. If the probability that the true, first cycle DLT rate exceeds 20% with 80% posterior probability given the accumulated data at these time points, further enrollment will be interrupted, and the DEC will be convened to assess the risk-benefit profile of the study regimen and provide recommendations regarding modifying or stopping the study (see Section 15.2.7.1 for safety stopping rules). Additionally, the occurrence of one Grade 5 event or two Grade 4 events that is considered at least possibly related to LANRA or gilteritinib will prompt an interruption of new patient accrual followed by a thorough safety analysis that will be submitted to health authorities in the countries where the study is being conducted for review prior to resuming enrollment.

5.0 Patient Population

5.1 Inclusion Criteria

Participants are eligible to be included in the study only if all the following criteria apply:

1. Adults ≥18 years of age with AML and at least 1 prior line of therapy.

   Note: Patients must meet the criteria for a partial response, stable disease or progressive disease as best response after the last prior line of therapy; primary refractory disease after 1st line induction; or recurrence of leukemia after CR, as defined by ELN 2017 response criteria (Appendix 2).

2. *FLT3*-mutated disease documented in a local reference laboratory at the time of consideration for enrollment in the study.

   Note: Eligible patients may have either ITD or TKD mutations or both as detected in either peripheral blood or bone marrow.

   Note: Patients with a history of exposure to midostaurin, other multikinase inhibitor (eg, sorafenib), or 2nd generation FLT3 inhibitors (including gilteritinib, quizartinib, or crenolanib) for the treatment of AML are eligible but must have discontinued treatment with these agents at least 7 days prior to Cycle 1, Day 1.

3. Have the ability to understand the requirements and procedures of the study and sign a written informed consent form (ICF).
4. Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0, 1 or 2.
5. Adequate hepatic and renal function defined as:

   a) serum AST and ALT < 2.5 times the upper limit of normal (ULN); total bilirubin < 1.5 times ULN unless elevated due to Gilbert's Disease or hemolysis
   b) calculated creatinine clearance >30 ml/min

6. Prothrombin time (PT), activated partial thromboplastin time (aPTT) and international normalized ratio (INR) ≤1.5x ULN unless receiving therapeutic anticoagulation.

   Note: Transition from a Vitamin K or Factor Xa antagonist to a low-molecular weight heparin preparation is recommended prior to the start of study treatment (see Appendix 7 for guidelines on anticoagulation management).

7. Negative serum ß-HCG test in women of child-bearing potential (WOCBP).
8. Left ventricular ejection fraction ≥ 50% confirmed by echocardiogram (ECHO) or multi-gated acquisition (MUGA) scan.
9. For WOCBP, willingness to abstain from heterosexual intercourse OR use a protocol-recommended method of contraception from 7 days prior to C1D1 throughout the study treatment period and for 6 months following the last dose of study treatment (Appendix 6).

10. For male patients with female sexual partners of childbearing potential, willingness to abstain from heterosexual intercourse OR use a protocol recommended method of contraception beginning 7 days prior to C1D1 throughout the study treatment period and for 4 months following the last dose of study treatment AND to refrain from sperm donation from the start of study treatment throughout the study treatment period and for 4 months following the last dose of study treatment (Appendix 6).
11. Willingness to comply with scheduled study visits, procedures, and treatment plan.

5.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

1. Known central nervous system (CNS) involvement with leukemia.
2. Clinical signs/symptoms of leukostasis that have failed therapy including hydroxyurea and/or leukapheresis of at least 3 days duration (see Exclusion Criterion #14 below).
3. Pregnant or breastfeeding women.
4. Active infection with hepatitis B, C or human immunodeficiency virus (HIV) infection.

   Note: Patients who are hepatitis B surface antigen (HBsAg) or anti-HIV positive at baseline are ineligible. Patients with a history of hepatitis B virus (HBV) infection (hepatitis B antibody [anti-HBc] seropositivity) must agree to receive HBV prophylaxis during the study treatment period and undergo regular surveillance for HBV reactivation with serial HBV DNA measurements in plasma. Patients with a history of hepatitis C virus (HCV) infection who completed curative therapy may enroll but must undergo regular surveillance monitoring for HCV reactivation.
5. Disseminated intravascular coagulation with active bleeding or signs of thrombosis.
6. Known active COVID-19 either symptomatic or asymptomatic, as determined by nasopharyngeal swab for severe acute respiratory syndrome (SARS) coronavirus 2 (SARS CoV-2) RNA or antigen.

   Note: In the absence of signs, symptoms or physical findings suggestive of COVID-19, testing for SARS CoV-2 infection is not required for eligibility. Patients with a history of SARS-CoV-2 nasopharyngeal carriage (either with or without symptoms), who have subsequently tested negative on follow-up nasopharyngeal swab and are without signs or symptoms of COVID-19 may enroll. Patients who have been vaccinated against SARS-CoV-2 at least 2 weeks prior to the start of study treatment may enroll. Patients without contraindications, may be vaccinated against COVID-19 while on study, preferably upon completion of the DLT assessment period (Cycle 1).
7. Administration of a live attenuated virus vaccine within 35 days before C1D1.
8. History of non-myeloid malignancy *except* for the following: adequately treated localized basal cell, or squamous cell carcinoma of the skin, or localized melanoma

(with TNM stage either Tis [melanoma in-situ] or T1aN0M0) with complete resection; cervical carcinoma in situ; superficial bladder cancer; asymptomatic prostate cancer without known metastatic disease, with no requirement for therapy or requiring only hormonal therapy and with normal prostate specific antigen for > 1 year prior to start of study therapy; or any other cancer that has been in complete remission without treatment for ≥ 3 years prior to enrollment.

Note: Patients who are on adjuvant hormonal therapy and ≥ 3 years from definitive therapy for their primary tumor are eligible to enroll.

9. Clinically significant heart disease defined as:
   a) New York Heart Association Class 3 or 4 congestive heart failure,
   b) Acute myocardial infarction ≤6 months before enrollment,
   c) Symptomatic cardiac ischemia/unstable angina ≤3 months before enrollment,
   d) History of clinically significant arrhythmias (eg, ventricular tachycardia or fibrillation; Torsades de Pointes) including Mobitz type II 2nd degree or 3rd degree heart block without a permanent pacemaker in place.
10. Patients with a corrected QT interval (using the Fridericia formula, QTcF) >480 msec or Long QT Syndrome.
11. Evidence of ongoing *uncontrolled* systemic bacterial, fungal, or viral infection at the time of study treatment initiation.

    Note: "Uncontrolled" infection would include (but is not limited to) persistence of fever or positive cultures in the setting of appropriate antimicrobial coverage.
12. Current (within 30 days of study enrollment) drug-induced liver injury, chronic active hepatitis, alcoholic liver disease, nonalcoholic steatohepatitis, primary biliary cholangitis with inadequate response to ursodeoxycholic acid or other health authority approved therapy, extrahepatic obstruction caused by cholelithiasis, cirrhosis of the liver, or portal hypertension.
13. Ongoing (within 6 weeks of study enrollment) hepatic encephalopathy.
14. Alcohol or drug addiction as determined by investigator.
15. Ongoing immunosuppressive therapy, including systemic chemotherapy for treatment of leukemia.

    Note: Patients may receive hydroxyurea or leukapheresis for treatment of hyperleukocytosis until signs/symptoms and/or the risk of complications from leukostasis have abated, in the judgement of the investigator.

    Note: Patients with a history of hematopoietic stem cell transplantation (HSCT) are eligible as long as they are receiving no more than 10 mg prednisone QD (or equivalent) for graft vs. host disease.
16. Concurrent (within 14 days of study enrollment) participation in an investigational drug study with therapeutic intent.

17. Patient requiring chronic treatment with strong cytochrome P450 (CYP) 3A4 inhibitors or inducers beginning 7 days prior to initiating study treatment until study treatment completion (see Appendix 4 for a list of strong CYP3A inducers or inhibitors; see Section 10.2 for LANRA treatment modification guidelines for patients requiring the use of strong CYP3A4 inhibitors during the Treatment Phase).
18. Unable to swallow capsules or concurrent disease affecting gastrointestinal function such as malabsorption syndrome, gastric or small bowel resection, bariatric surgery, inflammatory bowel disease or bowel obstruction.
19. Any prior or ongoing condition that, in the opinion of the investigator, could adversely affect the safety of the patient or impair the assessment of study results.
20. Known hypersensitivity to LANRA, gilteritinib, their metabolites or formulation excipient.

6.0 Organizational Framework

6.1 Screening and Enrollment

After signing the ICF, all screening assessments and procedures must be completed within 21 days before the start of study treatment. The study site is responsible for maintaining a record of all screened and enrolled patients. Patients who have failed 1 or more screening assessment may be re-tested for that assessment(s) within the designated time frame for final eligibility determination.

6.2 Treatment Phase

The treatment period starts with the first day of study treatment (C1D1) and continues until the End-of-Treatment Evaluation (see below). All treatment cycles are 28 days. Patients may discontinue study treatment at any time for reasons summarized in Section 13.0.

6.3 End of Treatment

All patients will undergo an End-of-Treatment Evaluation 30 ± 7 days after the last dose of either LANRA or gilteritinib (whichever is later) or prior to initiation of new antileukemic therapy, if sooner. Patients must discontinue study treatment and complete the End-of-Treatment Evaluation prior to HSCT.

6.4 Post-treatment Follow-up

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 new anti-leukemic therapy. Following progression/relapse or initiation of new anti-leukemic therapy, patients will be followed for survival every 3 months.

6.5 End of Study

The study will end 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.

7.0 Test product, dose, mode of administration

7.1 Gilteritinib:

Gilteritinib (XOSPATA®) is supplied as light yellow, round-shaped, film-coated tablets debossed with the Astellas logo and '235' on the same side. Gilteritinib is provided in either bottles of 90 tablets with child resistant closure or a carton containing 4 blister strips of 21 tablets each for a total of 84 tablets. Each tablet contains 40 mg gilteritinib as well as the following commonly used excipients: ferric oxide, hydroxypropyl cellulose, hypromellose, low-substituted hydroxypropyl cellulose, mannitol, magnesium stearate, talc, polyethylene glycol and titanium dioxide. Store gilteritinib tablets at 20ºC to 25ºC (68°F to 77°F); excursions between 15ºC to 30ºC (59°F to 86°F) are permitted. Keep in the original container until dispensed and protect from light, moisture and humidity.

Do not break or crush gilteritinib tablets. Administer gilteritinib orally about the same time each day. If a dose of gilteritinib is missed or not taken at the usual time, administer the dose as soon as possible on the same day, and at least 12 hours prior to the next scheduled dose. Return to the normal schedule the following day. Do not administer 2 doses within 12 hours. Gilteritinib may be taken in either the fed or fasted state either with or without gastric acid reducing agents, including proton pump inhibitors (PPIs).

7.2 LANRA:

LANRA is available as biconvex, blue film-coated tablets. Each tablet contains 10 mg or 30 mg of LANRA free base as the succinate form. LANRA tablets contain commonly used excipients, including microcrystalline cellulose, mannitol, croscarmellose sodium, magnesium stearate, polyvinyl alcohol, polyethylene glycol, titanium dioxide, talc, and FD&C blue #2/indigo carmine aluminum lake. LANRA tablets are packaged in white, high-density, polyethylene bottles with silica gel desiccant and polyester packing material. Each bottle is enclosed with a white, continuous thread, child-resistant screw cap with an induction sealed liner. LANRA tablets should be stored at a controlled room temperature of 15ºC to 30ºC (59°F to 86°F). Storage conditions are specified on the label. To ensure the stability of LANRA tablets, the drug product should not be dispensed into a container other than that in which it is supplied. Measures that minimize drug contact with the body should always be considered during handling, preparation, and disposal procedures. Appropriate precautions should be followed to avoid direct eye contact or exposure through inhalation when handling LANRA. If eye contact does occur, affected areas should be washed with a large amount of water.

