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University of Colorado Cancer Center
A NATIONAL CANCER INSTITUTE-DESIGNATED CONSORTIUM COMPREHENSIVE CANCER CENTER

HCTU Hematology Clinical Trials Unit

Protocol Administrative Letter

Date: 29AUG2025

Sponsor – Investigator: Daniel Pollyea, MD

Protocol #: 20-2350

Protocol Title: A Phase 1 Open-Label Study Of KPT-9274 In Patients With Relapsed or Refractory Acute Myeloid Leukemia

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This letter is to communication termination of this study by the funding sponsor.

On 28AUG2025, the sponsor-investigator received a notice of termination letter for IST-347 from the funding sponsor, Karyopharm Therapeutics. This letter directs that in accordance with Section 10.3 of the contract agreement, the site is to cease enrollment of subjects into the study and, as quickly as medically permissible, terminate the study with respect to enrolled subjects including completing all study wind-down activities. Effectively, upon approval of this letter, the final subject in follow up at the site will be discontinued from trial.

This letter must receive IRB approval prior to implementation at the site. Any questions should be directed to the Sponsor-Investigator, Dr Pollyea, at 720-848-8084.

Approval of Sponsor-Investigator: Signed by: 7092C598D95E4B4... Date: September 2, 2025 | 5:47:19 PM MDT

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Hematology Clinical Trials Unit Division of Hematology		**Document:** HCTU-1214 **Version:** A **Effective Date:** DEC2021
DLT Determination Memo		

To:	**Investigative Sites, TMF**	**From:**	**Daniel Pollyea, MD**
Protocol #	**20-2350**	**Date**	**29APR2025**
SC meeting Date	**Not applicable**	**SI**	**Daniel Pollyea, MD**

The SI reviewed data for subject in the following cohort:

- Cohort 1, 30 mg dose
- Subject 1-08

Summary of Findings:

☐ Yes ☒ No	Did subject 1-08 experience a DLT?

After reviewing the data, the following decision(s) have been made:

☒ Yes ☐ No	Study will proceed with enrolling up to 1 more subject in Cohort 1, 30 mg.

I am approving this document.		**Date**
Sponsor Investigator Signature	Signed by: 7092C598D95E4B4...	April 29, 2025 | 3:46:29 PM MDT
Sponsor Investigator Name	Daniel Pollyea, MD	

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A PHASE 1 OPEN-LABEL STUDY OF KPT-9274 IN PATIENTS WITH RELAPSED OR REFRACTORY ACUTE MYELOID LEUKEMIA

Study Phase:	1
Investigational Product:	KPT-9274
Protocol Number:	20-2350
IND Number:	156351
Indication:	Relapsed or refractory acute myeloid leukemia
Sponsor:	University of Colorado, Anschutz Medical Campus
Sponsor Contact:	Daniel A. Pollyea, MD, MS
Protocol Version and Date:	V7, 31JAN2025

Docusign Envelope ID: 0D99C498-8D2C-4C6C-954C-4BC685BF3FDB

INVESTIGATORS' AGREEMENT

STATEMENT OF COMPLIANCE

This is an investigator-initiated study. The principal investigator (PI), Daniel Pollyea, MD, is conducting the study and the University of Colorado is acting as the sponsor. As the sponsor-investigator, both the legal/ethical obligations of a PI and those of a sponsor will be followed.

The trial will be carried out in accordance with Good Clinical Practice (GCP) as required by applicable United States (US) laws and applications, including but not limited to United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812).

In accordance with 21 CFR 25.30/25.31, this protocol qualifies for a categorical exclusion from the requirement for an environmental assessment for the manufacture and formulation for use in human clinical trials. All waste from the investigational drug(s) will be properly controlled. The amount of waste expected to enter the environment may reasonably be expected to be nontoxic. To the Sponsor-Investigator's knowledge, no extraordinary circumstances exist.

The PI will assure that no changes to the protocol will take place without documented approval from the Institutional Review Board (IRB). All personnel involved in the conduct of this study have completed Human Subjects Protection Training.

I agree to ensure that all staff members involved in the conduct of this study are informed about their obligations in meeting the above commitments.

Investigator's Name:	Daniel Pollyea, MD, MS
Institution:	University of Colorado
Date:	March 14, 2025 | 10:48:32 AM MDT
Sponsor-Investigator Signature:	DocuSigned by: Daniel Pollyea, MD 7092C598D95E4B4...

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PROTOCOL SYNOPSIS

Sponsor: CU-AMC, Daniel Pollyea, MD	**Investigational Product:** KPT-9274	**Study Phase:** Phase 1

Title of Study: A Phase 1 Open-Label Study Of KPT-9274 In Patients With Relapsed or Refractory Acute Myeloid Leukemia

Name of Active Ingredient: (*E*)-3-(6-aminopyridin-3-yl)-*N*-((5-(4-(4,4-difluoropiperidine-1-carbonyl)phenyl)-7-(4-fluorophenyl)benzofuran-2-yl)methyl)acrylamide

Protocol Number: 20-2350

Study Center: University of Colorado, Anschutz Medical Campus

Patient Population: Patients with relapsed/refractory acute myeloid leukemia (AML)

Objectives and Endpoints:

This study will evaluate the safety and tolerability of oral KPT-9274 for the treatment of patients with relapsed or refractory acute myeloid leukemia

Objectives	Endpoints
• Primary Objective: To assess the maximum tolerated dose (MTD) • Secondary Objective: To establish a recommended phase 2 dose (RP2D)	• The occurrence of dose limiting toxicities (DLTs) and the occurrence, nature and severity of adverse events (AEs)
Dose Expansion (if conducted) • Primary Objective: Determine preliminary evidence of efficacy of KPT-9274 at the RP2D	*Dose Expansion (if conducted)* • Primary Endpoint: Overall response rate (ORR) • Secondary Endpoint: Duration of response (DOR), progression-free survival (PFS), overall survival (OS)

Rationale for the Study:

KPT-9274 is a first-in-class orally bioavailable, non-competitive, small molecule, dual modulator of p21 protein (Cdc42/Rac)-activated kinase 4 (PAK4) and nicotinamide phosphoribosyltransferase /PBEF/visfatin (NAMPT). NAMPT is the rate-limiting enzyme in the metabolic scavenging pathway that utilizes nicotinamide to replenish nicotinamide adenine dinucleotide (NAD), an essential metabolic cofactor and second messenger. Recent investigations have shown that in in vitro and in vivo models, NAMPT is uniquely essential for relapsed or refractory AML stem cells. Targeting relapsed AML stem cells, through targeting of NAMPT, may allow for a promising therapeutic opportunity for patients with relapsed or refractory AML.

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Methodology:

This is a first-in-disease, single-center, open-label dose-finding clinical study to determine safety and tolerability of KPT-9274, a dual inhibitor of PAK4 and NAMPT, in patients with relapsed or refractory acute myeloid leukemia (AML).

In the first-in-human solid tumor Phase 1 study, patients received oral KPT-9274 three times a week every other day (Days 1, 3, 5, 8, 10, 12, 15, 17, 19, 22, 24, and 26) during each 28-day cycle. A starting dose of 10 mg KPT-9274 was selected and escalated to 40 mg. The MTD was not reached, and there was only one DLT in a patient who received KPT-9274 (anemia).

Based on this experience, in the current study patients will receive oral KPT-9274 three times a week every other day (Days 1, 3, 5, 8, 10, 12, 15, 17, 19, 22, 24, and 26) during each 28-day cycle, and the first dose cohort will use 30 mg. Subsequent dose escalation cohorts, as well as a de-escalation cohort, will be administered per the table below. Dose escalation/de-escalation will continue until the MTD is determined. The MTD is defined as the highest dose at which ≤1 patient experiences a DLT in Cycle 1. A RP2D equal to or less than the MTD will be declared and used for the Dose Expansion Phase, if conducted.

Patients must complete a minimum of 1 cycle of treatment, defined as receiving ≥ 75% of KPT-9274 doses during Cycle 1 (e.g., ≥ 9 of 12 doses in the 3 doses/week schedule), or have a DLT within the first cycle of treatment to be evaluable for dose escalation decisions. The cycle length is 28 days; the DLT period is the first 28 days. Dose escalation decisions will occur when a cohort of patients has met these criteria.

KPT-9274 Dose Escalation Levels

Cohort	KPT-9274
	Days 1, 3, 5, 8, 10, 12, 15, 17, 19, 22, 24, 26 in a 28-day cycle
0 (de-escalation, if needed)	20 mg
1 (starting cohort)	30 mg
2	40 mg
3	60 mg
4	80 mg
5	100 mg

**after the MTD has been established, subjects at lower dose cohorts may have the option to change dose to the MTD, per investigator discretion*

Three patients will be enrolled in each cohort; if 1 of the first 3 patients in a cohort experiences a DLT, the number of patients in that cohort will be expanded to 6 patients. A maximum of 6 patients will be enrolled per cohort. The MTD is defined as the highest dose at which ≤1 patient out of a maximum potential cohort of 6 experiences a DLT.

A DLT will be defined as an AE or abnormal laboratory value that occurs within the first 28 days of treatment with KPT-9274, except for those that are clearly and incontrovertibly due to underlying disease, disease progression, or extraneous causes, and meets any of the criteria for defining dose-limiting toxicities as described in the table below. CTCAE, Version 5.0 will be used for grading. In addition, > 3 missed (consecutive or nonconsecutive) doses of KPT-9274 in the first 28 days due to a drug related toxicity will be considered a DLT.

Other events may occur which do not meet the definition of a DLT but are of concern to the Investigators may be considered DLTs.

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Criteria for Defining Dose-Limiting Toxicities

Toxicity	**Any of the following criteria (based on CTCAE [Version 5.0]) , with the exception of events that are clearly and incontrovertibly due to underlying disease, disease progression or extraneous causes:**
Non-Hematologic	Grade 3 AST (SGOT) or ALT (SGPT) for ≥7 days or grade 3 direct hyperbilirubinemia for >7 days
	Grade 2 AST (SGOT) or ALT (SGPT) accompanied by grade 2 direct hyperbilirubinemia
	All other clinically significant non-hematological ≥ grade 3 AEs with the following exceptions: • Grade 3 nausea, vomiting or diarrhea will be considered DLT only if not controlled with optimal therapy after 72 hours; however, if these AEs require hospitalization, total parenteral nutrition or tube feeding, they will be considered DLTs regardless of the time required for recovery. • ≥ Grade 4 nausea, vomiting or diarrhea will be considered a DLT regardless of duration. • < Grade 4 neutropenic fever • Grade 3 biochemical or electrolyte abnormalities may be considered exceptions to the DLT criteria only if they have no clinical consequences and resolve with appropriate management within 72 hours
	Any grade AE that is related to KPT-9274 that results in permanent discontinuation of therapy
	Any death related to KPT-9274
Hematologic	≥Grade 3 anemia, neutropenia and/or thrombocytopenia lasting for ≥28 days from cycle 1 day 1 in the absence of residual AML (<5% blasts by morphology or detectable disease by immunohistochemistry and/or flow cytometry or other methods)
CTCAE Version 5.0 will be used for grading AEs and laboratory abnormalities. Patients may receive supportive care as per local institutional guidelines.	

DOSE EXPANSION PHASE

After completion of the Dose Escalation, Dose Expansion in up to 10 additional patients may be conducted to further explore safety, tolerability and preliminary evidence of anti-tumor activity of the RP2D of KPT-9274.

After the MTD has been established, subjects at lower dose cohorts may have the option to change dose to the MTD, per investigator discretion.

Number of Patients (planned):

As many as 40 patients may be enrolled, a maximum of 30 in the dose escalation and 10 in the expansion. However, the number of patients required for completion of study enrollment cannot be defined *a priori* since this depends on the MTD.

Investigational product, dosage and mode of administration:

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KPT-9274 is an orally bioavailable small molecule and a tablet solid dosage form for oral administration is being used for clinical studies.

KPT-9274 tablets are designed for immediate-release oral administration and will be supplied in high-density polyethylene (HDPE) bottles with induction seals. KPT-9274 tablets will be film coated for ease of handling and provided in tablet strengths of 5 mg and 20 mg. KPT-9274 will be supplied by Karyopharm. Additional details on KPT-9274 are provided in the Investigator's Brochure. The investigational treatments will be administered as a flat dose and not by body weight or body surface area.

Permitted Concomitant Medications:

No significant inhibition of any of the CYP450 enzymes were observed after KPT-9274 treatment. Weak induction of CYPs 1A2, 2B6, and 3A4 were observed in an exploratory pre-clinical study after KPT-9274 treatment. There were no drug-drug interactions (DDIs) noted in the first 50 patients treated in Parts A and B. Therefore, the use of any concomitant medication/therapy (except for the medications listed in the prohibited concomitant medication section), including over-the-counter (OTC) medications (excluding herbal supplements, dietary supplements), deemed necessary for the care of the patient is permitted during the study. Medications required to treat AEs, manage cancer symptoms, concurrent stable diseases and supportive care agents (e.g., blood product transfusions, antibiotics with [if appropriate] granulocyte-colony stimulating factors [G-CSF] for neutropenic infection), pain medications, anti-emetics, and anti-diarrheals are allowed. Concurrent therapy with growth factors is allowed.

Hormonal contraceptives are permitted in women of child-bearing potential. Hormonal contraceptives include any marketed contraceptive agent that includes an estrogen and/or a progestational agent.