In Phase 1b, administer LANRA *without gilteritinib* on Cycle 1, Day 1. Beginning on Day 2 of Cycle 1, co-administer LANRA tablets with gilteritinib once daily at approximately the same time each day, with 8 ounces (240 mL) of water. **In Phase 2**, patients should initiate treatment with both LANRA and gilteritinib on Cycle 1, Day 1.

Patients who have a delay of < 12 hours should take the planned dose as soon as possible after the intended time of administration. For patients who have a delay of ≥ 12 hours, the missed dose should not be taken. Return to the normal schedule the following day. Do not

administer 2 doses within 12 hours of each other. Vomited doses should not be repeated except if the tablets are clearly visible in the vomitus.

LANRA may be taken in either the fed or fasted state and with or without acid reducing agents, including PPIs.

8.0 Treatment Modifications

Treatment interruptions and dose reductions for management of toxicities as described below are permitted at any time. In general, patients who experience Grade 1 or 2 toxicities should continue treatment without interruption or dose reduction, if these are manageable with supportive care interventions.

8.1 Non-hematologic toxicities

8.1.1 Gilteritinib

Table 2: Treatment Modifications for Gilteritinib-Associated Toxicities

Differentiation Syndrome (DS)*:	• If DS is suspected, administer systemic corticosteroids (IV dexamethasone, 10 mg every 12 hours or equivalent) for a minimum of 3 days and initiate hemodynamic monitoring until symptom resolution. • Interrupt gilteritinib if severe signs and/or symptoms persist for more than 48 hours after initiation of corticosteroids. • Resume gilteritinib at full dose when signs and symptoms improve to Grade ≤2.
Posterior reverse encephalopathy syndrome (PRES)**:	• Discontinue gilteritinib.
QTcF interval greater than 500 msec:	• Follow instructions provided in Section 11.7.3 regarding follow-up ECG assessments at the time of the event. • Interrupt gilteritinib. • Resume gilteritinib at 80 mg/day when QTcF interval returns to within 30 msec of baseline or ≤480 msec.
QTc interval increased by >30 msec on Day 8 of Cycle 1 compared to baseline:	• Confirm with repeat ECG on Day 9. • If confirmed, consider dose reduction to 80 mg/day.
Pancreatitis:	• Interrupt gilteritinib until pancreatitis is resolved. • Resume gilteritinib at 80 mg/day.
Liver function abnormalities:	• For Grade 1-2 abnormalities, continue gilteritinib at full dose. • For Grade ≥3 AST, ALT elevations interrupt gilteritinib and re-check

	values at least weekly. If AST, ALT elevations resolve to Grade 1 or baseline in ≤14 days, re-start gilteritinib at 80 mg/day. • Permanently discontinue gilteritinib for Grade ≥3 total bilirubin, interruptions lasting >14 days or recurrence of Grade ≥3 AST, ALT elevations despite dose reduction.
Diarrhea:	• For Grade 3 diarrhea, uncontrolled with anti-diarrheal medications, interrupt gilteritinib until diarrhea resolves to Grade ≤1. • Re-start at 80 mg/day if resolved after interruption lasting ≤14 days. If Grade 3 diarrhea does not recur after 2 weeks of reduced dose gilteritinib, escalation to full dose may be attempted at investigator's discretion. • Permanently discontinue gilteritinib for Grade 4 diarrhea, interruption lasting >14 days or recurrence of Grade 3 diarrhea despite dose reduction.
Other Grade ≥3 toxicity related to gilteritinib†:	• Interrupt gilteritinib. • Upon recovery to Grade ≤1 or baseline in ≤14 days after interruption, resume gilteritinib at 80 mg/day. For interruptions lasting >14 days or recurrence of Grade ≥3 toxicity despite dose reduction, permanently discontinue gilteritinib.

*DS is associated with rapid proliferation and differentiation of myeloid cells and may be life-threatening or fatal if not treated. Symptoms of DS include fever, dyspnea, pleural effusion, pericardial effusion, pulmonary edema, hypotension, rapid weight gain, peripheral edema, rash, and renal dysfunction. Some cases may present with concomitant acute febrile neutrophilic dermatosis. DS may occur as early as 2 days and up to 75 days after gilteritinib initiation and has been observed with or without concomitant leukocytosis.

**A diagnosis of PRES requires confirmation by brain imaging, preferably magnetic resonance imaging (MRI).

†Since patients will be receiving study treatment daily, chronic, low grade side effects, such as nausea, fatigue, mucositis and diarrhea, while not meeting criteria for treatment modifications, may not be tolerable when experienced for long periods of time. Dose reduction for chronic, low-grade toxicities attributed to gilteritinib may be permitted if these cannot be managed effectively with supportive care.

Patients who are intolerant of the study regimen beyond Cycle 1 may either permanently discontinue one or both study medications or interrupt study treatment in consultation with the medical monitor until the toxicity or laboratory abnormality has resolved to Grade 1. For additional details regarding modification of gilteritinib treatment for toxicities, consult the local prescribing information.

8.1.2 LANRA

Table 3: Dose Reductions for LANRA-Associated Toxicities

Dose Level:	20 mg QD	40 mg QD	60 mg QD	90 mg QD
Dose Reduction for Toxicity	Discontinue	30 mg QD	40 mg QD	60 mg QD

Table 4: Treatment Modifications for LANRA-Associated Toxicities

Liver function abnormalities:	• For Grade 1-2 abnormalities, continue study treatment at assigned dose. • For Grade ≥3 AST, ALT withhold LANRA and re-check values at least weekly. If AST, ALT resolves to Grade ≤1 or baseline ≤14 days after interruption, re-start LANRA at dose level -1 (Table 3). • Permanently discontinue LANRA for interruption lasting >14 days, Grade ≥3 total bilirubin or recurrence of Grade ≥3 AST, ALT elevations despite dose reduction.
Rash:	• For Grade 1-2 rashes that are clinically manageable with topical steroids, continue study treatment at assigned dose. • For Grade 3 rash, initiate treatment with topical steroids and interrupt LANRA until rash resolves to Grade ≤1. • Re-start at dose level -1 if resolved ≤14 days of interruption (Table 3). • If Grade 3 rash does not recur after 2 weeks of reduced dose LANRA, escalation to full dose may be attempted at investigator's discretion. • Permanently discontinue LANRA in patients with Grade 4 rash, interruption for >14 days or recurrent Grade 3 rash despite dose reduction.

Diarrhea:	• For Grade 3 diarrhea, uncontrolled with anti-diarrheal medications, interrupt treatment until diarrhea resolves to Grade ≤1. • Re-start at dose level -1 if resolved after interruption lasting ≤14 days. (Table 3). • Permanently discontinue LANRA for Grade 4 diarrhea, interruption lasting >14 days or recurrence of Grade 3 diarrhea despite dose reduction.
Other non-hematologic toxicities related to LANRA†:	• Interrupt LANRA until the toxicity resolves to Grade ≤1, and then restart at dose level -1 (Table 3) if resolution occurs ≤14 days of interruption. • Permanently discontinue LANRA for interruption lasting >14 days or recurrence of Grade ≥3 toxicity despite dose reduction.

†Since patients will be receiving study treatment daily, chronic, low grade side effects, such as nausea, fatigue, mucositis and diarrhea, while not meeting criteria for treatment modifications, may not be tolerable when experienced for long periods of time. Dose reduction for chronic, low-grade toxicities attributed to LANRA may be permitted if these cannot be managed effectively with supportive care.

Patients who are intolerant of the study regimen beyond Cycle 1 may either permanently discontinue one or both study medications or interrupt study treatment in consultation with the medical monitor until the toxicity or laboratory abnormality has resolved to Grade 1.

8.2 Hematologic toxicities

There will be no dose modifications for peripheral blood cytopenias unless patients achieve a CR with count recovery and subsequently exhibit recurrence of cytopenias that are not attributable to other causes. In this setting, performance of a bone marrow aspirate and/or biopsy to confirm AML has not recurred is mandated.

Table 5: Treatment Modifications for Hematologic Toxicities Attributed to Study Treatment

Grade 4 neutropenia without fever:	• Interrupt both study medications. • Upon recovery of absolute neutrophil count (ANC) to Grade ≤2 (with or without myeloid growth factor support), restart gilteritinib at 80 mg/day and LANRA at dose level -1 (Table 3). • If counts remain stable for 1 month after dose reductions, investigators may at their discretion, attempt to resume full dose gilteritinib followed by LANRA (≥2 weeks later), as tolerated. • For recurrence of Grade 4 neutropenia in the setting of reduced doses, or lack of ANC recovery to ≤Grade 2 after >28 days of treatment interruption, discontinue study treatment.
Febrile neutropenia (any grade):	• Interrupt both study medications. • Following resolution of fever and improvement of ANC to Grade ≤2 (with or without myeloid growth factor support), restart gilteritinib at 80 mg/day and LANRA at dose level -1. • For recurrence of febrile neutropenia in the setting of reduced doses or lack of ANC recovery to ≤Grade 2 after >28 days of treatment interruption, discontinue study treatment.
Grade 4 thrombocytopenia or Grade 3 thrombocytopenia with clinically significant bleeding requiring a platelet transfusion:	• Interrupt both study medications. • Upon recovery of platelet count to Grade ≤2 (and resolution of clinically significant bleeding, if present), restart gilteritinib at 80 mg/day and LANRA at dose level -1 (Table 3). • If counts remain stable for 1 month after dose reductions, investigators may at their discretion, attempt to

	resume full dose gilteritinib followed by LANRA (≥2 weeks later), as tolerated. • For recurrence of Grade 4 thrombocytopenia or Grade 3 thrombocytopenia with clinically significant bleeding in the setting of reduced doses or lack of platelet count recovery to ≤Grade 2 after >28 days of treatment interruption, discontinue study treatment.

9.0 Treatment of Overdose

Any dose of LANRA or gilteritinib greater than the dose assigned is considered an overdose. AEs associated with an overdose will be recorded on the AE electronic case report form (eCRF) log. Events that meet the criteria for seriousness must be reported immediately, without undue delay, and within 24 hours of awareness via the SAE reporting process (see Section 16.7.4). In the event of an overdose, contact the medical monitor immediately. The patient must be monitored for evidence of toxicity and standard supportive treatment should be provided, as necessary. It is unknown whether LANRA or gilteritinib can be removed by dialysis. There is no known antidote for LANRA or gilteritinib. In the case of symptomatic overdose, the patient should receive standard treatment and supportive therapy based on the patient's signs and symptoms.

10.0 Concomitant Medications and Supportive Care Measures

All concomitant medications will be recorded beginning on C1D1 through 30 ± 7 days after treatment completion. The medical monitor should be contacted if there are any questions regarding the acceptability of concomitant or prior therapies.

10.1 Permitted Medications

Patients should receive full supportive care including transfusions of blood and blood products, antibiotics, anti-emetics, antifungal agents, tumor lysis syndrome treatment or prophylaxis, etc., when appropriate. Patients may receive prophylactic anti-microbial therapy in accordance with institutional standards of care. The use of myeloid growth factors is permitted in accordance with institutional standards of care. The use of intrathecal chemotherapy for prophylaxis against CNS leukemia is permitted in accordance with institutional care standards.

10.2 Prohibited Medications

Recombinant erythropoietin (rEPO) is not permitted at any time during the study. No other direct anti-leukemia therapy is permitted except for hydroxyurea in Cycle 1 to control or prevent signs/symptoms of leukostasis as required. Palliative radiation therapy may not be administered while the patient is on study except for management of localized leukemic infiltrates in the skin.