Supportive Care:

Supportive care including anti-nausea/anti-emetic therapy, acid suppression (e.g., proton pump inhibitors [PPIs] ± H2-blockers), anti-diarrheal therapy, and other standard treatments may be administered as per institutional guidelines for symptomatic patients. For additional options, see NCCN Supportive Care Clinical Practice Guidelines in Oncology.

Prohibited Concomitant Medications:

The use of niacin or niacin-containing supplements (e.g., multivitamins and energy drinks) is not allowed. Investigational or commercial anticancer agents other than KPT-9274 are not allowed during the study.

Treatment Duration:

Treatment cycles are 28 days long. A patient may continue to receive KPT-9274 until the patient experiences progressive disease, withdraws consent or decides to withdraw from further treatment, is lost to follow-up, experiences intolerable toxicity which precludes further treatment with KPT-9274, or treatment is discontinued at the discretion of the Investigator.

Criteria for Evaluation:

Safety Endpoints:

The safety and tolerability of KPT-9274 will be evaluated by means of DLTs, AE reports, physical examination results, electrocardiogram results and laboratory safety evaluations. The National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0, will be used for grading of AEs.

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A DLT is defined as a pre-specified AE or abnormal laboratory value that occurs within the first 28 days of treatment with KPT-9274, except for those that are clearly and incontrovertibly due to underlying disease, disease progression, or extraneous causes, and meets any of the criteria for defining dose-limiting toxicities.

Efficacy Endpoints:

Efficacy is an endpoint of the dose expansion portion of the study, if conducted. Bone marrow biopsies will occur for efficacy assessment purposes at the conclusion of each cycle until the subject has achieved a MLFS, CRi or CR, or per investigator discretion. Efficacy will be assessed per the European Leukemia Network guidelines[1].

- **Overall response rate (ORR):** complete remission (CR), complete remission with incomplete hematologic recovery (CRi), morphologic leukemia-free state (MLFS), partial remission (PR).
- **Duration of response (DOR):** the duration of time from first meeting CR, PR, MLFS, CRi, measurement criteria (whichever occurs first) until the first date that progressive disease (PD) is objectively documented.
- **Progression-free survival (PFS):** the duration of time from date of first study treatment until the first date that disease progression is objectively documented or death due to any cause.
- **Overall survival (OS):** the duration of time from date of first study treatment until death from any cause.

Statistical Methods:

Sample size justification

The sample size for the Dose Escalation Phase is based on a standard 3+3 design for the purpose of determining the RP2D and MTD. For the Dose Expansion Phase, up to 10 additional patients may be enrolled at the RP2D for KPT-9274.

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Table 1 Schedule of Assessments: Screening and Cycle 1

	Screening		Cycle 1									
			Week 1			Week 2		Week 3		Week 4		
	Day -30 to Day -1	**Day -14 to Day -1**	**Day 1**	**Day 2**	**Dosing Days 3 & 5**	**Day 8**	**Dosing Days 10 & 12**	**Day 15**	**Dosing Days 17 & 19**	**Day 22**	**Dosing Days 24 & 26**	**Day 28**
Window for Assessments (days)	-	-	+/- 1		-	+/- 1	-	+/- 1	-	+/- 1		+/- 3
Visit Type	Clinic	Clinic	Clinic			Clinic		Clinic		Clinic		Clinic
Activity/Assessment												
Informed consent[1]	X											
Inclusion/exclusion criteria	X											
Patient History												
Demographics	X											
Medical history[2]	X											
Clinical Assessments												
Patient height	X											
Patient weight	X		X									
Vital Signs (BP, pulse, temp)[3]	X		X			X		X		X		
Complete physical exam	X											
Symptom-directed physical exam			X			X		X		X		
12-lead ECG[4]	X[4]		X[4]									
ECOG[6]	X		X									
TLS Monitoring[10]			X	X								
Clinical Labs												
CBC with differential[6]		X	X			X		X		X		
Complete metabolic panel [5,6]		X	X			X		X		X		
Serum hCG pregnancy test[7]		X										
Bone marrow aspirate and biopsy[8,9]	X					X						X
Dosing of KPT 9274			X		X	X	X	X	X	X	X	
Serious Adverse Events	Continuous *(during screening, only SAEs related to study procedures)*											
Adverse Events			Continuous									
Concomitant Medications	Continuous											

Abbreviations: AE = adverse event; CBC = complete blood count; D = Day; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EoT = End of Treatment

Historical records related to screening procedures are permitted per Investigator discretion. Sites should adhere to the 28-day cycle.

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[1] Prior to any study-specific measure.

[2] A complete medical history will be obtained from each patient. Medical history will include baseline symptoms of the disease under study as well as a detailed history of prior therapies for the patient's AML.

[3] Vital signs: blood pressure, pulse and body temperature; see Section 6.4.1.2 for a detailed description of vital sign assessments.

[4] 12-Lead ECG to be completed at Screening (Day -30 to Day -1) and C1D1 (pre-dose and 4 hours post-dose (+/- 30 minutes)).

[5] Complete metabolic panel (CMP) consists of sodium, potassium, chloride, carbon dioxide, glucose, blood urea nitrogen, creatinine, magnesium, phosphorous, uric acid, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, bilirubin, protein, albumin and lactate dehydrogenase

[6] The following procedures must be performed at Screening and pre-dose on C1D1 (and as shown in Table 1, 2, and 3): ECOG performance assessment (Day -30 to Day -1), CBC with differential (Day -14 to Day -1), Complete Metabolic Panel (Day -14 to Day -1).

[7] For females of childbearing potential, negative serum hCG pregnancy test must be performed ≤ 3 days of C1D1 and the EoT Visit. Repeat testing during the study as clinically appropriate.

[8] Bone marrow biopsies and aspirates will be taken within 30 days prior to first dose (baseline).

[9] BM - day 28 +/- 3 days; at conclusion of each cycle until the subject has achieved a MLFS, CRi or CR, or per investigator discretion

[10] TLS Monitoring is defined as "Tumor lysis syndrome monitoring," and occurs on day 1, 8 hours (+/- 2 hours) after the first dose, and on day 2, 24 hours (+/- 4 hours) after the first dose. Labs include potassium, uric acid, phosphorus, calcium, and serum creatinine. TLS labs must be collected at CU Anschutz.

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Table 2 Schedule of Assessments: Cycles 2 and Beyond

	Cycle 2					Cycle 3 and Beyond				
	Week 1-2		Week 3-4			Week 1-2		Week 3-4		
	Day 1	**Dosing Days 3,5,8,10,12**	**Day 15**	**Dosing Days 17,19,22, 24,26**	**Day 28**	**Day 1**	**Dosing Days 3,5,8,10,12**	**Day 15**	**Dosing Days 17,19,22, 24,26**	**Day 28**
Window for Assessments (days)	+/- 1		+/- 1		+/- 3	+/- 1				+/- 3
Visit Type	Clinic		Clinic		Clinic	Clinic				Clinic
Activity/Assessment										
Clinical Assessments										
Patient weight	X		X			X				
Vital Signs (BP, pulse, temp)[1]	X		X			X				
Symptom-directed physical exam	X		X			X				
ECOG	X					X				
Clinical Labs										
CBC with differential	X		X			X				
Complete metabolic panel [2]	X		X			X				
Bone marrow biopsy					X[3]					X[3]
Dosing of KPT 9274 at Home		X		X			X	X	X	
Adverse events	Continuous					Continuous				
Concomitant medications	Continuous					Continuous				

Abbreviations: AE = adverse event; CBC = complete blood count; D = Day; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EoT = End of Treatment

Sites should adhere to the 28-day cycle.

[1] Vital signs: blood pressure, pulse and body temperature; see Section 6.4.1.2 for a detailed description of vital sign assessments.

[2] Complete metabolic panel (CMP) equals: sodium, potassium, chloride, carbon dioxide, glucose, blood urea nitrogen, creatinine, magnesium, phosphorous, uric acid, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, bilirubin, protein, albumin and lactate dehydrogenase

[3] BM - day 28 +/- 3 days; conclusion of each cycle until the subject has achieved a MLFS, CRi or CR, or per investigator discretion

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Table 3 Schedule of Assessments: End-of-Treatment and Beyond

Activity/Assessment	End-of-Treatment (EoT) Visit ≤ 14 Days Post Last Dose	Safety Follow-up[3] 30 Days Post-Last Dose + 7 days	Durability of Response and Survival Follow-up Every 3 months for 1 year after the safety follow-up call ± 7 days
Clinical Assessments			
Patient weight	X		
Vital Signs (BP, pulse, temp)[1]	X		
Complete physical exam	X		
ECOG	X		
Bone marrow biopsy, if not performed <30 days prior to EoT	X		
Clinical Labs			
CBC with differential	X		
Complete metabolic panel[2]	X		
Serum hCG pregnancy test	X		
Adverse events	X	X	
Concomitant medications	X	X	
Survival and Response Status			X

Abbreviations: AE = adverse event; CBC = complete blood count; D = Day; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EoT = End of Treatment

Sites should adhere to the 28-day cycle.

1 Vital signs: blood pressure, pulse and body temperature; see Section 6.4.1.2 for a detailed description of vital sign assessments.

2 Complete metabolic panel (CMP) equals: sodium, potassium, chloride, carbon dioxide, glucose, blood urea nitrogen, creatinine, magnesium, phosphorous, uric acid, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, bilirubin, protein, albumin and lactate dehydrogenase

3 Safety follow-up with patient after 30 days post-last dose (+ 7 days) of their last dose of study treatment to record concomitant medications, AEs, including follow-up on any AEs that were not resolved at the EoT Visit, and collection of information on any antineoplastic therapies used after discontinuation of study treatment. This safety follow may occur via phone or in-person, by delegated staff.

Table 4 Dosing Schedule of KPT-9274

KPT-9274	Week 1							Week 2							Week 3							Week 4						
	D1	D2	D3	D4	D5	D6	D7	D8	D9	D10	D11	D12	D13	D14	D15	D16	D17	D18	D19	D20	D21	D22	D23	D24	D25	D26	D27	D28
	X		X		X			X		X		X			X		X		X			X		X		X		

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LIST OF TABLES

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms are used in this study protocol.

Abbreviation or Specialist Term	Explanation
°C	degrees Celsius
°F	degrees Fahrenheit
AE	adverse event
ALT	alanine aminotransferase
AML	acute myeloid leukemia
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AUC	area under the curve
B-ALL	B-cell acute lymphoblastic leukemia
BP	blood pressure
BSA	body surface area
CBC	complete blood count
CBR	clinical benefit rate
CI	confidence interval
CL/F	plasma clearance rate
C_{max}	maximum plasma concentration
cm	centimeter
CNS	central nervous system
COX-2	cyclooxygenase-2
CR	complete response
CrCl	creatinine clearance
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CXDX (e.g., C1D1)	Cycle X Day X (e.g., Cycle 1 Day 1)
DAP	Data Analysis Plan
DCR	disease control rate
DDA	deoxyribonucleic acid damaging agent
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
DOR	duration of response
DSMB	Data Safety Monitoring Board
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EORTC QLQ	European Organization for Research and Treatment of Cancer
EoT	end of treatment
ER	extended release
FACT-G	Functional Assessment of Cancer Therapy
FACT-Lym	Functional Assessment of Cancer Therapy-Lymphoma
FDA	Food and Drug Administration
FISH	fluorescence in situ hybridization

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Abbreviation or Specialist Term	Explanation
FLC	free light chain
GCP	Good Clinical Practice
G-CSF	granulocyte-colony stimulating factor
GI	gastrointestinal
GLP	Good Laboratory Practice
GM-CSF	granulocyte macrophage-colony stimulating factor
HAT	hormone ablation therapy
Hb	hemoglobin
HBsAg	hepatitis B virus surface antigen
HBV	hepatitis B virus
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
HDPE	high-density polyethylene
HIV	human immunodeficiency virus
HNSTD	highest non-severely toxic dose
HPLC/MS-MS	high performance liquid chromatography/tandem mass
hr	hour
IB	Investigator's Brochure
IC_{50}	50% inhibitory concentration
ICF	informed consent form
ICH	International Conference on Harmonization
IDH1	isocitrate dehydrogenase 1 (NADP+), soluble
IHC	immunohistochemistry
INR	International normalized ratio
IRB	Institutional Review Board
ITT	intent-to-treat
IV	intravenous
Karyopharm	Karyopharm Therapeutics Inc.
kg	kilogram
LLN	lower limit of normal
LVEF	left ventricular ejection fraction
MDR	multiple drug resistance
mIU	milli-international units
mL	milliliter
MM	multiple myeloma
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
MTD	maximum tolerated dose
MUGA	multiple gated acquisition
N	number of patients
NAD	nicotinamide adenine dinucleotide
NAMPT	nicotinamide phosphoribosyltransferase/PBEF/visfatin
NAPRT1	nicotinate phosphoribosyltransferase
NCI	National Cancer Institute

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Abbreviation or Specialist Term	Explanation
NHL	non-Hodgkin's lymphoma
Niacin	vitamin B3/nicotinic acid
NSAID	non-steroidal anti-inflammatory drug
ORR	overall response rate
OS	overall survival
OTC	over the counter
PAK4	p21 protein (Cdc42/Rac)-activated kinase 4
PCR	polymerase chain reaction
PD	progressive disease
PDn	pharmacodynamic(s)
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetic(s)
PP	per protocol
PPI	proton pump inhibitor
PR	partial response
QMSP	quantitative methylation specific
QOD	every other day
QoL	quality of life
qRT	quantitative real time
RAS	rat sarcoma viral oncogene homolog
RBC	red blood cell
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	ribonucleic acid
RP2D	Recommended Phase 2 Dose
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	stable disease
SUSAR	suspected unexpected serious adverse reaction
$t_{½}$	terminal plasma half-life
TEAE	treatment-emergent adverse event
t_{max}	time to peak plasma concentration
TLS	tumor lysis syndrome
TNM	tumor nodes metastasis
TOI	trial outcomes index
TSH	thyroid stimulating hormone
TTP	time to progression
ULN	upper limit of normal
V_d/F	volume of distribution
WBC	white blood cell

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1. INTRODUCTION

1.1. Indication

This study will enroll patients with relapsed or refractory acute myeloid leukemia (AML) for whom all standard therapeutic options considered useful by the investigator have been exhausted.