Patients must not receive medications that have a known risk to prolong the QT interval or induce Torsades de Pointes in light of the ability for gilteritinib to cause QT interval prolongation and the unknown potential for LANRA to do so (see Appendix 4).

In vitro data indicate that LANRA is predominantly metabolized by CYP3A4 in humans. As such, concurrent administration of strong CYP3A4 *inducers* is prohibited as these would be expected to cause reduced exposures to LANRA (see Section 6, LANRA Investigator Brochure; Appendix 4). Concurrent administration of strong CYP3A4 *inhibitors* should be avoided. If the use of a strong CYP3A4 inhibitor for patient management cannot be avoided, patients should interrupt treatment with LANRA for the time period that the strong CYP3A4 inhibitor is required*. Administration of LANRA can resume at its previous dose 24 hours after discontinuation of the strong CYP3A4 inhibitor. Since grapefruit is known to be a strong inhibitor of CYP3A4, and Saint John's wort is known to be a strong inducer of CYP3A4, patients must be instructed to refrain from consumption of grapefruit, its juice, or Saint John's wort.

*Most azole antifungal agents are strong CYP3A4 inhibitors (see Appendix 4), however, neither fluconazole nor isavuconazole are strong CYP3A inhibitors and can be concurrently administered with LANRA.

10.3 Potential Drug Interactions

10.3.1 Gilteritinib

Concomitant use of gilteritinib with rifampin (a combined P-glycoprotein [P-gp] and strong CYP3A *inducer*) decreases gilteritinib exposure which may decrease its efficacy. Avoid concomitant use of gilteritinib with combined P-gp and other strong CYP3A inducers. Concomitant use of gilteritinib with itraconazole (a strong CYP3A *inhibitor*) increased gilteritinib C_{max} and AUC by approximately 20% and 120%, respectively. Consider alternative therapies that are not strong CYP3A inhibitors. If the concomitant use of these inhibitors is considered essential for care of the patient, monitor the patient more frequently for gilteritinib-mediated adverse reactions and/or consider dose reduction. See Appendix 4 for a list of commonly prescribed P-gp and strong CYP3A inducers and strong CYP3A inhibitors. Concomitant use of gilteritinib may reduce the effects of drugs that target the $5HT_{2B}$ receptor or the sigma nonspecific receptor (eg, escitalopram, fluoxetine, sertraline). Avoid concomitant use of these drugs with gilteritinib unless their use is considered essential for the care of the patient.

See the local prescribing information for gilteritinib for further information on potential drug interactions.

10.3.2 LANRA

In vitro, LANRA is an inhibitor of the drug transporter P-gp, which could potentially result in inhibition of P-gp mediated intestinal efflux of co-administered drugs. As such, orally administered P-gp substrates (eg, digoxin, dabigatran, etexilate) that have narrow therapeutic indices should be avoided (Appendix 4). *In vitro*, LANRA is a weak inducer of CYP3A4, thus caution should be taken if co-administered with oral drugs that are sensitive substrates of CYP3A4.

11.0 Study Assessments & Procedures

Required study visits and corresponding assessments (except PK and PD assessments in Cycle 1 and Cycle 2) are outlined in Table 6 and Table 7 for the Screening evaluation through completion of Cycle 2 and for Cycle 3 through Post-treatment Follow-up, respectively. All study visits should be scheduled relative to the C1D1 date regardless of any treatment interruptions. 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. Acceptable windows for post-treatment follow-up visits are ± 1 week. Unscheduled study visits may be required as clinically indicated for evaluation of AEs or suspected leukemic progression. Results of diagnostic evaluations performed as part of an unscheduled study visit must be entered into the Unscheduled Visit eCRF. Consistent with guidances from the FDA and other health authorities regarding the on-going COVID-19 pandemic (Appendix 5), certain safety assessments may be performed in a licensed facility other than the designated trial site, up to 1 day prior to a scheduled study visit during the treatment phase beginning on Cycle 1, Day 22. These include hematology (complete blood count [CBC], differential, platelet count), clinical chemistries, urinalysis, coagulation studies and pregnancy testing (Table 6 and Table 7).

The schedule of PK and PD assessments on Cycle 1, Day 1 through Day 8 and Cycle 1, Day 15 through Cycle 2, Day 1 in **Phase 1b** are outlined in Table 8 and Table 9, respectively. The schedule of PK and PD assessments in Cycle 1 and Cycle 2 in **Phase 2**, are outlined in Table 10.

Table 6: 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
Adverse event 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 8 and Table 9 for full descriptions of PK and PD sampling time points in **Phase 1b**. See Table 10 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 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 in both **Phase 1b** and **Phase 2** (see Table 7 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)												

Table 7: 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 ± 1 week
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/biomarker 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)			
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 of 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 response; stable or progressive disease; primary refractory disease after 1st line induction or recurrence of leukemia after CR) per ELN criteria (Appendix 2); 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 (eg, midostaurin and/or selective FLT3 inhibitor) and presence of other somatic mutations (eg, *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 and 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 8 below for C1D1 paired PK sampling timepoints and Table 9 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, 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 (LFTs), 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 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. Perform 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. MRD 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 8). **In Phase 2,** patients will begin combination therapy with LANRA and gilteritinib on C1D1.

[o] Record all treatment-emergent adverse events (TEAEs) including clinically relevant laboratory abnormalities on the adverse event eCRF. TEAEs 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-CTCAE, v. 5.0. **See Section 16.0 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. After the Screening period, counseling will consist of reminding enrolled patients of the need to continue pregnancy prevention measures including the consistent use of effective contraception at time points stipulated in Table 6 and Table 7 and for 4 months (males) or 6 months (females) after the last dose of study drug.

[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 8: 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 9: 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 10: 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).

11.1 Informed Consent

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. Consent must be obtained using the most current version of the ICF approved by the study site's IRB/IEC. Once the patient signs the ICF, that will signal the beginning of the 21-day Screening Period. Patients who provide informed consent and subsequently do not meet eligibility criteria (or withdraw consent prior to enrollment) should be documented as screening failures, with the reason(s) for not meeting eligibility or not enrolling recorded.

11.2 Confirmation of Eligibility

All screening assessments and relevant medical history must be available and reviewed by the investigator before eligibility can be confirmed. Eligibility waivers will not be granted. After the investigator determines that a patient is eligible, study site personnel will complete an enrollment authorization form to be sent to the medical monitor for review/approval. Written authorization by the medical monitor is required before a patient can be officially enrolled and begin study treatment.

11.3 Medical and Leukemia History

Clinically significant medical history not pertaining to the underlying malignancy under study, which started prior to informed consent, will be captured on the eCRF. "Clinically significant" is generally regarded as any diagnosis requiring on-going treatment intervention and follow-up. Signs and symptoms of concurrent medical conditions must be adequately documented at Screening in order to establish baseline severities.

The following information regarding the history of AML will be collected and recorded on the eCRF: 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 response, stable or progressive disease; primary refractory disease after 1st line induction or recurrence of leukemia after CR) per ELN 2017 criteria (Appendix 2); number of relapses (0, 1, ≥2); type of *FLT3* mutation (ITD, TKD or both) and allelic frequency (high, low) at diagnosis (if applicable) and at baseline; history of hematopoietic stem cell transplant including post-transplant best response; prior exposure to a FLT3 inhibitor (eg, midostaurin and/or selective FLT3 inhibitor) and presence of other somatic mutations (eg, *NPM1*, *IDH1*, *IDH2*, *DNMT3A, TP53*) at diagnosis and baseline, if known.

11.4 Study Drug Dispensation

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 while 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 8). In Phase 2, patients will begin combination therapy with LANRA and gilteritinib on C1D1.**

Patients will be provided a dosing diary to record dosing information when at home. Patients will be instructed to record the date and time of study treatment administration along with any pertinent notes (eg, nausea, vomiting after ingestion of the dose) in the dosing diary. Deviation(s) from the prescribed treatment regimen should be recorded by the patient in the dosing diary. The dosing diary will be evaluated by study site personnel at study visits.

Patient compliance with the study treatment will be by direct questioning, counting returned tablets, and reviewing patient's dosing diaries. Treatment start and stop dates, including dates and reasons for treatment interruption and/or dose reductions will also be recorded in the eCRF.

11.5 Pharmacokinetics

Blood will be collected at specified intervals in order to measure the plasma concentrations of LANRA both alone and in combination with gilteritinib, and plasma concentrations of gilteritinib administered in combination. Plasma samples collected for PK analysis may also be used for an exploratory assessment of the LANRA metabolite profile. The schedule for PK blood sampling in Phase 1b, Cycle 1 is provided in Table 8 and Table 9 and for Phase 2, Cycle 1 in Table 10. On PK sample collection days, administration of study drug must occur under the supervision of study site personnel after the predose PK sample is collected. The time of study drug administration must be recorded on the eCRF and include the last administration of study medication (both LANRA and gilteritinib) prior to the predose sample collection as well as in other situations where dosing occurred outside of the clinic (eg, in conjunction with evaluation of AEs or QTc prolongation, see Section 11.7.3). For each blood sample collected, the actual time of collection (to the nearest minute) will be captured in the eCRF. Plasma concentrations of LANRA, gilteritinib, and their metabolite(s), if applicable, will be quantified by liquid chromatography with tandem mass spectrometry (LC-MS/MS) using validated assays.

Details concerning the processing and handling of PK samples, including labeling and shipping instructions, will be provided in the Laboratory Manual.

11.6 Pharmacodynamic (Biomarker) Assessments

Peripheral blood will be collected at Screening and specified intervals during Phase 1b and Phase 2 in order to characterize the pharmacodynamic activity of LANRA and to support selection of the RP2D. The schedules of blood sampling for biomarker assessments on Cycle 1 Day 1 through Day 8 and Cycle 1 Day 15 through Cycle 2 Day 1 in Phase 1b are outlined in

Table 8 and Table 9, respectively. The schedule of blood sampling for Cycle 1 and 2 biomarker assessments in Phase 2 is provided in Table 10. After Cycle 2, additional blood samples for biomarker assessments are requested on Day 1 of Cycle 3 and every 3 cycles thereafter until 2 consecutive response assessments of CR/CRh are documented, and at the End-of-Treatment Evaluation (Table 7).

Bone marrow aspirate for biomarker assessments will be collected at Screening, Day 1 of Cycle 2 and Cycle 3 and every 3 cycles thereafter (ie, coinciding with response assessments) until 2 consecutive response assessments indicate CR or CRh.

Biomarker assessments will include (but are not limited to) an evaluation of somatic mutations other than *FLT3* in baseline blood and bone marrow samples as well as pre- vs on-treatment changes in phosphorylated (p)SYK and gene expression in whole blood and/or bone marrow aspirate samples using standard proteomic, transcriptomic, and genomic tools such as immunohistochemistry (IHC), Nanostring®, and next-generation sequencing (NGS). Levels of circulating proteins (such as, but not limited to IL-1b, TNF-α, IL-6) in plasma may also be assessed and quantified throughout the Treatment Phase using technologies such as enzyme-linked immunosorbent assay (ELISA) or Luminex® (Austin, TX), for example.

Optional unstained slides (n=3-5) from bone marrow biopsies are requested to explore the immunologic profile in the bone marrow microenvironment of study patients. Results from preclinical studies suggest that a.) SYK inhibition may activate T-cell responses, and b.) integrin signaling via SYK plays a role in creating a permissive microenvironment for survival and propagation of leukemic cells in the bone marrows of AML patients. Immunologic profiling of biopsies from study patients may help us understand whether/if specific immune cell profiles correlate with response to the study regimen. Slides from archival bone marrow biopsies or those obtained from study patients either at Screening or during the Treatment Phase are acceptable for study.

11.7 Safety Assessments

Unless otherwise stated, all safety assessments will be conducted locally in accordance with institutional standards of care.