1.2. KPT-9274

KPT-9274 is a first-in-class orally bioavailable small molecule that is a non-competitive dual modulator of p21 protein (Cdc42/Rac)-activated kinase 4 (PAK4) and nicotinamide phosphoribosyltransferase/PBEF/visfatin (NAMPT). Co-inhibition of these targets leads to synergistic anti-tumor effects through energy depletion, inhibition of deoxyribonucleic acid (DNA) repair, cell cycle arrest, inhibition of proliferation, and ultimately apoptosis. Normal cells are more resistant to inhibition by KPT-9274 due in part to their relative genomic stability and lower metabolic rates.

KPT-9274 demonstrated potent anti-proliferative activity against cancer cell lines (solid tumor cells MTT median IC_{50}: 135 nM, range 0.007 to >10 μM; hematological cancer cells MTT median IC_{50}: 40 nM, range 0.003 to >10 μM) with minimal toxicity to normal cells (median MTT IC_{50}: ~0.9 μM, range 0.033 to >10 μM). In mouse xenograft studies, KPT-9274 (oral 50-200 mg/kg twice daily for 5 days/week) was well tolerated and resulted in a marked reduction in tumor size across a variety of tumors, including colon, pancreatic, lung, multiple myeloma, leukemia, and lymphoma. In approximately half of the tumor types studied, complete elimination of tumors in as short as 3 weeks was observed with no regrowth after cessation of treatment (up to 3 weeks). In other cell types tumor growth inhibition was observed. KPT-9274 was able to control systemic acute B lymphoblastic leukemia (B-ALL) and acute myeloid leukemia (AML) tumor growth and significantly extended overall survival. Moreover, KPT-9274 has shown preliminary efficacy in companion dogs with spontaneous advanced lymphomas and multiple myeloma (MM).

Unlike the Pan-PAK inhibitor (PF-3758309), or the NAMPT inhibitors (APO866 and GMX1777/GMX1778) that advanced to human clinical trials, the dual NAMPT/PAK inhibitor KPT-9274 demonstrates consistent pharmacokinetic (PK) properties (e.g., oral absorption), exhibits minimal brain penetration, and does not inhibit any of the cytochrome P450 (CYP450) enzymes. The nonclinical toxicity profile of KPT-9274 recapitulates the expected class level gastrointestinal (GI) and hematopoietic toxicities but not the retinal and cardiac effects observed preclinically with some NAMPT inhibitors. The lack of retinal and cardiac effects of KPT-9274 may be attributed to its minimal permeability and decreased potency compared to other NAMPT inhibitors. Furthermore, no orally available PAK4 selective inhibitors have been developed to date. Thus, KPT-9274 captures many of the favorable therapeutic aspects of targeting both NAMPT and PAK4 with the potential for reduced adverse effects.

Preliminary two-week non-good laboratory practices (GLP) toxicology studies in rats and dogs suggest that KPT-9274 has an acceptable tolerability profile. The dog has been identified as the most sensitive species for KPT-9274 GI toxicity, with rats also showing GI toxicity at significantly higher doses. The primary KPT-9274 toxicity that has been observed in dogs is gastrointestinal hemorrhages in the small intestine, colon, and rectum. Other target organ effects include hypocellularity in the bone marrow and lymphoid depletion in the lymphoid tissues.

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Nicotinamide adenine dinucleotide (NAD) regeneration pathways can bypass NAMPT inhibition by utilizing niacin (vitamin B3/nicotinic acid) through nicotinate phosphoribosyltransferase (NAPRT1). Supplemented niacin can alleviate adverse events due to NAMPT inhibition when tissues express NAPRT1. However, NAPRT1 is frequently repressed in tumors (through epigenetic modulation or isocitrate dehydrogenase 1 (NADP+), soluble [IDH1] mutation) while remaining intact in surrounding normal tissue potentially increasing therapeutic index in the presence of niacin. Additional exploratory studies and data from 4-week GLP studies indicate that co-administration of niacin can increase tolerability of KPT-9274 in dogs. These data demonstrate that a dose of KPT-9274 previously shown to have an adverse toxicologic profile was tolerable and had minimal GI macroscopic findings. For this reason, co-administration of KPT-9274 with niacin in patients with or without NAPRT1 or IDH1 mutation in their tumors is planned.

KPT-9274 demonstrated anti-tumor activity in dogs with spontaneous advanced lymphomas and multiple myeloma. Patient dog #1 was given 4 doses of 2 mg/kg KPT-9274 and had progressive disease after 1 week. This patient dog was given 25 mg/kg doxorubicin (Adriamycin) on Day 8 (~24 hours post-final KPT-9274 dose). The bulk disease responded shortly thereafter with a partial response (PR) at the end of week 2 that transitioned into a complete response (CR). As of October 2015, the patient dog remains in complete remission for >4 months off all therapy with no AEs reported to date. A T-cell lymphoma dog experienced a ~1 week PR at 2 mg/kg of KPT-9274 every other day (QOD) × 3 but subsequently progressed. A patient dog with refractory multiple myeloma (4 lines of previous therapy) treated with 3 mg/kg of KPT-9274 QOD x 3 plus prednisone had a PR with decreases in globulins and resolution of anemia and thrombocytopenia for ~5 weeks, but progressed during Week 6. Two additional B-cell lymphoma dogs did not respond to 2 mg/kg or 3 mg/kg of KPT-9274 QOD × 3 in which one dog (2 mg/kg dose) had low drug levels in the plasma. These preliminary results suggest that KPT-9274 show anti-tumor activity both as a single agent and in combination with DNA damaging agents (DDA) with minimal or no side effects observed. Dose escalation evaluation in patient dogs with lymphoma and solid tumors is on-going.

KPT-9274 has clear preclinical anti-tumor activity (*in vitro* and *in vivo*) as well as an encouraging safety profile (compared to previously described Pan-PAK and NAMPT inhibitors) making it an attractive novel drug candidate. Since both solid tumor and hematologic malignancies were seen to be susceptible to single-agent cytotoxicity with KPT-9274, development is planned in both areas.

1.2.1. Potential Risks

In the completed study, KCP-9274-901, 50 patients had received KPT-9274 alone or with niacin ER, and an additional 10 patients received KPT-9274 in combination with nivolumab. The most common AEs occurring across all patients include the following: anemia (81.7%, 49/60), fatigue (45.0%, 27/60), arthralgia (40.0%, 24/60), nausea (40%, 24/60), dyspnea (33.3%, 20/60), diarrhea (31.7%, 19/60), vomiting (26.7%, 16/60), myalgia (23.3%, 14/60), decreased appetite (21.7%, 13/60), flushing (21.7%, 13/60), and abdominal pain (20.0%, 12/60). The following events were identified as potential risks of KPT-9274: anemia, fatigue, arthralgia and myalgia, and nausea. . AEs were largely dose dependent and increased with higher doses of KPT-9274. A total of 3 DLTs were reported during the study, one at the 40 mg QODx3 dose and two at the 80 mg + niacin

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QODx3 dose. Maximum tolerable dose was not reached in either Part A (KPT-9274 monotherapy) or B (KPT-9274 with niacin ER).

1.2.2. Reproductive Risks of KPT-9274

It is unknown whether KPT-9274 might have reproductive toxicity in humans; therefore, all patients in this study must agree to use effective contraception (see Prevention of Pregnancy, Section 5.7.2.2) during the study, and for 3 months after their last dose of KPT-9274.

1.3. Study Rationale

KPT-9274 is a first-in-class orally bioavailable, non-competitive, small molecule, dual modulator of PAK4 and NAMPT. NAMPT is the rate-limiting enzyme in the metabolic scavenging pathway that utilizes nicotinamide to replenish nicotinamide adenine dinucleotide (NAD), an essential metabolic cofactor and second messenger.

Hematologic and solid tumor cells are susceptible to single-agent cytotoxicity by KPT-9274 as they become dependent on both the PAK4 and NAMPT pathways. KPT-9274 demonstrated potent anti-proliferative activity against cancer cell lines with minimal toxicity to normal cells. In mouse xenograft studies, KPT-9274 was well tolerated and resulted in a marked reduction/elimination of tumors, tumor growth inhibition or disease control across a variety of tumors, including colon, pancreatic, lung, sarcoma, multiple myeloma, leukemia, and lymphoma. In approximately half of the tumor types studied, complete elimination of tumors in as short as 3 weeks was observed with no regrowth after cessation of treatment (for up to 3 additional weeks). Moreover, KPT-9274 has shown preliminary efficacy in companion dogs with spontaneous advanced lymphomas and multiple myeloma.

In AML, pre-clinical studies have shown increased dependency of AML cells on NAMPT[2], and in the clinical setting, higher NAMPT expression is associated with decreased overall survival[3]. In an AML model, KPT-9274 depleted NAD+, resulting in loss of mitochondrial respiration and glycolysis and apoptosis, regardless of mutational/genomic profiles[4]. Furthermore, emerging data suggests that targeting NAMPT can specifically eradicate the relapsed/refractory leukemia stem cell population, which has previously not had any promising therapeutic opportunities (Jones et al, Cell Stem Cell 2020 Nov 5;27(5):748-764).

1.3.1. Rationale for the Starting KPT-9274 Dose

In the first-in-human solid tumor Phase 1 study, patients received oral KPT-9274 three times a week every other day (Days 1, 3, 5, 8, 10, 12, 15, 17, 19, 22, 24, and 26) during each 28-day cycle. A starting dose of 10 mg KPT-9274 was selected and escalated to 40 mg. The study was stopped but the MTD was not reached, and there was only one DLT in a patient who received KPT-9274 alone (anemia). Based on this experience, in the current study patients will receive oral KPT-9274 three times a week every other day (Days 1, 3, 5, 8, 10, 12, 15, 17, 19, 22, 24, and 26) during each 28-day cycle, and the first dose cohort will be 30 mg.

1.4. Objectives

1.4.1. Primary Objective

- To assess the maximum tolerated dose (MTD)

1.4.2. Secondary Objective

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- To establish a recommended phase 2 dose (RP2D)

Dose Expansion (if conducted)

- To determine preliminary evidence of efficacy of KPT-9274 at the RP2D

1.5. Endpoints

1.5.1. Safety Endpoints

- The occurrence of dose limiting toxicities (DLTs) and the occurrence, nature and severity of adverse events (AEs)

2.2.2. Efficacy Endpoints (if dose expansion is conducted)

- Primary Endpoint: Overall response rate (ORR)
- Secondary Endpoint: Duration of response (DOR), progression-free survival (PFS), overall survival (OS)

Disease response will be evaluated according to the European Leukemia Network (AML) (Appendix 2)[1] and will include the following:

- **Overall response rate (ORR):** complete remission (CR), complete remission with incomplete hematologic recovery (CRi), morphologic leukemia-free state (MLFS), partial remission (PR).
- **Duration of response (DOR):** the duration of time from first meeting CR, PR, MLFS, CRi, measurement criteria (whichever occurs first) until the first date that progressive disease (PD) is objectively documented.
- **Progression-free survival (PFS):** the duration of time from date of first study treatment until the first date that disease progression is objectively documented or death due to any cause.
- **Overall survival (OS):** the duration of time from date of first study treatment until death from any cause.

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2. INVESTIGATIONAL PLAN

2.1. Overall Study Design and Plan

This is a first-in-disease, single-center, open-label dose escalation clinical study to assess preliminary safety, tolerability, and efficacy of KPT-9274, a dual inhibitor of PAK4 and NAMPT, in patients with relapsed or refractory AML for whom all standard therapeutic options considered useful by the investigator have been exhausted.

During dose escalation, patients will receive oral KPT-9274 three times a week every other day (Days 1, 3, 5, 8, 10, 12, 15, 17, 19, 22, 24, and 26) during each 28-day cycle, and the first dose cohort will be 30 mg. Subsequent dose escalation cohorts, as well as a de-escalation cohort, will be administered per the table below. Dose escalation will continue until the MTD is determined. The MTD is defined as the highest dose at which ≤1 patient experiences a DLT in Cycle 1. A RP2D equal to or less than the MTD will be declared and used for the Dose Expansion Phase, if conducted.

Patients must complete a minimum of 1 cycle of treatment, defined as receiving ≥75% of KPT-9274 doses during Cycle 1 (e.g., ≥9 of 12 doses in the 3 doses/week schedule), or have a DLT within the first cycle of treatment to be evaluable for dose escalation decisions. The cycle length is 28 days the DLT period is the first 28 days of cycle 1. Dose escalation decisions will occur when a cohort of patients has met these criteria.

After the RP2D is determined, a dose expansion phase, of up to 10 additional patients, might be conducted, in which a preliminary determination of efficacy will be conducted, using the ELN criteria[1] (Appendix 2). After the RP2D has been established, subjects at lower dose Cohorts may have the option to change dose to the RP2D, per investigator discretion.

Screening will be performed within 30 or 14 days prior to the start of therapy (i.e., Day -30 to Day -1, or Day -14 to Day -1), as summarized in Table 1. The Follow-up period includes the EOT visit, the Safety Follow-up visit, and Durability of Response and Survival Follow-up; see Table 3 for assessments to be completed during the Follow-up period.

The number of patients required for completion of study enrollment cannot be defined *a priori* since this depends on the number of patients needed for the dose escalation; but the maximum number of patients from the escalation and expansion cohorts will be 40.

KPT-9274 Dose Escalation Levels

Cohort	**KPT-9274**
	Days 1, 3, 5, 8, 10, 12, 15, 17, 19, 22, 24, 26 in a 28-day cycle
0 (de-escalation, if needed)	20 mg
1 (starting cohort)	30 mg
2	40 mg
3	60 mg
4	80 mg
5	100 mg

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2.2. Replacement Policy

Patients who complete the first cycle of therapy will not be replaced during the Escalation Phase of the study. However, if a patient is considered as non-evaluable for DLT (i.e., did not complete the first cycle of therapy or the minimum number of doses of KPT-9274 and did not experience a DLT), enrollment of a new patient to the current cohort will be considered if there is less than the required number of evaluable patients.

During the Dose Expansion Phase, patients who have not completed 1 cycle will be replaced unless they were discontinued from the study due to a drug-related toxicity, PD, or death.

2.3. Treatment Duration

Treatment cycles are 28 days long. A patient may continue to receive KPT-9274 until that patient experiences PD, withdraws consent, is lost to follow-up, experiences intolerable toxicity which precludes further treatment with KPT-9274, or treatment is discontinued at the discretion of the Investigator.

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3. STUDY POPULATION SELECTION

3.1. Study Population

This study will enroll adult patients with relapsed or refractory AML for whom standard therapeutic options considered useful by the investigator have been exhausted, and meet all of the inclusion criteria and none of the exclusion criteria.

3.2. Eligibility

3.2.1. Inclusion Criteria

Patients must meet all of the following inclusion criteria to be eligible to enroll in this study.

1. Written informed consent obtained prior to any screening procedures
2. Age ≥18 years.
3. Patients with WHO-confirmed non-APL AML who have not responded to or relapsed after at least one prior therapy and for whom no standard therapy that may provide clinical benefit is available.
4. Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 2.
5. Adequate hepatic function:
    - Total bilirubin < 1.5 times the upper limit of normal (ULN) (except patients with Gilbert's syndrome [hereditary indirect hyperbilirubinemia], subjects with Gilbert's syndrome, total bilirubin needs to be ≤ 4 x ULN).
    - Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 times ULN (except patients with known liver involvement of their AML who must have AST and ALT ≤ 5.0 times ULN).
6. Adequate renal function: estimated creatinine clearance of ≥ 60 mL/min, calculated using CKD-EPI Creatinine Equation (2021). https://www.kidney.org/content/ckd-epi-creatinine-equation-2021.
7. Female patients of child-bearing potential must agree to use dual methods of contraception (including one highly effective and one effective method of contraception) and have a negative serum pregnancy test at Screening. For both male and female patients, effective methods of contraception must be used throughout the study and for 3 months following the last dose.
    a. Fertile female patients must agree to refrain from egg donation from first dose until at least 3 months following the last dose of KPT-9724.
    b. Women should not breastfeed during treatment with KPT-9724 and for 2 weeks after the last dose.
    c. Male patients must use 2 highly effective methods of contraception if sexually active with a female of child-bearing potential, during treatment with KPT-9724, during a period of 2 weeks (5 half-lives) after the last dose of KPT-9724 plus a period of 3 months. (for 3.5 months after their last dose of KPT-9724). Fertile male patients must agree to refrain from sperm donation from first dose until at least 3.5 months following the last dose of KPT-9724.

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3.2.2. Exclusion Criteria

Patients meeting any of the following exclusion criteria are not eligible to enroll in this study.

1. Female patients who are pregnant or lactating.
2. Radiation, chemotherapy, immunotherapy or any other anticancer therapy, including investigational anti-cancer therapy ≤ 2 weeks prior to C1D1. Hydroxyurea is not considered an anti-cancer therapy.
3. Patients who have not recovered or stabilized (Grade 1 or to their baseline for non-hematologic toxicities) from toxicities related to their previous treatment, except for alopecia.
4. White blood cell count $\geq 25 \times 10^9$/L (hydroxyurea or leukapheresis permitted to reduce to below the exclusion criteria threshold and allow eligibility)
5. Patients with known active central nervous system (CNS) disease
6. Clinically significant severe heart disease
7. Active clinically significant infection. Use of prophylactic antibiotics, antivirals or antifungals are permitted.
8. Known, active hepatitis A, B, or C infection; or known to be positive for HCV RNA or HBsAg (HBV surface antigen). Testing is not required.
9. Patients with significantly diseased or obstructed gastrointestinal tract or uncontrolled vomiting or diarrhea that could interfere with the absorption of KPT-9274.
10. Serious psychiatric or medical conditions that, in the opinion of the Investigator, could interfere with treatment, compliance, or the ability to give consent.

3.3. Screening and Registration

The Screening period starts once a patient has provided written informed consent to participate in the study and ends on the day of study entry (C1D1).

Patient eligibility (inclusion/exclusion criteria) will be reviewed for each patient participating in the study by the investigator before the patient receives study treatment on C1D1.

Upon signing consent, each patient will be assigned a unique patient number and will keep this number for the duration of the study.

3.3.1. Screen Failures

Patients who sign an informed consent but fail to start on treatment for any reason will be considered a screen failure. Date of consent and reason for ineligibility will be entered into the clinical database. No other data will be entered into the clinical database for patients who are screen failures, unless those patients experience serious adverse event (SAE) related to study procedures during the Screening Phase.

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4. DISCONTINUATION CRITERIA

4.1. Early Termination of the Study

This study may be discontinued at the discretion of the Sponsor for any reason. This could occur due to concerns related to safety, tolerability or efficacy of KPT-9274.

4.2. Discontinuation of Study Treatment and/or Withdrawal of Patients from the Study

The Investigator may remove a patient from study treatment for any of the following reasons:

- Unacceptable AEs or toxicity that cannot be managed by supportive care
- Any medically appropriate reason (e.g., clinical progression) or significant protocol violation, in the opinion of the Investigator

The Investigator must remove a patient from study treatment for any of the following reasons:

- Disease progression per response criteria
- Patient withdraws consent to continue study treatment
- Pregnancy

Patients who are removed from study treatment by the Investigator are not permitted to restart study treatment.

Patients may discontinue study treatment for any reason. Patients who choose to discontinue study treatment will be encouraged to continue in the study so that follow-up information on disease progression and survival status may be obtained. Patients may elect to withdraw consent and decline further participation in the study at any time.

The reason for the patient's discontinuation of study treatment/withdrawal from the study must be recorded on the eCRF.

All patients will be followed until PD, withdrawal of consent, occurrence of any withdrawal criteria, intolerable toxicity precluding further treatment with study treatment, death or lost to follow up.

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5. STUDY TREATMENTS

5.1. Treatments Administered

5.1.1. Study Treatments

KPT-9274 is an orally bioavailable small molecule prepared in a tablet solid dosage form for oral administration.

KPT-9274 tablets are designed for immediate-release oral administration and will be supplied in high-density polyethylene (HDPE) bottles with induction seals and polypropylene caps. KPT-9274 tablets will be film coated for ease of handling and provided in tablet strengths of 5 mg and 20 mg. KPT-9274 will be supplied by Karyopharm. Additional details on KPT-9274 are provided in the IB. The investigational treatments will be administered as a flat dose and not by body weight or body surface area.

5.2. Study Treatment Dose Schedules and Administration

5.2.1. Labeling

All labels will include conditions for storage, lot number, and other information required by the Food and Drug Administration (FDA), International Council for Harmonisation (ICH), and/or Annex 13, and all local regulations for investigational medications.

5.2.2. Dispensing Directions

The Investigator or responsible site personnel must instruct the patient or caregiver to take the study treatment(s) as per protocol. Study treatment(s) will be dispensed to the patient by authorized site personnel only.

5.2.3. Dosing Information

Patients will receive oral KPT-9274 three times a week every other day (Days 1, 3, 5, 8, 10, 12, 15, 17, 19, 22, 24, and 26) during each 28-day cycle.

5.2.4. Dosing Instructions for Patients

Study medications will be dosed according to the schedules provided in Table 4. Patients will be provided with a take home diary to complete; the patient diary will be reviewed prior to the next cycle.

Oral KPT-9274 should be given with food, or within 30 minutes after the patient has eaten, together with 240-355 mL (8-12 ounces) of fluids.

KPT-9274 tablets should be swallowed whole (not crushed).

5.2.5. Dose Schedules for Evaluation During the Dose Escalation Phase

The dose schedule for evaluation during the Dose Escalation Phase is presented in Table 8.

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Table 5 KPT-9274 Dose Escalation Levels

KPT-9274 Dose Escalation Levels

Cohort	KPT-9274
	Days 1, 3, 5, 8, 10, 12, 15, 17, 19, 22, 24, 26 in a 28-day cycle
0 (de-escalation, if needed)	20 mg
1 (starting cohort)	30 mg
2	40 mg
3	60 mg
4	80 mg
5	100 mg

Three patients will be enrolled in each cohort, if 1 of 3 patients in a cohort experiences a DLT, the number of patients in that cohort will be expanded to 6 patients. A maximum of 6 patients will be enrolled per cohort. The MTD is defined as the highest dose at which ≤1 patients out of a maximum potential cohort of 6 experiences a DLT.

5.2.6. Dose Escalation Guidelines

5.2.6.1. Dose Escalation Procedures

For the purposes of dose escalation decisions, a standard 3+3 dose escalation design will be used.

The initial cohort, Cohort 1, will consist of 3 enrolled patients who will be treated at 30 mg. If these patients do not experience a DLT during Cycle 1, the KPT-9274 dose will be escalated to 40 mg for another group of 3 patients (Cohort 2). If the MTD is exceeded at cohort 1, de-escalation to cohort 0 (20 mg) will occur. If the MTD is not exceeded in cohort 1, dose escalation will continue based on a standard 3+3 design at the dose levels specified in

Table 8.

A RP2D equal to or less than the MTD will be declared at the conclusion of the dose escalation, and potentially used for the Dose Expansion Phase. The RP2D will be based on an evaluation of any and all pharmacokinetic, pharmacodynamic and safety data, including an evaluation of SAEs that occur after the end of the DLT window to ensure the tolerability of the RP2D. The MTD is defined as the highest dose at which ≤ 1 patient experiences a DLT in Cycle 1.

Patients must complete a minimum of 1 cycle of treatment, defined as receiving ≥ 75% of KPT-9274 doses during Cycle 1 (e.g., ≥9 of 12 doses in the 3 doses/week schedule), or have a DLT within the first cycle of treatment to be evaluable for dose escalation decisions. Dose escalation decisions will occur when the cohort of patients has met these criteria.

Dose escalation will be conducted as follows:

- If 0 of 3 patients experiences a DLT, escalate to next higher dose cohort.

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- If 1 of 3 patients experiences a DLT, that cohort will be expanded to 6 patients. If 1 of 6 patients experiences a DLT, escalate to the next higher dose cohort;
- If ≥ 2 of 3 or ≥ 2 of 6 patients experience a DLT, MTD is exceeded. If the MTD is exceeded, the patients will be de-escalated to the next lower dose level (the MTD).

5.2.6.2. Dose-Limiting Toxicity

A DLT will be defined as an AE or abnormal laboratory value that occurs within the first 28 days of treatment with KPT-9274, except for those that are clearly and incontrovertibly due to underlying disease, disease progression, or extraneous causes, and meets any of the criteria for defining dose-limiting toxicities as described in the table below. The CTCAE, Version 5.0 will be used for grading. In addition, > 3 missed (consecutive or nonconsecutive) doses of KPT-9274 in the first 28 days due to a drug related toxicity will be considered to be a DLT.

Other events may occur which do not meet the definition of a DLT but are of concern to the Investigators may be considered to be DLTs.