11.7.1 Physical examination, vital signs, pulse oximetry

Perform a complete physical examination including neurological exam at Screening **within 14 days of C1D1**. At all other times, perform abbreviated, targeted examinations. Physical examination always includes body weight; height is obtained only at Screening. Report all treatment-emergent, clinically relevant abnormal physical findings on the AEs eCRF. Vital signs include resting heart rate, seated systolic/diastolic blood pressures and body temperature (°C); percent oxygen saturation is measured by pulse oximetry.

11.7.2 Laboratory assessments (hematology, clinical chemistries, coagulation, urinalysis, pregnancy testing)

CBCs are required at time points specified in Table 6 and Table 7 and includes hemoglobin concentration, hematocrit, platelet count, white blood cell (WBC) count with differential

including neutrophils (including bands), lymphocytes, monocytes, eosinophils, basophils and blasts. Coagulation screening studies (PT, aPTT and INR, fibrinogen, D-dimer levels) are required at Screening, on Days 1 and 15 of Cycle 1, Day 1 of Cycles 2 and 3 and as clinically indicated thereafter.

Chemistries include electrolytes (sodium, potassium, chloride, total CO_2 and/or bicarbonate, calcium, phosphate, magnesium), liver function studies (AST, 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, LFTs, 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.

Urinalysis includes dipstick evaluation for pH, glucose, protein, blood, and leukocyte esterase; conduct microscopic evaluation for red and white blood cells only if the dipstick result is abnormal. Perform urinalysis at Screening and as clinically indicated thereafter if urine dipstick is abnormal.

Perform a 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. Perform a serum pregnancy test for confirmation of a positive urine ß-hCG test result.

11.7.3 Cardiac function and ECG

Obtain triplicate ECG measurements, each separated by approximately 2 minutes with the patient in semi-recumbent position at the following time points in **Phase 1b**: Screening, on Days 1 (predose), 8 (pre- or post-dose) and 15 (predose) of Cycle 1, Day 1 of Cycle 2 and Cycle 3 (both pre- or postdose). **On Cycle 1, Day 1 and Cycle 1, Day 15, additional triplicate ECGs paired with PK blood samples are required at Hours 1, 2, 4 and 6 post-dose (see** Table 8 **and** Table 9**)**. In **Phase 2**, obtain triplicate ECG measurements at Screening, Cycle 1 Day 8, Cycle 1 Day 15, Cycle 2 Day 1, and Cycle 3 Day 1 (all pre- or post-dose).

All ECG recordings will be performed using a high-quality, high-fidelity digital electrocardiograph and centrally reviewed and interpreted. To minimize postural variability, ECG recordings must be obtained after the patient has been resting in a semi-recumbent position for at least 10 minutes. When coinciding with blood draws or other procedures (eg, vital sign measurements), ECG assessments should precede these. Environmental factors that may induce changes in heart rate (eg, television, radio, etc.) should be avoided as much as possible.

For safety monitoring purposes, the investigator or his/her designee should review, sign and date all ECG tracings with paper copies kept as part of the patient's permanent study file at the site. Digital recordings of ECGs sent to the central reading facility will be stored in a repository under the supervision of the reading facility or with the sponsor/designee. If QTc interval prolongation is observed (mean QTcF > 500 msec and/or >60 msec longer than baseline) during study treatment, another triplicate ECG must be obtained within the next 5 minutes. If confirmed on repeat triplicate ECG, an unscheduled PK sample should be collected (Section 11.5) and follow-up ECGs recorded at least hourly, until the prolongation is reversed or stabilized, or the

investigator determines that there is no significant arrhythmic risk. Other possible causes for QTc prolongation should be investigated including electrolyte abnormalities, concurrent medication use known to prolong QT interval, etc. The medical monitor should be notified, and a decision made whether to discontinue study treatment. **See Table 2 for gilteritinib treatment modification in the setting of QTcF interval prolongation to > 500 msec at any time and/or a >30 msec increment on Cycle 1, Day 8 compared to baseline.**

The sponsor will evaluate the relationship between LANRA PK parameters and ECG intervals on an on-going basis and may modify the schedule of Cycle 1, Day 1 PK/ECG paired assessments based on updated information during the study.

An assessment of left ventricular ejection fraction will be performed at Screening and as clinically indicated during the treatment phase. An ECHO or MUGA scan is acceptable.

11.7.4 ECOG performance status

ECOG PS will be assessed at time points indicated in Table 6 and Table 7 and in accordance with criteria outlined in Appendix 3.

11.7.5 Prior and concomitant medications and procedures

Record all medications (including over-the-counter medications) patient is taking from the time of informed consent until Cycle 1, Day 1 (C1D1). All new or continuing medications including dose, frequency, route of administration and start and stop dates, which are administered between C1D1 and the End-of-Treatment Visit must be recorded in the eCRF concomitant medication log. Record all surgical and diagnostic procedures (eg, X-rays, scans) on the designated eCRFs.

11.7.6 Adverse events

During the Screening period, record only serious AEs. Beginning on C1D1 until the End-of-Treatment Evaluation, record all new AEs as well as any that predate C1D1 but that worsen in intensity or recur during the Treatment Phase. After the End-of-Treatment Evaluation, only serious AEs that are assessed as causally related to LANRA must be reported. Guidelines for the reporting of AEs and serious AEs are provided in Section 16.0.

12.0 Efficacy Assessments

Assessments that define the quality of response to study treatment will include physical examination, peripheral blood counts, and bone marrow examination. All assessments of response will be made by the investigator in accordance with ELN 2017 criteria (Döhner 2017). See Appendix 2 for criteria that define each response category.

12.1 Bone Marrow Examination

Perform bone marrow aspiration at Screening for morphology, karyotyping/fluorescence in situ hybridization (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 aspirate (or biopsy) for response assessments and biomarker assessments (Section 11.6) on Day 1 of Cycle 2 and Cycle 3 and every 3 cycles thereafter (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.

12.1.1 Measurable Residual Disease (MRD)

MRD will be assessed retrospectively in peripheral blood and bone marrow aspirate concurrently as an exploratory efficacy endpoint. MRD assessments will be performed in a central testing facility designated by the Sponsor beginning with the 1st documented CR or CRh.

13.0 Criteria for Study Treatment Discontinuation

Study treatment will be discontinued for the following reasons:

- Unequivocal leukemic progression or recurrence of leukemia after a response
- Failure to achieve at least a PR after completion of 6 cycles of study treatment
- Pregnancy
- Death
- Withdrawal of consent
- A TEAE that:
    - is ≥Grade 3 and unresponsive to treatment modification guidelines outlined in Table 2 and Table 4 (for gilteritinib and LANRA non-hematologic toxicities, respectively) and Table 5 (for hematologic toxicities associated with either or both drugs) OR,
    - chronic, Grade 1 or 2 toxicities that may not be tolerable when experienced for long periods of time either with or without treatment modification, thereby prompting the decision by the investigator, patient, or both to discontinue study treatment
- Need for, or use of a prohibited concomitant medication
- Hematopoietic stem cell transplantation
- Non-compliance with the study regimen
- Trial is discontinued by the study sponsor

Patients who discontinue study treatment must complete the End-of-Study Visit 30 ± 7 days after the last dose of either gilteritinib or LANRA (whichever is later) or prior to initiation of new anticancer therapy.

During Part 1 (dose escalation), any dosing interruption resulting in administration of <80% of the cumulative, Cycle 1 dose for either LANRA or gilteritinib in the absence of DLT will require the patient to be replaced.

14.0 Criteria for Study Discontinuation

Study participation will be discontinued for the following reasons:

- Death
- Withdrawal of consent
- Trial is discontinued by the study sponsor

15.0 Statistical Considerations

Detailed methodology for summary and statistical analyses of the data collected in this study will be documented in a Statistical Analysis Plan (SAP), which will be maintained by the sponsor. This document may modify the plans outlined in the protocol, however, any major modifications of the primary endpoint definition and/or its analysis will also be reflected in a protocol amendment.

Summary statistics and listings will be used to analyze the study data. Continuous variables will be summarized by means, standard deviations, medians, interquartile ranges, minimal and maximal values. Categorical variables will be summarized by number and percent.

Unless otherwise specified, data summaries and analyses described below will be reported by dose group and overall in Phase 1b and overall in Phase 2 using all available data. Missing data will not be imputed unless otherwise described in the SAP.

15.1 Study Endpoints

See Section 3.0 for a description of study endpoints for Phase 1b and Phase 2.

15.2 Statistical Analysis

15.2.1 Analysis populations

Patients will be evaluable for DLT in Part 1 if one of the following occurs:

- They experience a DLT (as defined in Appendix 1) 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.

  Note: If there are patients within a dose cohort who receive less than the intended cumulative dose of either study medication, due to reasons other than a DLT, additional patients will be enrolled to ensure the desired number of evaluable patients.

Note: 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 to be safe and adequately tolerated by the DEC, if there are no available patient slots in the dose cohort currently under evaluation. 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 agreement 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 (Appendix 2): CR, CRh, CRi, PR, MLFS. The 3+3 dose escalation rule will continue to be followed for each successively higher dose cohort however, should DLT(s) occur in 1 or more patients enrolled to backfill cohorts, these will be taken into account for purposes of future dose escalation decisions. Specifically, if a DLT occurs in a patient allocated to a backfill cohort, the DLT rate will be re-calculated for that cohort. If the

updated DLT rate exceeds 20% with 80% probability, the updated DLT rate will be taken into consideration by the DEC when deciding whether to stop or continue dose escalation to the next higher dose level. The safety population will include all patients who receive ≥1 dose of gilteritinib or LANRA and have at least 1 on-treatment safety -related observation (ie, report of an AE or post-dose assessment of vital signs, ECGs, or safety laboratory assessments).

The PK analysis population will include all patients with at least 1 post-dose LANRA plasma concentration.

The PD analysis population will include all patients with a baseline and at least 1 post-dose pharmacodynamic assessment.

The efficacy evaluable population will include all patients who receive ≥1 dose of gilteritinib or LANRA and complete the first protocol-specified response assessment or have discontinued study treatment for toxicity or die prior to the first response assessment.

15.2.2 Patient Disposition

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 study discontinuation will be summarized separately for Phase 1b and Phase 2 in accordance with the reasons specified in Section 13.0 and Section 14.0, respectively.

15.2.3 Demographics

Demographics (age, sex, race) and ECOG PS will be summarized for the safety populations in Phase 1b and Phase 2 separately, using descriptive statistics.

15.2.4 Medical History

All clinically relevant prior or concurrent medical conditions will be mapped to a system organ class (SOC) and preferred term (PT) using the version of the Medical Dictionary for Regulatory Activities (MedDRA) in effect at the time of database lock. The number and percent of patients in the safety populations in Phase 1b and Phase 2 reporting medical conditions will be summarized separately.

15.2.5 Leukemia History

The following baseline characteristics will be summarized using descriptive statistics for patients in Phase 1b and Phase 2 separately: age and years 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 response, stable or progressive disease, primary refractory disease after 1st line induction or recurrence of leukemia after CR) per ELN criteria (Appendix 2); 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 (eg, midostaurin and/or selective FLT3 inhibitor) and presence of other somatic mutations (eg, *NPM1*, *IDH1*, *IDH2*, *DNMT3A*, *TP53*) at diagnosis and baseline, if known.

The median, minimal and maximal 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 and Phase 2 patients separately. 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 and Phase 2 patients separately.

15.2.6 Prior and Concomitant Medications

Prior medications (defined as all medications administered from signing of informed consent until C1D1) will be summarized by frequency distributions and percentages for Phase 1b and Phase 2 patients separately. Concomitant medications (defined as all new or on-going medications administered from C1D1 until the End-of-Treatment Evaluation) will be summarized by frequency distributions for Phase 1b and Phase 2 patients separately. Both prior and concomitant medications will be classified using WHO Drug Dictionary codes preferred name and ATC Classification for therapeutic indication.