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Table 6 Criteria for Defining Dose-Limiting Toxicities in AML Patients

Toxicity	**Any of the following criteria (based on CTCAE [Version 5.0]), with the exception of events that are clearly and incontrovertibly due to underlying disease, disease progression or extraneous causes:**
Non-Hematologic	Grade 3 AST (SGOT) or ALT (SGPT) for ≥7 days or grade 3 direct hyperbilirubinemia for >7 days
	Grade 2 AST (SGOT) or ALT (SGPT) accompanied by grade 2 direct hyperbilirubinemia
	All other clinically significant non-hematological ≥grade 3 AEs with the following exceptions: • Grade 3 nausea, vomiting or diarrhea will be considered DLT only if not controlled with optimal therapy after 72 hours; however, if these AEs require hospitalization, total parenteral nutrition or tube feeding, they will be considered DLTs regardless of the time required for recovery. • ≥ Grade 4 nausea, vomiting or diarrhea will be considered a DLT regardless of duration. • Grade<4 neutropenic fever • Grade 3 biochemical or electrolyte abnormalities may be considered exceptions to the DLT criteria only if they have no clinical consequences and resolve with appropriate management within 72 hours
	Any grade AE that is related to KPT-9274 that results in permanent discontinuation of therapy
	Any death related to KPT-9274
Hematologic	≥Grade 3 anemia, neutropenia and/or thrombocytopenia lasting for ≥28 days from cycle 1 day 1 in the absence of residual AML (<5% blasts by morphology or detectable disease by immunohistochemistry and/or flow cytometry or other methods)
CTCAE Version 5.0 will be used for grading AEs and laboratory abnormalities. Patients may receive supportive care as per local institutional guidelines.	

5.2.7. Dose Schedule for Evaluation During the Dose Expansion Phase

After completion of the Dose Escalation, Dose Expansion in up to 10 additional patients who meet the inclusion/exclusion criteria may be conducted to further explore safety, tolerability and preliminary evidence of anti-tumor activity of the RP2D of KPT-9274.

5.2.8. KPT-9274 Dose Reduction Guidelines for Toxicity

Prior to achieving a morphologic remission, KPT-9274 will not be held for any toxicities that are not attributable to KPT-9274.

After patients have achieved a morphologic remission, dose adjustments of KPT-9274 are permitted for those who do not tolerate the protocol-specified dosing schedule. The criteria for dose modifications of KPT-9274 for toxicities are outlined in Table 10.

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If, after the DLT period, interruption of treatment is required and this results in the resolution of the event, treatment will be resumed at the same dose. If after re-introduction the same toxicity reoccurs with the same severity, treatment re-initiation can resume at 25% of the current dose if the AE recovers to ≤grade 1 or baseline within 28 days. Patients who do not recover (i.e., ≤ Grade 1 or baseline) within 28 days of discontinuation of study treatment will not be permitted to re-start study treatment and will be discontinued from the study.

In the event of a DLT (Cycle 1) during the Dose Escalation Phase the patient must discontinue KPT-9274.

In the event of any other possibly related, likely related or related toxicity (≥ Grade 3) during the Dose Escalation Phase after a patient has achieved a morphologic remission, one of the following actions may be taken at the Investigator's discretion:

- Patients can continue treatment with KPT-9274 without a dose delay or reduction.
- If the decision is made to hold KPT-9274:
    - Patients may be re-started on KPT-9274 either at the original dose OR at 25% of the dose upon recovery to Grade ≤ 1 or baseline (see Table 9 for pre-specified dose modifications for AEs and Table 10 for dose modification guidelines for KPT-9274).

5.2.8.1. Conditions Not Requiring KPT-9274 Dose Reduction

The following conditions are exceptions to the dose-modification guidelines. KPT-9274 does not need to be held in the following cases:

- Alopecia of any grade
- Electrolyte or serum analyte (e.g., urate) abnormalities that are reversible with standard interventions
- Anemia

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Table 7 KPT-9274 Dose Modification and Supportive Care Guidelines

Toxicity and Intensity	Dose Modification
Non-hematologic Toxicity	
Grade 1	Maintain dose. Consider instituting supportive care medications per institutional guidelines.
Grade 2	Institute supportive care medications per institutional guidelines. If modifications are desired, guidelines for AEs ≥ Grade 3 should be followed. At the Investigator's discretion, patients may continue on KPT-9274 uninterrupted at their current dose.
≥ Grade 3	Optimal supportive care medications according to institutional guidelines should be instituted. Hold KPT-9274 until the event resolves to ≤ Grade1 or baseline (as appropriate): • First occurrence of ≥ Grade 3: o If supportive care results in the AE improving to Grade ≤1 or baseline within 3 days, restart KPT-9274 at the current dose. o If the improvement to Grade ≤1 or baseline takes longer than 3 days, KPT-9274 should be resumed at 25% of the dose. • Second or greater occurrence of ≥ Grade 3, restart KPT-9274 at 50% of the dose upon improvement to Grade ≤ 1 or baseline irrespective of duration. **If the toxicity does not resolve to ≤ Grade 1 or baseline within 28 days, study treatment will be discontinued permanently.
Hematological Toxicity for AML Patients	
AML patients typically have abnormal peripheral blood counts at diagnosis; myelosuppression is an expected event during the course of any therapy. Therefore, no dose adjustments or treatment interruption for hematological toxicity will occur during the first cycle or at any cycle in the presence of residual AML. Dose adjustments and/or treatment interruptions for hematological toxicity will be considered after the first cycle, in the absence of residual disease, according to the following guidelines: • Patients in morphological remission (<5% blasts in the bone marrow by morphology, immunohistochemistry or flow cytometry) with pre-cycle ANC>1x10^9/L, platelets >50x10^9/L and hemoglobin ≥9.0 g/dL who have sustained neutropenia (ANC <0.5x10^9/L), anemia hemoglobin ≤7.0 g/dL) or thrombocytopenia (platelets <20 x10^9/L) for more than two consecutive weeks in the current cycle may hold KPT-9274, with growth factors per institutional policies, until the ANC recovers to ≥1 x10^9/L, hemoglobin recovers to ≥9.0 g/dL and platelets recover to ≥50 x10^9/L. • Patients in morphological remission (<5% blasts in the bone marrow by morphology, and no detectable disease by immunohistochemistry and/or flow cytometry or other methods) with pre-cycle ANC<1x10^9/L, hemoglobin ≤7.0 g/dL and platelets <50x10^9/L may continue KPT-9274 regardless of neutrophil, red blood cell or platelet count, with supportive care as needed. • Patients with active or residual disease (>5% blasts in the bone marrow by morphology, immunohistochemistry and/or flow cytometry or other methods) may continue treatment regardless of neutrophil, red blood cell or platelet counts with supportive care as needed.	

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5.2.9. Missed or Vomited Doses

5.2.9.1. Missed Doses of Study Treatments

If a dose must be skipped (e.g., due to recommendation of Investigator), the next dose will be taken as per schedule; all missed doses should be documented.

5.2.9.2. Vomited Doses of Study Treatments

If a dose is vomited within 1 hour of ingestion, it will be replaced. If vomiting occurs more than 1 hour after dosing, it will be considered a complete dose.

5.3. Study Treatment Storage

Study treatments must be received by designated personnel at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designated site personnel have access. Upon receipt, KPT-9274 should be stored according to the instructions specified on the drug labels and in the IB for KPT-9274.

Reference the Pharmacy Manual: KPT-9274 Investigator Sponsored Trials for more information.

5.4. Study Treatment Accountability

The Investigator or designee must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Study treatment accountability will be noted by the clinical research monitor during site visits and at the completion of the study. Patients will be asked to return all unused study treatment and packaging on a regular basis, at the end of the study or at the time of study treatment discontinuation.

KPT-9274 should not be used for any purpose outside the scope of this protocol, nor may KPT-9274 be transferred or licensed to any party not participating in the clinical study.

5.5. Selection and Timing of Dose for Each Patient

The rationale for the dose to be used is provided in Section 1.3.1. Guidelines for modifying the dose of KPT-9274, if needed due to AEs, are given in Table 10.

5.6. Compliance

The Investigator or other study staff will instruct the patient on study medication self-administration, as appropriate. Patients will be provided with a take home diary to complete; the patient diary will be reviewed prior to the next cycle.

Patients will be asked to bring their study medication containers with them at the conclusion of each cycle and compliance with protocol-defined study treatment intake will be checked by tablet count.

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Compliance to study medication will be assessed by the clinical trials team at the completion of each cycle and recorded in source documents after discussion with the patient and performing drug accountability. Dates will be recorded as per study treatment schedule. The Investigational Pharmacy will account for the number of tablets dispensed against those returned by the patient. Any dosing deviations and missed doses will be recorded in the eCRF.

5.7. Supportive Care, Contraception Requirements, and Concomitant Medications

5.7.1. Supportive Care

Patients are expected to be aggressively treated to minimize the likelihood and/or severity of side effects at the discretion of the Investigator, including hematologic and musculoskeletal (arthralgias and myalgias) symptoms.

Supportive care including anti-nausea/anti-emetic therapy, acid suppression (e.g., PPIs ± H2 blockers), anti-diarrheal therapy, and other standard treatments may be administered as per institutional guidelines for symptomatic patients. For additional options, please see NCCN Supportive Care Clinical Practice Guidelines in Oncology.

5.7.2. Non-study Related Concomitant Medication and Treatment

No significant inhibition of any of the CYP450 enzymes were observed after KPT-9274 treatment. Weak induction of CYPs 1A2, 2B6, and 3A4 were observed in an exploratory pre-clinical study after KPT-9274 treatment; however, it is unlikely that a potential drug-drug interaction will occur in a clinical setting. Therefore, the use of any concomitant medication/therapy (except medications listed in the prohibited medications section, see Section 5.7.3), including over-the-counter (OTC) medications (excluding herbal supplements, dietary supplements), deemed necessary for the care of the patient is permitted during the study.

5.7.2.1. Permitted Concomitant Medication

Medications required to treat AEs, manage cancer symptoms, concurrent stable diseases and supportive care agents (e.g., blood product transfusions [see Section 5.7.2.4], antibiotics with [if appropriate] granulocyte-colony stimulating factors [G-CSF] for neutropenic infection), pain medications, anti-emetics, and anti-diarrheals are allowed. Concurrent therapy with growth factors is allowed.

Hormonal contraceptives are permitted in women of child-bearing potential. Hormonal contraceptives include any marketed contraceptive agent that includes an estrogen and/or a progestational agent. Since the effect of KPT-9274 on oral contraceptives is unknown at this time, it is required that patients use at least 2 forms of contraceptives while on study.

5.7.2.2. Prevention of Pregnancy

Patients should not become pregnant or father a child while on this study because it is unknown whether KPT-9274 can affect an unborn baby. Women should not breastfeed a baby while on this study. Fertile female patients must agree to refrain from egg donation from first dose until at least 3 months following the last dose of KPT-9274. Women should not breastfeed during treatment with KPT-9274 and for 2weeks after the last dose.

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Female patients of child-bearing potential must agree to use dual methods of contraception and have a negative serum pregnancy test at Screening; male patients must use two highly effective barrier method of contraception if sexually active with a female of child bearing potential, during treatment with KPT-9274, during a period of 2 weeks (5 half-lives) after the last dose of KPT-9274 plus a period of 3 months. (for 3.5 months after their last dose of KPT-9274). Fertile male patients must agree to refrain from sperm donation from first dose until at least 3.5 months following the last dose of KPT-9274.

The use of two forms of contraception are required, including one highly effective and one effective method of contraception, from the following lists.

- Highly effective methods include:
  - Hormonal contraceptives (e.g., combined oral contraceptives, patch, vaginal ring, injectables, and implants)
  - Intrauterine device (IUD) or intrauterine system (IUS)
  - Vasectomy and tubal ligation
- Effective methods include:
  - Barrier methods of contraception (e.g., male condom, female condom, cervical cap, diaphragm, contraceptive sponge)

    Notes:
    - *No barrier method by itself achieves a highly effective standard of contraception*
    - *The proper use of diaphragm or cervical cap includes use of spermicide and is considered one barrier method.*
    - *The cervical cap and contraceptive sponge are less effective in parous women.*
    - *The use of spermicide alone is not considered a suitable barrier method for contraception.*
    - *When used consistently and correctly, "double barrier" methods of contraception (e.g., male condom with diaphragm, male condom with cervical cap) can be used as an effective alternative to the highly effective contraception methods described above.*
    - *Male and female condoms should not be used together as they can tear or become damaged.*

Acceptable methods of contraception also include:

- A sexual partner who is surgically sterilized or post-menopausal.
- Total (true) abstinence (when this is in line with the preferred and usual lifestyle of the patient), is an acceptable method of contraception. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

For both male and female patients, effective methods of contraception must be used throughout the study and for 3 months following the last dose.

See Section 1.2.2 for additional safety information related to pregnancy.

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5.7.2.3. Glucocorticoid Therapy

Glucocorticoids ≥10 mg oral prednisone (or equivalent) per day are not permitted at baseline; however physiological doses ≤10 mg oral or inhaled prednisone (or equivalent) for non-malignant conditions (e.g., asthma, IBD, etc.) are permitted as needed.

As part of supportive care (e.g., for nausea or anorexia), oral dexamethasone, up to 40 mg/week, may be given to patients.

5.7.2.4. Use of Blood Products

During treatment, patients may receive RBC or platelet transfusions per institutional guidelines.

Appropriate anti-coagulation is allowed during the study (e.g., low molecular weight heparin, direct factor Xa inhibitors, etc.).

Patients may receive supportive care with erythropoietin, darbepoetin, G-CSF or granulocyte macrophage-colony stimulating factor (GM-CSF), pegylated growth factors, and platelet stimulatory factors, in accordance with clinical practice or institutional guidelines prior to entry and throughout the study.

5.7.3. Prohibited Concomitant Medications

The use of niacin or niacin-containing supplements (e.g., multivitamins and energy drinks) is not allowed. Investigational or commercial anticancer agents other than KPT-9274 are not allowed during the study. The initiation of any non-protocol specific anti-tumor treatment is considered an indication of disease relapse/progression and should be recorded appropriately in the eCRFs.