15.2.7 Safety Analyses

Dose-limiting toxicities will be summarized for Phase 1b and Phase 2 patients separately. Descriptive summaries will be generated for all safety data including TEAEs as well as changes from baseline in selected laboratory assessments, vital signs, physical findings and ECGs. All AEs will be graded for severity using NCI-CTCAE v5.0 (Common Terminology Criteria for Adverse Events (CTCAE) (cancer.gov)).

15.2.7.1 Safety Stopping Rules

For Part 2, evaluation of DLTs will be assessed coincident with the first cycle of treatment, initially after the first 6 patients and each additional patient thereafter. If the true incidence of DLTs exceeds 20% with 80% posterior probability given the accumulated data at these time points, further enrollment will be interrupted. Using the Bayesian stopping rules with the defined parameters, the stopping rule is given in Table 11.

Table 11: Safety Stopping Rules for Part 2

# Patients (inclusive)	# of Patients with DLTs
6	≥ 2
7	≥ 3
8	≥ 3
9	≥ 3
10	≥ 4
11	≥ 4
12	≥ 4
13	≥ 4
14	≥ 5
15	≥ 5
16	≥ 5
17	≥ 5
18	≥ 5
19	≥ 6
20	≥ 6
21	≥ 6
22	≥ 6
23	≥ 7
24	≥ 7
25	≥ 7
26	≥ 7
27	≥ 8
28	≥ 8
29	≥ 8
30	≥ 8
31	≥ 9
32	≥ 9
33	≥ 9
34	≥ 9
35	≥ 9
36	≥ 10
37	≥ 10

Reference: Lee 2021

If enrollment is halted based on implementation of the safety stopping rules, the DEC will be convened to assess the risk-benefit profile of the study treatment and provide recommendations regarding modifying or stopping the study.

15.2.8 Extent of Exposure

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.

15.2.9 Pharmacokinetic Analyses

Plasma concentrations of LANRA and gilteritinib will be tabulated and summarized by dose level, study day, and time in Phase 1b. The PK parameters for gilteritinib and LANRA (and if possible, LANRA major metabolites, if any) will be derived from plasma concentrations using standard non-compartmental methods and actual sample times. Minimally, the following PK parameters will be calculated: C_{max}, T_{max}, $AUC_{0\text{-last}}$, accumulation ratio (R_{acc}) and if data permit, half-life ($t_{½}$), $AUC_{0\text{-inf}}$, CL/F, and apparent volume of distribution at steady state (V_{ss}/F). PK parameters such as C_{trough} will be calculated in conjunction with sparse sampling in Phase 2. PK parameters will be summarized using descriptive statistics (N, arithmetic means, standard deviations, minimal, median and maximal values, geometric means and percent coefficient of variation).

The relationship between changes from baseline in QTc at specified time points post-dose and plasma concentrations of LANRA may be assessed. A separate analysis plan for such analyses will be generated in accordance with principles outlined in ICH E14 (Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs) with results reported separately from the main clinical study report for this trial. Other exposure-response relationships (efficacy, safety and biomarkers) may be conducted, if supported by sufficient data.

15.2.10 Efficacy Analyses

Best response (CR, CRh, CRi, partial response [PR], stable disease [SD], and progressive disease [PD]) will be summarized for the efficacy-evaluable population by frequency distributions and percentages in accordance with ELN criteria (Appendix 2). Patients with no post-baseline response assessments will be considered non-responders. The 80% CIs 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, 80% CIs for the estimates of the proportion of patients with any CR (CR, CRh or CRi) will be constructed in a similar manner.

EFS is defined as the time from C1D1 until treatment failure (ie, failure to achieve CR or CRh), relapse from CR/CRh or death from any cause. DOR is defined as the time from the first documented CR/CRh until relapse or death. Kaplan-Meier (KM) methodology will be used to estimate the medians for EFS and duration of response and at specified landmark timepoints. The 80% CIs for estimates of the medians and landmark rates for EFS and duration of response will be calculated using the log-log transformation (Kalbfleisch and Prentice, 1980). Duration of follow-up will be estimated using the reverse KM method. Patients who do not experience the event of interest will be censored at the last assessment at which they are deemed relapse-free. All summaries of EFS and duration of response will employ the safety and efficacy evaluable populations, respectively. OS will be estimated using KM methodology. Patients alive at last follow-up will be censored at the date of last contact.

15.2.11 Pharmacodynamic Analyses

Descriptive summaries for results of individual biomarkers of interest will be generated. A separate analysis plan for evaluating changes in pre- vs. on-treatment biomarkers of interest will be generated with results reported separately from the main clinical study report for this trial.

15.3 Sample Size Considerations

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 (including those patients enrolled to backfill cohorts) 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). 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 (Calculations made using PASS 2020).

15.4 Interim Analysis

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.

In Phase 2, a review of the first stage composite CR rate will be evaluated after 12 patients are enrolled at the RP2D and evaluated for response.

15.5 Final Analysis

The final analysis will occur at the End of Study, as defined in Section 6.5.

15.6 Other Statistical Issues (eg, Multiplicity Adjustment, If Applicable)

Not applicable.

16.0 Safety Monitoring and Reporting

16.1 Definitions

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.

When an AE occurs, it is the responsibility of the investigator to review all documentation (eg, progress notes, laboratory results, diagnostic reports) relevant to the event. The investigator or his/her designee will record all relevant information regarding the event in the eCRF. There may be instances when copies of medical records are requested by the study sponsor. In these instances, all patient identifiers will be redacted on copies of medical records prior to submission to the sponsor.

A serious AE (SAE) is any untoward medical occurrence that:

- Results in death
- Is life-threatening

Note: Life-threatening implies that the patient was at risk of imminent death at the time of the event; it does not refer to an event that hypothetically might have caused death, were it more severe.

- Requires or prolongs a pre-existing hospitalization.

Note: Hospitalization signifies that the patient was admitted to a hospital or emergency ward for an overnight stay (at least) for observation and/or treatment.

- Results in disability/incapacity.

Note: Disability refers to a substantial disruption of person's ability to conduct daily functions.

- Is a congenital anomaly/birth defect.
- Is considered a significant medical event by the investigator that may jeopardize the patient or require medical or surgical intervention to prevent one of the outcomes listed above.

A suspected, unexpected serious adverse reaction (SUSAR) is an AE that is both unexpected (ie, not listed in the Reference Safety Information for the investigational agent) and meets the definition of a serious adverse drug reaction, the specificity or severity of which is not consistent with those noted in the Reference Safety Information (ie, the Investigator's Brochure for an investigational agent).

16.2 Assessment of Severity

The investigator will make an assessment of severity for each AE reported during the study. AEs should be assessed and graded for severity based on the NCI-CTCAE v. 5.0 (Common Terminology Criteria for Adverse Events (CTCAE) (cancer.gov).

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 noninvasive 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

Note: The terms "severe" and "serious" are not synonymous. Severity is a measure of intensity (as characterized above) whereas seriousness as defined above, defines the requirements for reporting obligations from the sponsor to applicable regulatory authorities.

16.3 Assessment of Causality

The investigator will assess the causal relationship between and the occurrence of all AEs using best clinical judgement and taking into consideration the natural history of the underlying disease, concomitant therapies, biological plausibility, the mechanism of action of the study drug and the temporal relationship between the event and the administration of study drug. The investigator should consult relevant safety information and "Guidance for the Investigator" in the IB in formulating his/her assessment of causality.

Each AE should be assessed as either "related" or "not related" to, based on all available information at the time of reporting. Causality assessments may be modified in the context of additional information or details pertaining to the event, after the initial causality assessment is made. An event should be considered related if any of the following criteria are met:

- There is clear evidence to suggest a causal relationship and other possible causal factors can be ruled out.
- There is evidence to suggest a causal relationship and the influence of other factors is unlikely.
- There is evidence to suggest a causal relationship, however, other factors (eg, the patient's underlying condition or other concurrent AEs) may have contributed to the occurrence of the event.

16.4 Follow-up of Adverse Events

After an initial AE or serious AE is reported, those that are designated as ongoing from a previous visit/contact must be reviewed at subsequent visits. All AEs will be followed until resolution, stabilized, or considered chronic, or the study participant is either lost to follow-up or withdraws consent. The investigator will ensure that follow-up reporting includes any supplemental investigations that were obtained to further elucidate the nature and/or causality of the event, including additional laboratory or radiographic evaluations, histopathologic examination, or consultation with other health care professionals.

The sponsor may request that the investigator perform or arrange for the conduct of supplemental evaluations to elucidate as fully as possible the nature and/or causality of any event. If a study participant dies while on study or during a pre-specified follow-up period, the sponsor will be provided with a redacted copy of any postmortem findings, including histopathologic findings.

16.5 Abnormal Laboratory Results

Abnormal laboratory test results (eg, chemistries, blood counts, coagulation studies or urinalysis) or other abnormal assessments (eg, ECGs, X-rays) that are judged by the investigator as clinically significant will be recorded as AEs or serious AEs, as appropriate. This includes clinically significant blood, urine or other abnormalities that are present at baseline and significantly worsen during the study. In general, clinically significant laboratory test abnormalities are those associated with signs or symptoms, require active medical intervention, lead to study treatment interruption or dose reduction and/or require more frequent follow-up or further diagnostic investigation.

16.6 Adverse Event Reporting Period

Report only SAEs after signing of the ICF, but before administration of study drug. Beginning on C1D1 until the End-of-Treatment Evaluation (or until initiation of new anticancer therapy, whichever is sooner), report all AEs regardless of the relationship to study treatment. Thereafter, only SAEs assessed as related to LANRA must be reported.

16.7 Instructions for Reporting Adverse Events

16.7.1 Leukemic progression

Leukemic progression should not be reported as an AE. Signs, symptoms, or clinical sequelae of leukemic progression should be reported (eg, worsening cytopenias, fatigue, infection as manifestations of recurrence or worsening of AML should be reported as such on the AE eCRF).

16.7.2 Death

Death is an outcome and not usually considered an event. For example, in the case of overwhelming sepsis leading to death, “overwhelming sepsis (Grade 5)” would be recorded as the event with death as the outcome. If the cause of death is unknown, the death is then reported as an event (ie, “death due to unknown cause” or “death unexplained”).

16.7.3 Differentiation Syndrome (DS)

Differentiation syndrome is associated with rapid proliferation and differentiation of myeloid cells and may be life-threatening or fatal if not treated. Symptoms of differentiation syndrome include fever, dyspnea, pleural effusion, pericardial effusion, pulmonary edema, hypotension, rapid weight gain, peripheral edema, rash, and renal dysfunction. Some cases may present with concomitant acute febrile neutrophilic dermatosis. Differentiation syndrome may occur as early as 2 days and up to 75 days after gilteritinib initiation and has been observed with or without concomitant leukocytosis (Fathi 2021). In this study, DS is considered an adverse event of special interest (AESI) for reporting purposes. AESIs are collected from the time of informed

consent until the End-of-Treatment evaluation or until initiation of new anticancer therapy, whichever is sooner.

Presumptive DS events, whether serious or non-serious, must be promptly entered into the electronic data capture (EDC) system by the investigator within 24 hours of knowledge of the event. For DS events that meet the criteria for seriousness, sites must follow the reporting procedures outlined in Section 16.7.4 below.