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6. ASSESSMENTS

6.1. Informed Consent

Study-specific assessments may not be performed until the patient provides written informed consent (see Section 9.4).

6.2. Demographic and Baseline Characteristics Assessments

6.2.1. Demographics

Patient demographics (including date of birth, sex, race, ethnicity, and age at time of consent) will be collected at study entry.

6.2.2. Medical History

A complete medical history will be obtained from each patient. Medical history will include baseline symptoms of the disease under study as well as a detailed history of prior therapies.

6.2.3. Baseline Characteristics and Determination of Eligibility

Baseline characteristics will include ECOG performance status, duration from initial diagnosis, response to previous therapy, types of prior therapy, and height/weight.

Inclusion/exclusion criteria will be reviewed to determine eligibility.

Patients with known active HAV, HBV, HBC, or HIV infection will be excluded from this study. However, testing for these viruses is not required as part of this study.

6.3. Efficacy Assessments

6.3.1. Bone Marrow Aspirate and Biopsy

Bone marrow biopsy and aspirate will be taken within 30 days prior to first dose (baseline) for all AML patients. This will be repeated on cycle 1 day 8. It will again be repeated, for efficacy purposes according to the ELN criteria[1], at the conclusion of each cycle until the subject has achieved a MLFS, CRi or CR, or per investigator discretion. . It will also be performed as an end of treatment assessment if this occurs >30 days from another scheduled or unscheduled bone marrow biopsy. Bone marrow biopsies will also be performed at any time at the discretion of the investigator in accordance with standard of care (i.e. at the time of suspected progression, etc).

6.3.2. Response Assessments

Response assessments will occur at each bone marrow biopsy starting with cycle 1 day 28. Responses will be assessed per the ELN criteria[1] (Appendix 2).

6.4. Safety Assessments

Safety evaluations will be conducted as described below. Refer to Table 1, Table 2, and Table 3 for the timing of all safety assessments.

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6.4.1. Clinical Safety Assessments

6.4.1.1. Weight and Height

Height in centimeters (cm), at screening, and weight in kilograms (kg) will be measured.

6.4.1.2. Physical Examination, Vital Signs, and ECOG Performance Status

These examinations will be performed according to the institution's standards. Vital signs include systolic and diastolic BP, pulse measurements, and body temperature (°C or °F). ECOG performance status assessments will be performed at the timepoints in the schedule of assessments. Reference the ECOG grading table in (Appendix 1).

6.4.1.3. Electrocardiography

A single standard 12-lead ECG will be performed at Screening (Day -30 to Day -1) and C1D1 (pre-dose and 4 hours post-dose (+/- 30 minutes) and institutional standards as needed.

6.4.1.4. Tumor Lysis System Monitoring

TLS Monitoring is defined as "Tumor lysis syndrome monitoring," and occurs on day 1, 8 hours (+/- 2 hours) after the first dose, and on day 2, 24 hours (+/- 4 hours) after the first dose. Labs include potassium, uric acid, phosphorus, calcium, and serum creatinine.

6.4.1.5. Concomitant Medications

Concomitant medications will be documented for each patient at the completion of each cycle. A detailed history of medications will be documented during Screening and C1D1. All concomitant medications including dietary supplements, over-the-counter medications, and oral herbal preparations, as well as changes in medication, will be recorded on the eCRFs.

Necessary supportive care such as appetite stimulants, anti-emetics, and anti-diarrheals, etc., are allowed (see Section 5.7.1).

6.4.1.6. Adverse Events

Information regarding AEs and SAEs will be collected. See Section 7. It is the responsibility of the Investigator to record and document all SAEs (occurring from the signing of the informed consent form [ICF]) and all AEs (occurring from the first dose of study treatment on C1D1) throughout the study and for 30 days after the last dose of study treatment.

Each AE will be graded according to the CTCAE v5.0 at every visit (Section 7.1.3).

6.4.2. Laboratory Safety Assessments

6.4.2.1. Clinical Laboratory Tests

Table 11 presents the clinical laboratory tests that will be performed during the study.

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Table 8 Clinical Laboratory Tests

Complete Blood Count with Differential
Complete metabolic panel

The Investigator or designee will review the laboratory results and assess the clinical significance of all abnormal values. Appropriate action will be taken for any clinically significant abnormal values.

In addition, laboratory safety assessments will be collected and analyzed on the scheduled day, even if study treatment is being withheld. More frequent assessments may be performed if clinically indicated, or at the Investigator's discretion.

Any laboratory value that remains abnormal at the EoT Visit and that is considered clinically meaningful will be followed according to accepted medical standards for up to 30 days or until resolution of the abnormality or return to baseline. Toxicity will be graded using CTCAE Version 5.0.

6.4.2.2. Pregnancy Testing

For females of childbearing potential, a negative serum human chorionic gonadotropin (hCG) pregnancy test must be obtained $\leq$ 3 days prior to Cycle 1 Day 1 and at the EoT Visit. Pregnancy testing is to be performed as clinically indicated at the discretion of the Investigator during the study.

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7. SAFETY DEFINITIONS, RECORDING, AND REPORTING

7.1. Adverse Events

7.1.1. Definitions

- *Adverse event (AE)*: Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of study treatment, whether or not considered related to the study treatment.
- *Treatment-emergent adverse event (TEAE)*: Any event that was not present prior to the initiation of study treatment or any event already present that worsens in either intensity or frequency following exposure to study treatment.
- *Serious adverse event (SAE):* Any untoward medical occurrence that, at any dose, results in death; is life threatening (i.e., an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe); requires inpatient hospitalization or prolongation of existing hospitalization; results in persistent or significant disability/incapacity; or is a congenital anomaly/birth defect. (See Section 7.2.2 for additional information about SAE reporting.)

7.1.2. Recording of Adverse Events

Adverse Events will be reported and recorded in the eCRF from the time of the first dose of study drug through 30 days after the last dose of study drug or until the start of subsequent antineoplastic therapy, whichever occurs first. That is, if a patient begins a new antineoplastic therapy, the AE reporting period for nonserious AEs ends at the time the new treatment is started. SAEs during screening will only be reported if related to study procedure.

AE monitoring should be continued for at least 30 days following the last dose of study treatment (ie, through 30 days following last dose or until resolution or through the end of the study for events considered related to study treatment by the Investigator).

Adverse events (including laboratory abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be recorded as a separate AE.

The Investigator should ask the patient non-leading questions to determine if any AEs have occurred during the study, since the last study visit. Adverse events may also be recorded when they are volunteered by the patient, or through physical examination, laboratory tests, or other clinical assessments.

An AE should be followed, and an assessment should be made at each visit (or more frequently, if necessary) for any changes in severity of the event, the suspected relationship to the study treatment, the interventions required to treat the event, and the outcome.

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7.1.2.1. Laboratory Test Abnormalities

Laboratory abnormalities and changes in vital signs are AE only if they result in study discontinuation, necessitate medical intervention, meet protocol specific criteria, and/or are considered by the investigator to be clinically significant or AEs. Whenever possible, a diagnosis, rather than a symptom should be provided (e.g., anemia instead of low hemoglobin).

Laboratory abnormalities that meet the criteria for an AE should be followed until they have returned to baseline levels (as measured during the Screening Visit) or an adequate explanation of the abnormality is identified. When an abnormal laboratory or test result corresponds to a sign/symptom of an already reported AE, it is not necessary to separately record the laboratory/test result as an additional event.

A laboratory abnormality that does not meet the definition of an AE should not be reported as an AE. A Grade 3 or 4 event (severe per NCI CTCAE v5.0) does not automatically indicate an SAE unless it meets the definition of serious as defined in Section 7.1.1 and/or as per Investigator's discretion. A laboratory abnormality that results in a dose being held or modified would, by definition, be an AE and must be recorded as such in the eCRFs.

7.1.3. Adverse Event Severity

The term "severe" is used to describe the intensity of an AE; the event itself could be of relatively minor clinical significance (eg, 'severe' headache). This is not the same as a "serious" AE.

The severity of the AE will be graded by the Investigator according to the NCI CTCAE Grading Scale, v. 5.0 (the NCI CTCAE files can be accessed online at the following URL: http://evs.nci.nih.gov/ftp1/CTCAE/About.html).

If NCI CTCAE grading does not exist for an AE, the severity will be characterized as "mild," "moderate," "severe," or "life-threatening (corresponding to Grades 1 to 4) according to the following definitions:

- Mild events are usually transient and do not interfere with the patient's daily activities.
- Moderate events introduce a low level of inconvenience or concern to the patient and may interfere with daily activities.
- Severe events interrupt the patient's usual daily activities.
- Life-threatening.

The term "severe" is used to describe the intensity of an AE; the event itself could be of relatively minor clinical significance (e.g., 'severe' headache). This is not the same as a "serious" AE.

7.1.4. Adverse Event Causality

The Investigator will make a judgment regarding the relationship of the AE to study treatment, as outlined in Table 12

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Table 9 Classification of Adverse Events by Causality

Not related	These events will lack a temporal relationship of the event to the study treatment, making a causal relationship not reasonably possible. Exposure to other drugs, therapeutic interventions, or underlying conditions may provide a sufficient explanation for the event.
Possibly Related	Some evidence to suggest a causal relationship (e.g. occurrence within a reasonable time after administration of the trial medication), but other factors may have contributed to the event (e.g. another clinical condition or other concomitant treatment).
Likely Related	Evidence to suggest a causal relationship; the influence of other factors is unlikely.
Related	There is a temporal relationship of the event to the study treatment making a definitive relationship, and the event is more likely explained by exposure to the study treatment than by any other drugs, therapeutic interventions, or underlying conditions.

7.2. Serious Adverse Events

See Section 7.1.1 for the definition of an SAE. Please note that SAEs related to study procedures that occur at any time between the signing of the ICF up to the first dose of study treatment, must be reported (in addition to SAEs that occur after the first dose of study treatment).

Important medical events that may not result in death, are not life-threatening, or do not require hospitalization may be considered SAEs when, based on appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent 1 of the outcomes listed in this definition. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in in-patient hospitalization, or the development of drug dependency or drug abuse.

7.2.1. Events that Do Not Meet the Definition of a Serious Adverse Event

Elective hospitalizations to administer, or to simplify study treatment or study procedures (ie, an overnight stay to facilitate 24-hour urine collection) or other medical procedures are not considered SAEs. A ‘serious’ hospitalization is defined as any inpatient hospital admission that includes a minimum of an overnight stay in a health care facility. An emergency room visit is not considered a hospitalization unless it results in an official admission as in inpatient to the hospital (eg, undesirable effects of any administered treatment) and must be documented as an SAE. Progression of the AML (including fatal outcomes) should not be reported as an SAE during the study or within the safety reporting period (see Section 7.2.2). Sudden and unexplained death should be reported as an SAE. If there is any uncertainty about a finding being due solely to progression of malignancy, the finding should be reported as an AE or SAE, as appropriate.

7.2.2. Recording of Serious Adverse Events

It is the responsibility of the Sponsor-Investigator to record and document all SAEs occurring from the signing of the ICF, during screening only those related to study procedures, until at least 30 days after the patient has stopped study treatment. All SAEs must be reported on Karyopharm’s

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SAE Report Form in addition to being recorded in the sponsor-investigator's database. The original SAE Report Form must be retained in the Investigator's site file.

All applicable sections of the form must be completed in order to provide a clinically thorough report. The Investigator must assess and record the relationship of each SAE to study treatment and complete the SAE Report Form (in English).

See ICH E2A (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, Attachment 1) for key data elements that are required for expedited reporting.

7.2.3. Reporting of Serious Adverse Events

Every SAE, regardless of the causal relationship to the study treatment, occurring after the patient has signed informed consent, until at least 30 days after the patient has stopped study treatment, must be reported to the HCTU Quality Team and Karyopharm Pharmacovigilance Department within *24 hours* of learning of its occurrence. The investigational site personnel must use the SAE Report Form provided by Karyopharm for reporting any SAE to the Karyopharm Pharmacovigilance Department (Appendix 1).

Upon completion, the SAE Report Form must be immediately emailed or faxed to:

Pharmacovigilance Department

Karyopharm Therapeutics Inc.

Email: pharmacovigilance@karyopharm.com and HCTU.quality@ucdenver.edu

Fax: +1-617-334-7617 (USA)

Any SAE observed after the 30-day follow-up period should only be reported to HCTU Quality Team and Karyopharm if the Investigator suspects that the SAE has causal relationship to the Karyopharm study drug. Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode within 24 hours of the Investigator receiving the follow-up information.

An SAE should be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity of the event, the suspected relationship to the study treatment, the interventions required to treat the event, and the outcome.

Sponsor-Investigator is responsible as applicable for notifying their appropriate Health Authorities, Institutional Review Board, Local and Central Ethics Committees (EC) and Food and Drug Administration of all SAEs in accordance with regulations.

7.2.4. Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are SAEs that are unexpected (per the current version of the IB) and judged by the Sponsor-Investigator or Karyopharm to be related to the Karyopharm study drug administered. All SUSARs will be collected and reported to the competent authorities and relevant ethics committees in accordance with the FDA's "Safety Reporting Requirements for Investigational New Drugs and Bioanalytical/Bioequivalence Studies" (FDA 2012).

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7.2.5. Adverse Event Reporting

The Investigator will report all AEs (including all non-serious AEs) to Karyopharm Pharmacovigilance twice per year in the form of line-listings in an excel spreadsheet.