16.7.4 Reporting Serious Adverse Events (SAEs)

Once an investigator becomes aware that a SAE has occurred, a SAE report must be completed as thoroughly as possible with all available details relevant to the event and forwarded to the sponsor or designee immediately, without undue delay, and within 24 hours. If the investigator does not have access to all relevant details related to an event, he/she is not to wait to receive additional information before notifying the sponsor or designee of the SAE. Additional details of the event as they become available will be forwarded to the sponsor or designee in a follow-up report. The investigator must always provide an assessment of causality at the time of the initial SAE report. The sponsor will provide contact information to the investigator for SAE report submission. The investigator, or responsible individual (in accordance with local standard operating procedures) will comply with all applicable requirements related to reporting of SAEs to regulatory authorities and their IRB/IEC.

The sponsor will promptly assess all SAEs against cumulative safety experience to identify and communicate new safety findings to regulatory authorities, investigators and IRBs/IECs based on applicable regulations. To define the reporting requirement for individual SAEs, the sponsor will assess “expectedness” using the IB as the reference safety document. All SUSARs will be submitted to all applicable regulatory authorities and investigators.

16.7.5 Pregnancy Reporting

If a female patient becomes pregnant while receiving or within 6 months of discontinuing study treatment, OR the female partner of a male patient becomes pregnant while he is receiving or within 4 months of discontinuing study treatment, a pregnancy report form must be completed and submitted to the sponsor to facilitate outcomes follow-up. While pregnancy itself is not considered an AE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be recorded as an AE. An abortion whether therapeutic or spontaneous must be reported as a SAE.

For pregnancies taken to term, details on the status of the mother and child will be forwarded to the sponsor, with follow-up generally no longer than 6-8 weeks after the delivery date. Any congenital anomaly in a child born to a patient exposed to study treatment must be reported as a SAE.

17.0 Study Committees and Communication of Results

17.1 Dose-escalation committee (DEC)

As noted in Section 4.0, this study will utilize a DEC consisting of all study investigators with enrolled patients and sponsor representatives including (but not limited to) the sponsor's medical monitor, safety officer, and PK and translational science leads. The DEC will convene by conference call or videoconference as promptly as possible upon completion of the DLT assessment period for all patients within a dose cohort in Phase 1b. Representation by at least 1 medically qualified member (ie, an MD) from each trial site with at least 1 patient enrolled to any cohort will be required for all DEC convocations. Ad hoc meetings of the DEC may be conducted for adjudication of individual safety-related events, if requested by an individual investigator. All decisions regarding dose escalation including declaration of the MTD/RP2D will require unanimous consent of the participating investigators. These will be documented within the study's trial master file along with the minutes of each DEC meeting.

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 most recently enrolled dose cohort. 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 agreement 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 (Appendix 2): CR, CRh, CRi, PR, MLFS. The 3+3 dose escalation rule will continue to be followed for each successively higher dose cohort however, should DLT(s) occur in 1 or more patients enrolled to backfill cohorts, these will be taken into account for purposes of future dose escalation-making decisions. Specifically, if a DLT occurs in a patient allocated to a backfill cohort, the DLT rate will be re-calculated for that cohort. If the updated DLT rate exceeds 20% with 80% probability, the updated DLT rate will be taken into consideration by the DEC when deciding whether to stop or continue dose escalation to the next higher dose level (Section 2.6; Section 15.2.1).

The frequency of DLTs as defined in Appendix 1 will be assessed coincident with the first cycle of treatment during Part 2, initially after the first 6 patients and each subsequent patient thereafter. If the true incidence of DLTs exceeds 20% with 80% posterior probability given the accumulated data at these time points (see Section 15.2.7.1 for additional detail), further enrollment will be interrupted, and the DEC will be convened to assess the risk-benefit profile of the study treatment and provide recommendations regarding modifying or stopping the study. Additionally, the DEC will be convened for discussions and recommendations in the setting of one Grade 5 event or two Grade 4 events that are considered at least possibly related to LANRA or gilteritinib coincident with the interruption of new patient accrual. Recommendations proffered by the DEC in this setting will not preempt a final decision on the resumption of enrollment by FDA, which will be based on a thorough safety analysis that will be submitted to

FDA and any other applicable authority per local requirement for review prior to resuming enrollment.

17.2 Provision of Study Results and Information to Investigators

When a clinical study report is completed for this study, the sponsor will provide the major findings of the study to the investigators. The sponsor will not routinely inform the investigator or patient of individual test results because the information generated from this study will be preliminary in nature and the significance and scientific validity of the results may be undermined at such an early stage of research.

18.0 Administrative Requirements of the Investigator and Sponsor

18.1 Regulatory Authority Approval

The sponsor will submit the study protocol and obtain approval to conduct the study from the appropriate regulatory agency in accordance with any applicable country-specific regulatory requirements before the study is initiated within that country.

18.2 Investigator Responsibilities

18.2.1 Good Clinical Practice

The investigator will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki, ICH GCP, and other country-specific requirements, as applicable.

18.2.2 Ethical Study Conduct and IRB/IEC Approval

The investigator is responsible for ensuring that this protocol, the study site's ICF and any other information that will be presented to potential study participants (eg, advertisements or information that supports or supplements the ICF) are reviewed and approved by the appropriate IRB/IEC. The IRB/IEC must be constituted in accordance with applicable regulatory requirements. The sponsor will provide the investigator with relevant documents that are needed for IRB/IEC review and approval of the study. Before study drug can be dispatched to the study site, the sponsor (or its designee) must receive copies of the IRB/IEC approval letter, the ICF that the study site will use, and any other information that the IRB/IEC has approved for presentation to prospective study participants. If the protocol, ICF or any other information presented to prospective study participants as approved by the IRB/IEC is amended, the investigator is responsible for ensuring that the IRB/IEC reviews and approves amended study documents, where applicable. The investigator must adhere to applicable regulatory requirements pertaining to the use of an amended ICF before new study participants can consent to take part in the study. Copies of all IRB/IEC correspondence including those related to approval of an amended ICF, protocol or other information as well as copies of said amended documents must be forwarded to the study sponsor or its designee promptly.

18.2.3 Informed Consent

The investigator is responsible for obtaining written, informed consent from each prospective study participant using the IRB/IEC-approved consent form, after adequately explaining the objectives, methods, and potential hazards of study participation and before conducting study-related procedures or assessments. Each ICF will be signed and dated by the patient or the patient's legally authorized representative and the person obtaining consent. The process of obtaining informed consent and contents of the ICF will be in accordance with all applicable regulatory requirements.

18.2.4 Investigator Reporting Requirements

The investigator (or sponsor, where applicable) is responsible for reporting SAEs to their IRB/IEC in accordance with all applicable regulations (see Section 16.7.4). The investigator may be required to provide periodic safety updates during the conduct of the study and notification of study closure to their IRB/IEC. Such periodic safety updates and notifications are the responsibility of the investigator and not the sponsor.

18.2.5 Confidentiality

Information on steps to maintain patient confidentiality in accordance with local and national patient privacy regulations must be provided to each study participant as part of the informed consent process, either as part of the ICF or as a separate signed document (eg, a site-specific Health Insurance Portability and Accountability Act [HIPAA] consent form in the US). The investigator must assure that the anonymity of study participants will be strictly maintained and that their identities are protected from unauthorized parties. Only the date and an identification code (not names) should be recorded on any form or biological sample submitted to the sponsor, IRB/IEC or the sponsor's designated central laboratories. The investigator will maintain a screening log including patient codes, names and contact details or local medical record identifiers for all prospective study participants screened and for patients subsequently enrolled into the study.

The investigator and sponsor will maintain confidentiality by following applicable data privacy laws covering the collection, storage, transmission, and processing of personal and medical information of study participants. Medical information on study participants obtained during the study may only be disclosed to third parties as permitted by the signed ICFs or a separate authorization for the use and disclosure of personal health information that has been signed by the study participant, unless permitted or required by law. Medical information may be given to a study participant's personal physician or other appropriate medical personnel responsible for the study participant's health and welfare, for treatment purposes. Data generated by this study must be available for inspection upon request by representatives of the FDA and all other national and local health authorities, the sponsor's study monitors, representatives and collaborators as well as the IRB/IEC for each study site, as appropriate.

In the event of a breach of confidentiality, the investigator and sponsor, as appropriate, shall undertake all remediation efforts and obligations to report said breach under applicable data privacy laws.

18.2.6 Data Collection

Data required by the study protocol will be entered into eCRFs in an EDC system that is compliant with all regulatory requirements. All study-related data collected or received by the investigator or study team shall be promptly entered into the eCRFs after the data is collected or received by the investigator or study team in a time frame consistent with what is stipulated in the study site contract.

Data recording onto eCRFs must follow the data entry instructions provided in the eCRF completion guidelines. The investigator has ultimate responsibility for the collection and

reporting of all clinical data. The investigator or his/her designee in the "Statement of Investigator Form" at the front of this protocol must sign the completed casebooks to attest to its accuracy, authenticity, and completeness.

18.2.7 Data Management/Coding

All final patient data recorded onto eCRFs as well as external data (eg, central laboratory assessments) collected in accordance with this protocol will be stored at Kronos Bio or a designated off-site facility at the end of the study. Data will be reviewed for the presence of potential outliers or inconsistencies as well as for logic and completeness. Standard procedures including data review guidelines, computerized validation for query generation and maintenance of an audit file that includes database modifications will be followed to ensure accurate data collection.

During the course of the study, a study monitor will make regular visits to the study site or engage with the study site via videoconference or through other digital media to review protocol compliance, compare data entered onto eCRFs with individual study participants' medical records (ie, source data verification) and ensure that the study is being conducted in accordance with pertinent regulatory requirements. The source data verification process will be conducted in a manner to ensure that the confidentiality of study participants is maintained. Direct access to source data will also be required for inspections and audits and be carried out with due consideration to data protection and confidentiality.

18.2.8 Drug Accountability

The investigator or his/her designee (ie, pharmacist) is responsible for ensuring adequate accountability of all used and unused study drug. This includes acknowledgement of receipt of each shipment of study product (including quantity and condition), patient drug dispensation records, and returned or destroyed study product. Dispensing records will document quantities received from Kronos Bio, and quantities dispensed to study participant, including lot number, date dispensed, patient identifier and the initials of the person dispensing the medication. All drug supplies and associated documentation will be periodically reviewed and verified by the study monitor during the conduct of the study.

At study initiation, the sponsor's study monitor will evaluate each site's standard operating procedures for study drug disposal/destruction to ensure it complies with Kronos Bio's requirements. During and at the end of the study, the study site will dispose of and/or destroy all unused study drug supplies and study drug returned by study participants (including empty containers) according to standard operating procedures after drug inventory reconciliation by the study monitor. If the site cannot meet Kronos Bio's requirements for disposal, arrangements will be made for off-site destruction or return of unused study drug and study drug supplies.

18.2.9 Inspections

Investigators should understand that source documents for this study must be made available to appropriately qualified personnel from Kronos Bio or its representatives, IRBs/IECs, or regulatory authority inspectors.

18.2.10 Protocol Adherence

Investigators are responsible for ensuring that the study is conducted in accordance with the procedures and evaluations outlined in this protocol and assert that they will apply due diligence to avoid protocol deviations. Investigators must document and explain to the sponsor any deviations from the IRB/IEC-approved protocol and must report any major deviations that might impact patient safety and/or the integrity of study data to the sponsor and the IRB/IEC, in accordance with established IRB/IEC policies and procedures.

18.2.11 Financial Disclosure

Investigators are required to provide the sponsor with complete and accurate financial information in accordance with regulations to allow the sponsor to submit disclosure or certification of the absence of certain financial interest or to disclose those financial interests as required, to the appropriate health authorities. This is to ensure that financial interests and arrangements between clinical investigators and Kronos Bio, which could affect the reliability of data submitted to health authorities, are identified and disclosed. Investigators are responsible for providing information about their financial interests before their participation in the study, and to update this information if any relevant changes occur during the study, and for 1 year after completion of the study.