Karyopharm, the drug supplier, will supply the cut-off dates of each requested line listing. The line listings will contain the following information: study ID, unique subject ID, adverse event term, serious event (yes or no), onset date (complete or partial), end date (complete or partial), action taken with KPT-9274, causality to KPT-9274, event ongoing (yes or no), outcome of AE, severity CTCAE Grade (1-5), subject dosed with KPT-9274 (yes or no), date of first dose of KPT-9274, preferred term, system organ class (optional)

See the excel spreadsheet template in Appendix 4.

7.3. Procedures for Handling Special Situations

7.3.1. Pregnancy

Note: Pregnancy *per se* is not considered to be an AE; however, it is discussed here because of the importance of reporting pregnancies that occur during studies and because a medical occurrence observed in the mother or fetus/newborn would be classified as an AE.

Female patients of childbearing potential and fertile male patients will be informed as to the potential risk of conception while participating in this study and will be advised that they must use highly effective contraception listed below (ie, results in a low failure rate when used consistently and correctly) during the dosing period and for a period of at least 3 months after the end of treatment.

A list of highly effective methods of contraception is provided in Section 5.7.

A pregnancy test will be performed on each premenopausal female patient of childbearing potential prior to the first dose of study drug, on Day 1 of Cycles ≥2 while on treatment, and again at treatment discontinuation during the End-of-Treatment visit. A negative pregnancy test must be documented prior to administration of study drug.

If a patient is confirmed pregnant during the study, study drug administration must be discontinued immediately. The Investigator must immediately notify the Sponsor investigator of this event and record the Pregnancy on the Pregnancy Form. The initial information regarding a pregnancy must be forwarded to Karyopharm's Pharmacovigilance Department by email or fax within 24 hours of first knowledge of its occurrence. A pregnancy report form is provided by Karyopharm Pharmacovigilance.

The pregnancy should be followed up to determine the outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

All pregnancies occurring within 3 months after the patient's last dose of study drug must be reported to Karyopharm, regardless of whether the patient received the Karyopharm study drug or other study drugs, withdraws from the study, or the study is completed. Patients should be instructed to inform the Investigator regarding any pregnancies.

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Any SAE that occurs during pregnancy must be recorded on the SAE report form (eg, maternal serious complications, therapeutic abortion, ectopic pregnancy, stillbirth, neonatal death, congenital anomaly, or birth defect) and reported within 24 hours in accordance with the procedure for reporting SAEs (described in Section7.2.

A pregnancy in a female partner of a male patient must be reported to Karyopharm Pharmacovigilance within 24 hours of learning of its occurrence. Pregnancies in female partners should only be followed if the male patient is being treated with a KPT-9274-containing regimen. Consent to report information regarding these pregnancy outcomes should be obtained from the female partner.

It is not known whether KPT-9274 passes into the breast milk. Mothers should not breastfeed while being treated with a KPT-9274-containing regimen and for 2 weeks after the last dose.

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8. STATISTICAL METHODS

8.1. General Considerations

Tabulations will be produced for appropriate disposition, demographic, baseline, efficacy, and safety parameters. For categorical variables, summary tabulations of the number and percentage of patients within each category (with a category for missing data) of the parameter will be presented. For continuous variables, the number of patients, mean, median, standard deviation, minimum, and maximum values will be presented. Time-to-event data will be summarized using Kaplan-Meier methodology with median event time and associated 2 sided 95% confidence intervals, as well as number and percentage of patients with events and censored patients.

Patients who are in the Dose Escalation Phase being treated at the RP2D chosen for expansion will be included in the efficacy and safety assessment of the Dose Expansion Phase.

8.2. Determination of Sample Size

8.2.1. Sample size

The sample size for the Dose Escalation Phase is based on a standard 3+3 design for the purpose of determining the RP2D and MTD. Each cohort will consist of 3 or 6 patients per cohort.

For the Dose Expansion Phase, up to 10 additional patients may be enrolled at the RP2D for KPT-9274

Assuming that 4 dose levels of KPT-9274 are evaluated during the Dose Escalation Phase and up to 10 additional patients are enrolled in the Dose Expansion Phase, the total combined enrollment is estimated to be at most 34 patients.

8.3. Analysis Populations

8.3.1. Intent-to-Treat Population

The intent to treat (ITT) population for will consist of all patients who receive at least one dose of the RP2D chosen for expansion.

ITT population will be used for analyses of efficacy.

8.3.2. Safety Population

All patients who receive any amount of the study treatment will be included in the safety population for analysis. All safety analyses will be performed on the safety population.

8.3.3. DLT Evaluable Population

All patients who complete a minimum of 1 cycle of treatment, defined as having received ≥ 75% of KPT-9274 doses during Cycle 1 (e.g., ≥ 9 of 12 doses in the 3 doses/week schedule), or who have a DLT within the first cycle of treatment, will be included in the DLT evaluable population.

8.4. Data Analysis and Presentation

Summary tabulations will be provided for disposition, demographic, baseline, efficacy and safety data as noted in the following sections. All data collected on the eCRF will be provided in by-patient data listings.

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8.4.1. Disposition of Patients

A tabulation of patient disposition will be presented including the number in each analysis population, the number lost to follow-up, the number that withdrew, and reason(s) for withdrawal.

8.4.2. Demographic Characteristics

Demographic characteristics will be summarized by dose cohort, as well as overall, and will include date of birth, sex, race, ethnicity, and age at time of consent. For sex, race, and ethnicity, the summary statistics will be the number and percentage of patients within each category. The categories for race will be those recorded in the database. For age at time of consent, the mean, median, minimum, maximum, and standard deviation will be provided for each arm and the total sample. No formal hypothesis testing of differences among dose cohorts will be performed.

8.4.3. Baseline Characteristics and Medical History

Baseline characteristics include ECOG performance status, duration from initial diagnosis, response to previous therapy, types of prior therapy, and height/weight. Baseline data will be tabulated for the same categories as used for demographics, using summary statistics; no formal hypothesis testing of dose cohort differences will be performed. Medical history and physical examination results at baseline will be tabulated by treatment cohort.

8.5. Efficacy Analysis

- **Overall response rate (AML):** complete remission (CR), complete remission with incomplete hematologic recovery (CRi), morphologic leukemia-free state (MLFS), partial remission (PR).
- **Duration of response (DOR):** the duration of time from first meeting CR, PR, MLFS, CRi, measurement criteria (whichever occurs first) until the first date that PD recurrence is objectively documented.
- **Progression-free survival (PFS):** the duration of time from date of first study treatment until the first date that PD is objectively documented or death due to any cause.
- **Overall survival (OS):** the duration of time from date of first study treatment until death from any cause.
- **Time to Progression** (**TTP):** The duration of time from date of first study treatment until the first date that PD is objectively documented or death due to PD. Patients without documented PD will be censored on the date of last disease assessment.

8.6. Safety Analysis

All safety analyses will be made on the Safety Population.

The safety and tolerability of KPT-9274 will be evaluated by means of DLTs, AE reports, physical examination results, electrocardiogram results and laboratory safety evaluations. NCI CTCAE, Version 5.0 will be used for grading of AEs.

The MTD will be based on the assessment of DLTs during the first cycle of therapy and will be defined as the highest dose at which ≤1 patient experiences DLTs within Cycle 1.

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Interim safety data will be examined on an ongoing basis to ensure patient safety.

8.6.1. Adverse Events

Analyses of AEs will be performed for those events that are considered to be treatment-emergent AEs (TEAEs), defined as any AE with onset or worsening of a pre-existing condition on or after the first administration of study medication through 30 days following last dose or any event considered drug-related by the Investigator through the end of the study. Adverse events with partial dates will be assessed using the available date information to determine if treatment-emergent; AEs with completely missing dates will be assumed to be treatment-emergent.

Adverse events will be summarized by frequency counts at patient level. Tabulations will be provided for all TEAEs, for TEAEs assessed by the Investigator as at least possibly related to treatment, for ≥ Grade 3 TEAEs, and for serious AEs (SAEs).

No formal hypothesis-testing analysis of AE incidence rates will be performed.

All AEs (treatment-emergent and post-treatment) will be listed in patient data listings. Separate by-patient listings will be provided for the following: patient deaths, SAEs, and AEs leading to withdrawal.

8.6.2. Clinical Laboratory Data

Clinical laboratory values will be expressed using conventional SI units.

The actual value and change from Baseline for each on study evaluation will be summarized for each clinical laboratory parameter, including hematology and clinical chemistry.

Severity of select clinical lab measures will be determined using CTCAE criteria (i.e., those measures that have a corresponding CTCAE grade classification). Shift tables that present changes from baseline to worst on-study and baseline to last on-study values relative to CTCAE classification ranges will be produced.

8.6.3. Vital Signs and Examinations

The actual value and change from baseline to each on-study evaluation will be summarized.

Physical examination results at Screening will be summarized; all other abnormal physical examination data are to be recorded on the AE eCRF. All examination findings will be presented in a data listing. ECOG performance status scores, and 12-lead ECG results will be summarized.

8.6.4. Concomitant Medications

Concomitant medications will be tabulated based on the current version of the World Health Organization (WHO) Drug Dictionary.

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9. ADMINISTRATIVE MATTERS

9.1. Regulatory and Ethical Compliance

This clinical study was designed and will be implemented and reported in accordance with the ICH Harmonised Tripartite Guidelines for Good Clinical Practice (GCP). Applicable local regulations, including European Directive 2001/20/EC and United States Code of Federal Regulations Title 21, and the ethical principles outlined in the Declaration of Helsinki will be followed.

9.2. Ethics Committees

The protocol, the proposed ICF, and any other relevant records must be reviewed and approved by a properly constituted ethics committee (eg, IRB) before study start.

9.3. Regulatory Authority Approval

Before implementing this study, the protocol must be approved by relevant, competent regulatory authorities.

9.4. Protocol Adherence

Prior to study start, the Investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with the instructions and procedures found in this protocol and to give access to all relevant data and records to the drug supplier, Quality Assurance representatives, designated agents of the Sponsor-Investigator, ethics committees, and regulatory authorities as required. Investigators attest they will apply due diligence to avoid protocol deviations. All significant protocol deviations will be recorded and reported in the clinical study report (CSR). A significant protocol deviation is defined as any change to the execution of the protocol, that affects the scientific integrity or design of the study, or the rights, safety or welfare of study patients.

9.5. Amendments to the Protocol

Any significant change or addition to the protocol by the Sponsor-Investigator can only be made in a written protocol amendment that must be provided by the Sponsor-Investigator, reviewed/approved by the drug supplier, and approved by Health Authorities where required, and the ethics committee (eg, IRB). Only amendments that are required for clarification or patient safety, by the Sponsor-Investigator, may be implemented prior to ethics committee (eg, IRB) approval. Notwithstanding the need for approval of formal protocol amendments, the Investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol. In such cases, the Sponsor-Investigator should be notified of this action and the ethics committee (eg, IRB) at the study site should be informed according to local regulations but not later than 10 working days.

9.6. Informed Consent

Eligible patients may only be included in the study after providing written (witnessed, where required by law, ethics committee [eg, IRB], or regulation), ethics committee (eg, IRB)-approved informed consent.

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Informed consent must be obtained before conducting any study-specific procedures. Procedures that are part of the clinical routine evaluations during the initial diagnostic work-up of the patient may be performed before the ICF is signed and dated (ie, procedures that are not specific to the conduct of the study).

Informed consent must also be obtained for patients before conducting any study-specific procedures for treatment.

The process of obtaining informed consent should be documented in the patient source documents. A copy of the ICF must be given to the patient or to the person signing the form on behalf of the patient. The Investigator or designee must record the date when the study ICF was signed in the medical records of the patient. The name and role of the witness, if required, should also be documented.

The Sponsor-Investigator will provide to the drug supplier, in a separate document, a proposed ICF that is appropriate for this study and complies with the ICH GCP guideline and regulatory requirements.

9.7. Patient Confidentiality and Disclosure

The Investigator must ensure anonymity of all patients; patients must not be identified by names in any documents submitted to the drug supplier or its designee. Signed ICFs and patient enrollment logs must be kept strictly confidential.

9.8. Collection, Auditing Study Documentation, and Data Storage

9.8.1. Study Documentations, Record Keeping and Retention of Documents

Each participating site will maintain appropriate medical and research records for this study, in compliance with Section 4.9 of ICH E6 GCP, and according to the regulatory and institutional requirements.

Source data include all information, original records of clinical findings, observations, or other activities in a clinical study necessary for the reconstruction and evaluation of the study.

Data collection is the responsibility of the clinical study staff at the site under the supervision of the site Investigator. The study database is the primary data collection instrument for the study. The Investigator is responsible for the accuracy, completeness, and timeliness of the data reported in the database and all other required reports. Data reported in the database, which are derived from source documents, should be consistent with the source documents or the discrepancies should be explained. All data requested on the source documents must be recorded. Any missing data must be explained. If electronic records are used, an audit trail will be maintained by the system, in compliance with 21 CFR Part 11.

The Investigator/institution should maintain study documents as specified in Essential Documents for the Conduct of a Clinical Trial (ICH E6 Section 8) and as required by applicable regulations and/or guidelines. The Investigator/institution should take measures to prevent accidental or premature destruction of these documents.