18.3 Protocol Amendments

Except for those intended to reduce immediate risk to study patients, protocol amendments may be initiated only by Kronos Bio. All protocol amendments must be submitted to regulatory authorities according to local requirements as well as to the IRB/IEC together with, if applicable, a revised model ICF. Written documentation indicating approval of the amendments from regulatory authorities (if applicable) and from the study site's IRB/IEC must be obtained by the sponsor before changes to study conduct can be implemented.

New or updated information that indicate a change in risk and/or study scope must be provided to study participants already actively participating in the study in an amended ICF and they must read, understand, and sign each revised ICF confirming their willingness to remain in the study.

18.4 Study Report and Publications

A clinical study report will be prepared detailing the outcomes of this study and provided to regulatory bodies including the US FDA and others, as applicable. Kronos Bio will ensure that this report meets the standards set out in the ICH Guideline for Structure and Content of Clinical Study Reports (ICH E3). The final clinical study report will be signed by the coordinating (principal) investigator, if applicable. Note that an abbreviated report may be prepared in certain cases.

Results from this study will be published or presented at scientific meetings in a timely and objective manner, regardless of the outcome of the study, consistent with good science, industry, and regulatory guidance, and in accordance with the terms of the applicable clinical study agreement. Data generated in this clinical study are the exclusive property of the sponsor and will remain confidential until such time as they are publicly disclosed. As this is a multicenter

study, the first publication or disclosure of study results shall be a joint, multicenter publication or disclosure coordinated by the sponsor or its designee. Thereafter, any secondary publications will reference the first (original) publication. Authorship shall be determined by mutual agreement and all authors must meet the criteria for authorship established by the International Committee of Medical Journal Editors Uniform Requirements for manuscripts or alternatively, stricter local criteria (International Committee of Medical Journal Editors, 2013).

No communication, presentation or publication will include Kronos Bio's confidential information.

Each investigator agrees to submit all manuscripts, abstracts, posters, publications, and presentations (both oral and written) to the sponsor prior to submission for peer-review or presentation in accordance with the terms outlined in the clinical study agreement. This will allow the sponsor to protect proprietary information, provide comments based on information from other studies that may not yet be available to the investigator, and ensure scientific and clinical accuracy. The procedure for reviewing manuscripts and presentations that are based on results from this study is detailed in the investigator's clinical study agreement. Each investigator acknowledges and agrees that in accordance with the clinical study agreement, a delay in publication/presentation may be requested by the sponsor to allow for patent filings in advance of the latter or deletion of sponsor's confidential information.

18.5 Study/Study Center Closure

Upon completion of the study, the study monitor will conduct the following close-out activities in collaboration with the investigator or other study center personnel, as appropriate:

- Retrieval of all outstanding study data
- Resolution and closure of all outstanding data queries
- Accountability, reconciliation and arrangement for disposal/destruction of unused study drug
- Review of study records for completeness
- Return of treatment codes to the sponsor
- Shipment of final PK or PD samples to central laboratories

The sponsor reserves the right to suspend or prematurely discontinue this study either at a single or multiple study sites, or in its entirety, at any time for reasons including but not limited to safety or ethical issues or severe noncompliance. If it is determined that such action is warranted, the sponsor will discuss this with the investigator (including the reasons for taking such action) at that time. When feasible, the sponsor will provide advanced notification to the investigator of the impending action prior to it taking effect.

The sponsor will promptly inform all investigators and/or institutions conducting the study if it is to be suspended or terminated for safety reasons and will also inform regulatory authorities of the suspension or termination and the reason for the action. If required by applicable regulations, the investigator must inform the IRB/IEC promptly and provide the reason for the suspension or termination.

If the study is prematurely discontinued, all study data must be returned to the sponsor. Arrangements for the disposal or destruction of all unused study drug will be made in accordance with the applicable sponsor procedures. Financial compensation to investigators and/or institutions will be in accordance with the agreement established between the investigator and the sponsor.

18.6 Record Retention and Study Files

The investigator must maintain accurate and up-to-date records to enable an assessment of study conduct (ie, investigator's study files) as well as the veracity and completeness of the study data (ie, patient source documents).

The investigator's study file will contain the protocol/protocol amendments, eCRF and query forms, IRB/IEC and regulatory agency approval (if applicable) along with correspondence, informed consent, drug records, staff curriculum vitae and authorization forms as well as other appropriate documents and correspondence. Patient source documents would generally include but are not limited to, patient hospital/clinic records, physician/nurse's notes, original laboratory reports, ECG, X-ray and pathology reports, consultant notes/letters, special assessment reports, screening, and enrollment log, etc.

Following closure of the study, the investigator must maintain all study records in a safe and secure location. The records must be maintained in a manner that will allow for easy and timely retrieval when needed (eg, for audit or inspections) and whenever feasible, to allow for subsequent review of data in conjunction with assessment of the facility, supporting systems and personnel. Where permitted by local laws/regulations or institutional policy, some or all of these records may be maintained in a format other than hard copy (eg, scanned, electronic); however, the investigator must assure that all reproductions are legible, a true and accurate copy of the original and meet accessibility and retrieval standards, including re-generating a hard copy, if required.

The sponsor will inform the investigator of the time period for retaining these records. The minimal retention time will meet the strictest standard applicable to that study center as dictated by any institutional requirements, local laws or regulations or the sponsor's standards/procedures. In the absence of any of these, the retention period will default to 15 years. The investigator must notify the sponsor of any changes in the archival arrangements including but not limited to the following: archiving at an off-site facility and transfer of ownership of the records in the event the investigator leaves the study site.

The sponsor may conduct genomics, transcriptomic, and/or proteomic studies in the future utilizing residual biospecimens that may be left over after completion of the planned biomarker studies described herein. The focus of such future research would be limited to oncology indications. Biospecimen retention for such future research will be optional for patients enrolled into the current study, with the ability to withdraw consent. If the patient withdraws consent for use of retained biospecimens, he/she must notify the study investigator in writing. The investigator will notify Kronos Bio forthwith, after which any retained samples will be destroyed as soon as is feasible. Retained biospecimens will be de-identified and stored in a central repository for the shorter of a period of up to 10 years or as allowed by the site's IRB/IEC. Data generated as a consequence of future testing may be used indefinitely. Specimens and data

generated will be accessible by only Kronos Bio, and/or contracted third parties for any future research involving retained biospecimens. Data and results generated will not be shared with patients and investigators but may be included anonymously in clinical study reports, scientific presentations, or publications. Any data generated from the analysis of retained biospecimens will be de-identified and patient confidentiality will be maintained.

18.7 Information Disclosures

All information provided by the sponsor including but not limited to the investigator's brochure, this protocol, eCRFs, the investigational drug and any other study information, as well as all data generated as part of the study, is the sole and exclusive property of the sponsor. Study data may be included in patient medical records, but the sponsor makes no claim of ownership with respect to such patient medical records. This information will not be used by the investigator or other study personnel for any purpose other than conducting the study and will not be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from the sponsor. The investigator agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the study site to any third party or into the public domain.

Any inventions or discoveries arising from the study will be handled in accordance with the applicable clinical study agreement.

18.8 Joint Investigator/Sponsor Responsibilities

18.8.1 Access to Information for Monitoring/Source Data Verification

In accordance with ICH GCP guidelines, the study monitor must have direct access to the investigator's source documentation in order to corroborate the veracity of data entered into the eCRFs. The monitor will review the eCRFs at regular intervals throughout the study to verify adherence to the study protocol and the completeness, consistency and accuracy of data being entered onto them. The monitor must have access to any and all patient records needed to verify eCRF entries. The investigator agrees to cooperate with the monitor to ensure that issues/problems detected in the course of his/her monitoring activities are addressed.

18.8.2 Access to Information for Auditing or Inspections

Regulatory authorities or representatives of Kronos Bio may conduct inspections or audits any time during or after completion of this clinical study. If the investigator is notified of an inspection by representatives from a regulatory authority, he/she agrees to notify the sponsor or its designee immediately. The investigator agrees to provide regulatory authority inspectors or those retained by Kronos Bio access to records, facilities, and study site personnel for the effective conduct of any inspection or audit.

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Appendix 1: Definition of DLT

During Part 1 (dose escalation), the DLT assessment period is defined as Cycle 1, Day 1 through Cycle 1, Day 28 and includes the pre-dose assessments for Day 1 of Cycle 2.
NCI-CTCAE Version 5.0 (Common Terminology Criteria for Adverse Events (CTCAE) (cancer.gov) will be used to grade the severity of all AEs. A DLT is defined as any of the following toxicities occurring within the DLT assessment period:

- 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 (Section 8.1) 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 patient unevaluable for purposes of MTD determination and require the patient 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.

Appendix 2: Response Criteria

Assessments of response will be made according to the European LeukemiaNet 2017 criteria (Döhner 2017) with minor modifications. The major criteria for judging response will include physical examination and examination of peripheral blood and bone marrow. All laboratory studies that are abnormal prior to study will be repeated to document the degree of maximal response.

Complete Remission (CR):

CR 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):

CRh 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)*:

CRi 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 rod
- 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

Morphologic 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 pretreatment

Stable Disease (SD):

- 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 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 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 ***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 IDH proteins, other kinase or targets may cause a Differentiation Syndrome, ie, 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.

Treatment Failure

Treatment failure will be classified as one of the following:

- Primary refractory disease: failure to achieve CR or CRh after induction excluding patients with death in the setting of bone marrow aplasia or death due to indeterminate cause

- Death in the setting of bone marrow aplasia: death occurring ≥7 days following completion of initial treatment while cytopenic with an aplastic or hypoplastic bone marrow documented within 7 days of death and without evidence of persistent leukemia

- Death from indeterminate cause: deaths occurring either before completion of initial therapy or <7 days following its completion, or deaths occurring ≥7 days following completion of initial therapy without circulating blasts but no bone marrow examination is available

Recurrence

Recurrence for patients with prior CRh, CRi or MLFS is defined as:

- 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 5-20% 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.

Appendix 3: ECOG Performance Status Scale

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

Source: Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5:649-655.

Appendix 4: Potential for Drug-Drug Interactions

Concomitant administration of study treatment with medications listed below could result in drug-drug interactions that potentially lead to reduced activity or enhanced toxicity of the concomitant medication, gilteritinib and/or LANRA.

$5HT_{2B}$ receptor inhibitors	Escitalopram, fluoxetine, sertraline
Strong CYP3A inducers*	Rifampin, mitotane, avasimibe, rifapentine, apalutamide, ivosidenib, phenytoin, carbamazepine, enzalutamide, St John's wort, lumacaftor, phenobarbital
Strong CYP3A inhibitors**	Boceprevir, clarithromycin, cobicistat, conivaptan, grapefruit juice, indinavir, itraconazole, ketoconazole, mibefradil, mifepristone, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, troleandomycin, voriconazole
P-gp substrates with narrow therapeutic index	Digoxin, dabigatran

*P-gp inducers already listed as CYP3A inducers.

** See Section 10.2 for instructions on the interruption and subsequent resumption of LANRA in patients who require treatment with a strong CYP3A inhibitor. Note that neither fluconazole nor isavuconazole are strong CYP3A inhibitors and can be administered concurrently with LANRA.

A more comprehensive listing of strong CYP3A inducers and inhibitors can be found at: Flockhart DA. Drug Interactions: Cytochrome P450 Drug Interaction Table, Indiana University School of Medicine (2007). https://drug-interactions.medicine.iu.edu

QT interval prolongation:

Gilteritinib has been reported to be associated with QT interval prolongation in 9% of patients (see Section 2.5.1, XOSPATA [gilteritinib] U.S. Prescribing Information, 2022; XOSPATA [gilteritinib] Summary of Product Characteristics 2021); the potential for LANRA to induce QT interval prolongation is not currently known.