Essential documents (written and electronic) should be retained for a period of not less than 15 years from the completion of the clinical study unless the Sponsor provides written permission to dispose of them or, requires their retention for an additional period of time because of applicable laws, regulations, and/or guidelines.

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9.8.2. Monitoring and Oversight

The sponsor investigator will be responsible for monitoring the trial per the trial monitoring plan, in addition to overseeing the safety and efficacy of the trial including any specimens collected, executing the data and safety monitoring (DSM) plan, and complying with all reporting requirements to local and federal authorities. This oversight will be accomplished through additional oversight from the Data and Safety Monitoring Committee (DSMC) at the University of Colorado Cancer Center (CU Cancer Center). The DSMC is responsible for ensuring data quality and study participant safety for all clinical studies at the CU Cancer Center, which is the coordinating institution of this trial.

A summary of the DSMC's activities is as follows:

- Conduct of internal audits
- Ongoing review of all serious adverse events (SAEs) and unanticipated problems (UAPs)
- May submit recommendations for corrective actions to the CU Cancer Center's Executive Committee

Per the CU Cancer Center Institutional DSM Plan, SAEs and UAPs are reported to the DSMC, IRB and the sponsor investigator per protocol. All SAEs and UAPs are to be reported to the DSMC within 7 (for fatal or life-threatening events) or 15 (non-life-threatening events) calendar days of the sponsor investigator receiving notification of the occurrence.

Each subject's treatment outcomes will be discussed by the site PI and appropriate staff at regularly scheduled meetings. Data regarding number of subjects, significant toxicities, dose modifications, and treatment responses will be discussed and documented in the meeting's minutes.

The sponsor investigator will provide a DSM progress report to the CU Cancer Center DSMC on a recurring basis (either every six or twelve months based on DSMC vote). The DSM report will include a protocol summary, current enrollment numbers, summary of toxicity data to include specific SAEs, UAPs and AEs, any dose modifications, all protocol deviations, and protocol amendments. The DSM progress report submitted to the DSMC will also include, if applicable, the results of any efficacy data analysis conducted. Results and recommendations from the review of this progress report by the DSMC will then be provided to the sponsor investigator in a DSMC review letter. The sponsor investigator is then responsible for ensuring this letter is submitted to the site's IRB of record at the time of IRB continuing review.

9.8.3. Clinical Monitoring, Audit Procedures

Clinical site monitoring will be conducted to ensure that the rights and well-being of human participants are protected, that the reported trial data are accurate, , legible, attributable, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/ amendment(s), with GCP, and with applicable regulatory requirement(s).

Source documents (paper or electronic) are those in which patient data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at pharmacies, laboratories, and medico technical departments involved in a clinical trial.

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Monitoring for this study will be performed by a qualified research monitor in accordance with the clinical monitoring plan (CMP). The CMP describes in detail who will conduct the monitoring, at what frequency monitoring will be done, at what level of detail monitoring will be performed, and the distribution of the monitoring reports.

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records.

To facilitate source data verification, the investigators and institutions must provide the study monitor(s) direct access to applicable source documents and reports for trial-related monitoring, Sponsor audits, and IRB/EC review. The study site must also allow inspection by applicable health authorities.

9.9. Termination of the Study

It is agreed that, for reasonable cause, either the Sponsor-Investigator or drug provider, may terminate the Investigator's participation in this study after submission of a written notice. The drug provider may terminate the study at any time upon immediate notice for any reason including the drug provider's belief that discontinuation of the study is necessary for patient safety.

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10. REFERENCES

1. Dohner H, Estey E, Grimwade D, et al. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. *Blood.* 2017;129(4):424-447.
2. Nahimana A, Attinger A, Aubry D, et al. The NAD biosynthesis inhibitor APO866 has potent antitumor activity against hematologic malignancies. *Blood.* 2009;113(14):3276-3286.
3. Cagnetta A, Caffa I, Acharya C, et al. APO866 Increases Antitumor Activity of Cyclosporin-A by Inducing Mitochondrial and Endoplasmic Reticulum Stress in Leukemia Cells. *Clin Cancer Res.* 2015;21(17):3934-3945.
4. Mitchell SR, Larkin K, Grieselhuber NR, et al. Selective targeting of NAMPT by KPT-9274 in acute myeloid leukemia. *Blood Adv.* 2019;3(3):242-255.

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APPENDIX 1. EASTERN COOPERATIVE ONCOLOGY GROUP PERFORMANCE STATUS CRITERIA

Table 10 ECOG Performance Status Scale

Grade	Descriptions
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed < 50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed > 50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

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APPENDIX 2. EUROPEAN LEUKEMIA NETWORK RESPONSE CRITIERA FOR AML (DOHNER ET AL, 2017)

Table 11 European leukemia network response criteria for AML

Response	Definition	Comment
Complete remission (CR)	Bone marrow blasts <5%, absence of circulating blast and blasts with Auer rods; absence of extramedullary disease; ANC≥1.0x10^9/L; platelet count ≥100x10^9/L	MRD status to be reported if known
CR with incomplete hematologic recovery (CRi)	All CR criteria except for residual neutropenia (<1.0 x 10^9/L) or thrombocytopenia (<100x10^9/L)	
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 merely be "aplastic"; at least 200 cells should be enumerated or cellularity should be at least 10%
Partial remission (PR)	All hematologic criteria of CR; decrease of bone marrow blast percentage to 5% to 25%, and decrease of pretreatment bone marrow blasts percentage by at least 50%	

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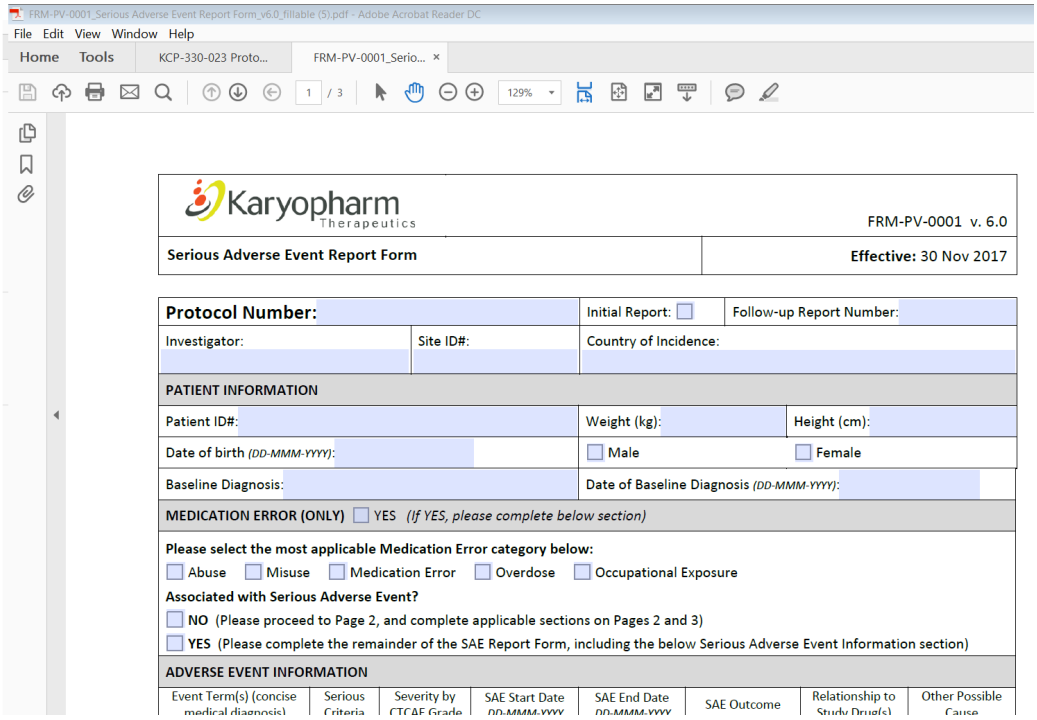
APPENDIX 3. SAMPLE SERIOUS ADVERSE EVENT REPORT FORM



FRM-PV-0001_Serious Adverse Event Report Form_v6.0_fillable (5).pdf - Adobe Acrobat Reader DC

File Edit View Window Help

Home Tools KCP-330-023 Proto... FRM-PV-0001_Serio...

Karyopharm Therapeutics

FRM-PV-0001 v. 6.0

Serious Adverse Event Report Form | **Effective:** 30 Nov 2017

Protocol Number:		Initial Report: ☐	Follow-up Report Number:
Investigator:	Site ID#:	Country of Incidence:	
PATIENT INFORMATION			
Patient ID#:		Weight (kg):	Height (cm):
Date of birth *(DD-MMM-YYYY)*:		☐ Male	☐ Female
Baseline Diagnosis:		Date of Baseline Diagnosis *(DD-MMM-YYYY)*:	

MEDICATION ERROR (ONLY) ☐ YES *(If YES, please complete below section)*

Please select the most applicable Medication Error category below:

☐ Abuse ☐ Misuse ☐ Medication Error ☐ Overdose ☐ Occupational Exposure

Associated with Serious Adverse Event?

☐ **NO** (Please proceed to Page 2, and complete applicable sections on Pages 2 and 3)

☐ **YES** (Please complete the remainder of the SAE Report Form, including the below Serious Adverse Event Information section)

ADVERSE EVENT INFORMATION

Event Term(s) (concise medical diagnosis)	Serious Criteria	Severity by CTCAE Grade	SAE Start Date *DD-MMM-YYYY*	SAE End Date *DD-MMM-YYYY*	SAE Outcome	Relationship to Study Drug(s)	Other Possible Cause

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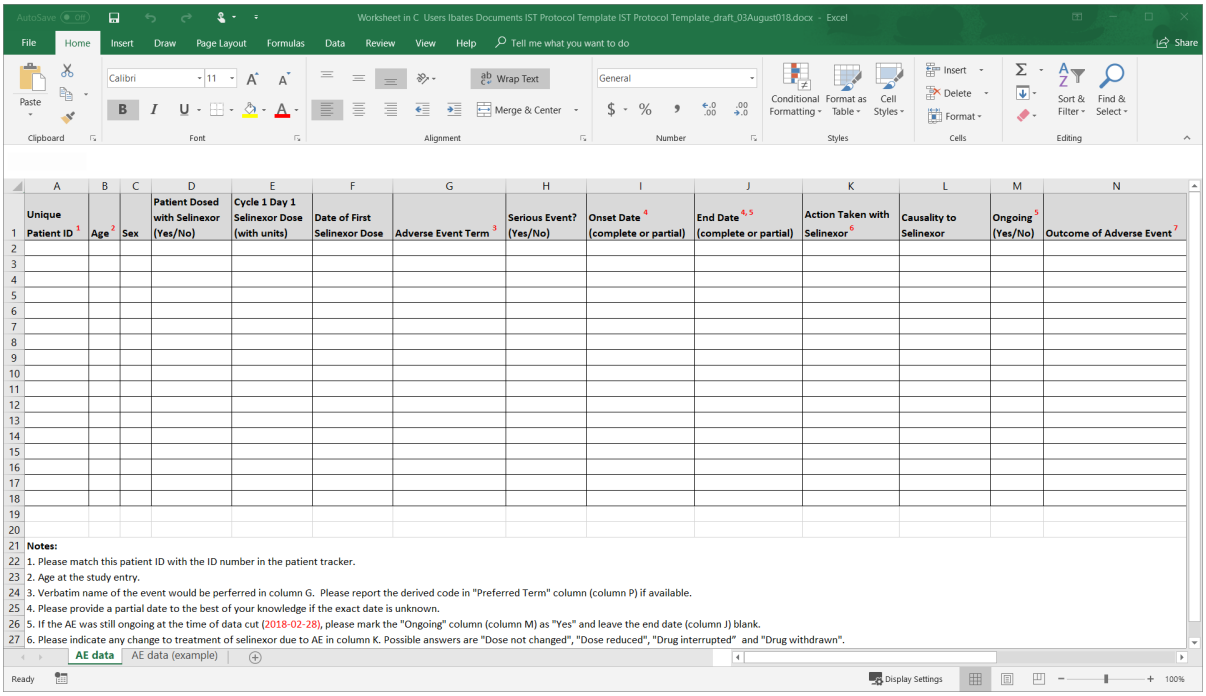
APPENDIX 4. TEMPLATE FOR LINE LISTING OF ADVERSE EVENTS



Unique Patient ID [1]	Age [2]	Sex	Patient Dosed with Selinexor (Yes/No)	Cycle 1 Day 1 Selinexor Dose (with units)	Date of First Selinexor Dose	Adverse Event Term [3]	Serious Event? (Yes/No)	Onset Date [4] (complete or partial)	End Date [4,5] (complete or partial)	Action Taken with Selinexor [6]	Causality to Selinexor	Ongoing [5] (Yes/No)	Outcome of Adverse Event [7]

Notes:

1. Please match this patient ID with the ID number in the patient tracker.
2. Age at the study entry.
3. Verbatim name of the event would be perferred in column G. Please report the derived code in "Preferred Term" column (column P) if available.
4. Please provide a partial date to the best of your knowledge if the exact date is unknown.
5. If the AE was still ongoing at the time of data cut (2018-02-28), please mark the "Ongoing" column (column M) as "Yes" and leave the end date (column J) blank.
6. Please indicate any change to treatment of selinexor due to AE in column K. Possible answers are "Dose not changed", "Dose reduced", "Drug interrupted" and "Drug withdrawn".

Template is a guide. Sponsor-Investigator may provide equivalent information in a differing format

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