Thus, patients must not receive medications that have a known risk to prolong the QT interval or induce Torsades de Pointes in light of the ability for gilteritinib to cause QT interval prolongation and the unknown potential for LANRA to do so.

Commonly Prescribed Drugs with Potential for QT Interval Prolongation*:

Indication	Drug With Known QT/Torsades de Pointe Effect
Antiarrhythmics	amiodarone, disopyramide, dofetilide, ibutilide, procainamide, quinidine, sotalol
Antibiotics	clarithromycin, erythromycin, gatifloxacin, moxifloxacin, sparfloxacin
Antipsychotics	chlorpromazine, haloperidol, mesoridazine, pimozide, risperidone, thioridazine, ziprasidone
Antidepressants	amitriptyline, desipramine, doxepin, imipramine, maprotiline, venlafaxine
Antifungals (azoles)	ketoconazole, itraconazole
Antimalarials	chloroquine, halofantrine
Antiemetics	dolasetron, domperidone, droperidol, ondansetron, tropisetron
Miscellaneous	arsenic trioxide, bepridil, methadone, pentamidine, cisapride, tacrolimus

*A more comprehensive listing of drugs can be found at: https://crediblemeds.org/druglist. Accessed 25 May 2021

Appendix 5: Guidance on the Management of Clinical Trials During COVID-19 Pandemic

FDA Guidance on the Conduct of Clinical Trials of Medical Products During the COVID-19 Public Health Emergency

EU Guidance on the Management of Clinical Trials During COVID-19 Pandemic

In other jurisdictions (eg, South Korea) that have published similar guidances referring to precautionary measures to be taken during clinical trial execution in the COVID-19 pandemic era, these may be followed in deference to those cited above for the US and EU.

Appendix 6: Contraceptive and Barrier Guidance

Definitions

Women in the following categories are <u>not</u> considered Women of Childbearing potential (WOCBP)

1. Premenopausal female with one of the following:
   - Documented hysterectomy.
   - Documented bilateral salpingectomy.
   - Documented bilateral oophorectomy.

   Documentation can come from a review of the patient's medical records, medical examination, or medical history interview.

2. Postmenopausal female
   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
   - Females on HRT and whose menopausal status is in doubt will be required to use one of the nonhormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Guidance

Male patients

Male patients with female partners of child-bearing potential are eligible to participate if they agree to the following during the study:

- Are abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinence on a long term and persistent basis) and agree to remain abstinent for the duration of study and for at least 4 months after the last dose of study medication.
- Female partner is using a highly effective contraceptive method, including one of the highly effective contraceptives listed in the table below.
- Agree to use a male condom.
- Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a condom during the study.
- Refrain from donating sperm for the duration of study and for at least 4 months after the last dose of study medication.

Highly Effective Contraceptive Methods That Are User Dependent *Failure rate of <1% per year when used consistently and correctly,*[a]
Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation.[b] • Oral • Intravaginal • Transdermal
Progestogen-only hormonal contraception associated with inhibition of ovulation.[b] • Oral • Injectable
Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation [b] • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) • Bilateral tubal occlusion
Vasectomized partner A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP, and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.
Sexual abstinence Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the patient.

a) Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for patients participating in clinical studies.

b) Based on current knowledge, drug-drug interactions are not expected between LANRA and hormonal contraceptives that could potentially reduce their effectiveness in pregnancy prevention. Nevertheless, WOCBP using one of the highly effective, hormonal contraceptives described above (either birth control pills or implantable devices) will be required to also employ a barrier method of contraception (eg, condom use by a male partner, diaphragm, or cervical cap) for at least 6 months after the last dose of study treatment.

Female patients

Female patients of reproductive potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in the table above in combination with a barrier method (eg, condom use by a male partner, diaphragm, or cervical cap) during the Treatment Phase and for at least 6 months after the last dose of study treatment.

Pregnancy Testing

WOCBP should only be included after a confirmed menstrual period and a negative highly sensitive serum pregnancy test at Screening and a negative urine pregnancy test on Day 1 of each cycle of study treatment and at the End-of-Treatment Evaluation.

Collection of Pregnancy Information

Male patients with partners of reproductive potential who become pregnant

- The investigator will attempt to collect pregnancy information on any female partner of a male study patient who becomes pregnant while participating in this study. This applies only to patients who receive study treatment.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor or designee within 24 hours of learning of the partner's pregnancy.
- The partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the sponsor or designee.
- Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for procedure.

Female Patients who become pregnant

- The investigator will collect pregnancy information on any female patient, who becomes pregnant while participating in this study.
- Information will be recorded on the appropriate form and submitted to the sponsor or designee within 24 hours of learning of a patient's pregnancy.
- The patient will be followed to determine the outcome of the pregnancy. The investigator will collect follow up information on the patient and the neonate, which will be forwarded to the sponsor or designee. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date.
- Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE.
- A spontaneous abortion is always considered to be an SAE and will be reported as such.
- Any SAE occurring as a result of a post-study pregnancy that is considered reasonably related to the study treatment by the investigator, will be reported to the sponsor or designee. While the investigator is not obligated to actively seek this information in former study patients, he or she may learn of an SAE through spontaneous reporting.

Any female patient who becomes pregnant while participating will discontinue study treatment but may continue to be followed for leukemic progression/relapse, first salvage therapy and survival. Further treatment options will be discussed.

Appendix 7: Recommended Adjustments to Anti-Platelet and Anti-Coagulant Therapy in AML

1. If aspirin is administered for primary prevention of cerebrovascular events, discontinue. If given for secondary prevention of cerebrovascular events, interrupt when platelets count is < 30,000/μL. Resume when platelet count is ≥ 30,000/μL.

2. Coronary artery stents (bare metal and drug eluting): Work closely with a consulting cardiologist to adjust anti-platelet therapy especially within first month of bare stent placement and first year of drug eluting stent placement. Consider holding aspirin and Plavix® when platelet count is < 20,000/μL and then resume when ≥ 20,000/μL if supported by cardiology consult recommendations, especially within first year of stent placement.

3. Atrial fibrillation: If patient is on aspirin only, hold when platelet count is < 50,000/μL and restart when consistently ≥ 50,000/μL. If patient is on anti-coagulant therapy (eg, anti-Factor Xa), treat with therapeutic doses of low molecular weight heparin (LMWH) until platelet count is < 50,000/μL, treat with prophylactic doses for platelet counts between 20-50,000/μL and hold for platelet counts < 20,000/μL.

4. Mechanical heart valves: Work closely with a consulting cardiologist. Treat with therapeutic doses of LMWH until platelet count < 40,000/μL. Treat with prophylactic doses when platelet count is between 20-40,000/μL. Consider holding for platelet counts < 20,000/μL. Alternatively, consider platelet transfusions in order to allow continuation of anti-coagulant therapy, based on a recommendation from cardiology consultation.

5. Acute events:
    a. Catheter thrombosis: Remove catheter, consider anticoagulation if symptomatic and platelet count ≥ 50,000/μL.
    b. Distal thrombosis: Follow-up scans in 3 days and every week for 6 weeks to make sure thrombosis does not progress.
    c. Proximal thrombosis and pulmonary embolism: Treat with therapeutic doses of LMWH if platelet count is >40,000/μL, prophylactic doses if platelet count is 20-40,000/μL and retrievable inferior vena filter if platelet count is < 20,000/μL on a case-by-case basis after discussion with cardiology consult and the medical monitor.

6. Acute coronary syndrome: administer aspirin to all patients, regardless of platelet count. Individualize therapy based on cardiology consultation (patient may need to discontinue study participation after discussion with medical monitor).

Appendix 8: List of Abbreviations and Terms

Abbreviation/Term	Definition
ADL	activities of daily living
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AML	acute myeloid leukemia
ANC	absolute neutrophil count
anti-HBc	hepatitis B antibody
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
ATC	Anatomic Therapeutic Chemical
AUC	area under the concentration × time curve
$AUC_{0\text{-inf}}$	area under the concentration × time curve from time 0 extrapolated to infinity
$AUC_{0\text{-last}}$	area under the concentration × time curve from time 0 until the last measurable plasma concentration
BID	twice a day
BUN	blood urea nitrogen
C1D1	Cycle 1 Day 1
CALBG	Cancer and Leukemia Group B
CBC	complete blood count
cCR	composite complete remission
CFR	Code of Federal Regulations
CI	confidence interval
CL/F	apparent clearance
CLE	cutaneous lupus erythematosus
C_{max}	maximal plasma concentration
CNS	central nervous system
COVID-19	coronavirus disease 2019
CPK	creatine phosphokinase

Abbreviation/Term	Definition
CR	complete remission
CR/CRh	composite CR rate
CRh	complete remission with partial hematologic recovery
CRi	complete remission with incomplete blood count recovery
C_{trough}	trough plasma concentration
CYP	cytochrome P450
DEC	Dose Escalation Committee
DLT	dose-limiting toxicity
DOR	duration of response
DS	Differentiation Syndrome
ECG	electrocardiogram
ECHO	echocardiogram
ECOG PS	Eastern Cooperative Oncology Group Performance Status
eCRF	electronic case report form
EDC	electronic data capture
EFS	Event free survival
ELN	European LeukemiaNet
ENTO	entospletinib
FDA	Food and Drug Administration
FISH	fluorescence in situ hybridization
FLT3	FMS-like tyrosine kinase 3
GCP	Good Clinical Practice
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HOXA9	homeobox protein
HR	hazard ratio
HSCT	hematopoietic stem cell transplantation
IB	Investigator's Brochure

Abbreviation/Term	Definition
IC_{50}	half-maximal inhibitory concentration
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
INR	international normalized ratio
IRB	Institutional Review Board
ITD	internal tandem duplication
IV	intravenous
LANRA	lanraplenib
LDH	lactate dehydrogenase
LFT	liver function test
LMN	lupus membranous nephritis
MedDRA	Medical Dictionary for Regulatory Activities
MLFS	morphologic leukemia-free state
MRD	measurable residual disease
MRI	magnetic resonance imaging
MTD	maximally tolerated dose
MUGA	Multi-gated acquisition
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NCCN	National Comprehensive Cancer Network
MGS	next generation sequencing
NPM1	*nucleophosmin-1*
OS	overall survival
P-gp	P-glycoprotein
PD	pharmacodynamic(s) *or* progressive disease
PK	pharmacokinetic(s)
PPI	proton pump inhibitor

Abbreviation/Term	Definition
PR	partial remission or partial response
PRES	Posterior Reversible Encephalopathy Syndrome
pSYK	phosphorylated spleen tyrosine kinase
PT	prothrombin time *or* preferred term
QD	once daily
RA	rheumatoid arthritis
R_{acc}	accumulation ratio
rEPO	recombinant erythropoietin
RLS	relapse-free survival
RP2D	recommended Phase 2 dose
R/R	relapsed/refractory
RT-PCR	reverse transcriptase polymerase chain reaction
SAE	serious adverse event
SAP	Statistical Analysis Plan
SARS CoV-2	severe acute respiratory syndrome (SARS) coronavirus 2 (CoV-2)
SD	stable disease *or* standard deviation
SUSAR	suspected, unexpected serious adverse reaction
SLE	Systemic lupus erythematosus
SOC	system organ class
SYK	spleen tyrosine kinase
TEAE	treatment-emergent adverse event
TKD	tyrosine kinase domain
$t_{½}$	half-life
T_{max}	time to maximal plasma concentration
ULN	upper limit of normal
URI	upper respiratory tract infection

Abbreviation/Term	**Definition**
UTI	urinary tract infection
US	United States
V_{ss}/F	apparent volume of distribution at steady state
WBC	white blood cell
WHO	World Health Organization
WOCBP	woman of child-bearing potential