**Protocol Number:** TROV-052

**Official Title:** A Phase 1b/2 Study of Onvansertib (PCM-075) in Combination with Either Low-dose Cytarabine or Decitabine in Subjects with Acute Myeloid Leukemia (AML)

**NCT Number:** NCT03303339

**Document Date:** 07 Aug 2019

# 1 CLINICAL STUDY PROTOCOL

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| **Protocol Title:** | A Phase 1b/2 Study of Onvansertib (PCM-075) in Combination with Either Low-dose Cytarabine or Decitabine in Subjects with Acute Myeloid Leukemia (AML) |
| **Protocol Number:** | TROV-052 |
| **Study Phase:** | 1b/2 |
| **Product Name:** | Onvansertib (PCM-075) |
| **IND Number:** | 135237 |
| **Sponsor:** | Trovagene, Inc.<br>11055 Flintkote Avenue<br>San Diego, CA 92121<br>[redacted] |
| **Issue Date:** | 07 Aug 2019 |
| **Amendment Number:** | Amendment 2 |
| **Protocol Version:** | Version 6.0 |
| **Prior Protocol Version:** | Version 5.0, dated 16 May 2018 |

This study will be performed in compliance with Good Clinical Practice (GCP), the Declaration of Helsinki (with amendments), and local legal and regulatory requirements.

# 2 TABLE OF CONTENTS

## LIST OF TABLES

**A Phase 1b/2 Study of Onvansertib (PCM-075) in Combination with Either Low-dose Cytarabine or Decitabine in Subjects with Acute Myeloid Leukemia (AML)**

PROTOCOL APPROVAL SIGNATURES
Trovagene, Inc.

[redacted]
Printed Name

[redacted]
Signature

Chief Executive Officer
Title

8/12/2019
Date

[redacted]
Printed Name

[redacted]
Signature

Chief Scientific Officer
Title

8/12/2019
Date

[redacted]

[redacted]
Signature

Vice President, Scientific Services
PRA Health Sciences
Title

[redacted]
Date

# INVESTIGATOR SIGNATURE PAGE

**Protocol No:** TROV-052

**Protocol Version:** Amendment 2, Version 6.0

**Protocol Date:** 07 Aug 2019

**Protocol Title:** A Phase 1b/2 Study of Onvansertib (PCM-075) in Combination with Either Low-dose Cytarabine or Decitabine in Subjects with Acute Myeloid Leukemia (AML)

I have read the attached protocol and hereby agree that it contains all the necessary details for performing the Product Study.

I will provide copies of the protocol to the Investigational Review Board and all members of the Study team responsible to me who participate in the Study. I will discuss this material with them to ensure that all participating personnel at the Study site are fully informed regarding the investigational device and the conduct of the protocol.

Once the Investigational Review Board approves the protocol, I will not modify this protocol without obtaining the prior approval of both the Sponsor and the Investigational Review Board. I will submit the protocol modifications and/or any informed consent modifications to the Sponsor and the Investigational Review Board, as applicable, and approval will be obtained before any modifications are implemented.

| | |
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| Investigator's Signature | Date |
| Investigator's Printed Name | |
| Study Site Name | |
| Address | |
| City, State, Zip Code, Country | |

# 3 SYNOPSIS

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| **Protocol Title:** | A Phase 1b/2 Study of Onvansertib (PCM-075) in Combination with Either Low-dose Cytarabine or Decitabine in Subjects with Acute Myeloid Leukemia (AML) |
| **Protocol Number:** | TROV-052 |
| **IND Number:** | 135237 |
| **Number of Study Sites:** | This study is being conducted at 8 study centers. |
| **Phase:** | 1b/2 |
| **Objectives:** | **Primary Objectives**<br><u>Phase 1b:</u><br>• To evaluate the dose limiting toxicities (DLTs) and maximum tolerated dose (MTD) or recommended Phase 2 dose (RP2D) of onvansertib (PCM-075) in combination with either low-dose cytarabine or decitabine in subjects with AML<br><u>Phase 2:</u><br>• To assess the safety and tolerability of the combination of either onvansertib (PCM-075) at the MTD (or RP2D) and low-dose cytarabine or the combination of onvansertib (PCM-075) at the MTD (or RP2D) and decitabine in subjects with AML<br>• To evaluate the preliminary anti-leukemic activity of the combination of either onvansertib (PCM-075) at the MTD (or RP2D) and low-dose cytarabine or the combination of onvansertib (PCM-075) at the MTD (or RP2D) and decitabine in subjects with AML<br>**Secondary Objectives**<br><u>Phase 1b:</u><br>• To assess the incidence and severity of adverse events (AEs) according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) (version 4.03) of onvansertib (PCM-075) in combination with either low-dose cytarabine or decitabine in subjects with AML<br>• To analyze the pharmacokinetics (PK) of onvansertib (PCM-075) when given in combination with either low-dose cytarabine or decitabine in subjects with AML |

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| | Phase 2:<br>• To assess the incidence and severity of AEs according to the NCI-CTCAE version 4.03 of onvansertib (PCM-075) in combination with either low-dose cytarabine or decitabine in subjects with AML<br>• To analyze the PK of onvansertib (PCM-075) when given in combination with either low-dose cytarabine or decitabine in subjects with AML<br>**Exploratory Objectives**<br>Phase 1b and Phase 2:<br>• To explore additional analyses evaluating potential pharmacodynamic (PD) and diagnostic biomarkers of onvansertib (PCM-075) in subjects with AML |
| **Study Design:** | This is a Phase 1b/2, open-label study of the safety and anti-leukemic activity of onvansertib in combination with either low-dose cytarabine or decitabine in subjects with AML.<br>In Phase 1b, subjects will have relapsed or refractory disease and must have received no more than 3 prior regimens for the treatment of their AML. Subjects may be treatment naïve as long as they are not candidates for or have refused intensive induction therapy.<br>In Phase 2, subjects must have received no more than 1 prior regimen for the treatment of their AML. Subjects may be treatment naïve as long as they are not candidates for or have refused intensive induction therapy.<br>In both phases, prior treatment with either low-dose cytarabine or decitabine for myelodysplastic syndromes (MDS) will not be considered a prior regimen. For subjects who have undergone hematopoietic stem cell transplantation, the preparative (conditioning) regimen and transplant will be considered to be a single line of prior therapy.<br>**Phase 1b:**<br>Subjects in Phase 1b will receive either a combination of onvansertib and low-dose cytarabine, or a combination of onvansertib and decitabine in 2 separate arms using a standard 3+3 design in each arm.<br>In Arm A, onvansertib will be administered in escalating doses orally (p.o.) Day 1 through Day 5 every 21 to 28 days in combination with cytarabine, which will be administered in all cohorts as 20 mg/m$^2$ subcutaneously (SC) once daily on Day 1 through Day 10 every 28 days. Onvansertib administration, in combination with cytarabine, will be initiated at a starting dose of 12 mg/m$^2$ p.o. daily for 5 days (Dose Level 0). On days where both agents are administered (Days 1-5), cytarabine will be administered first followed by onvansertib. Investigator assessment of subjects may allow them, |

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| | at their discretion, to treat more frequently than every 21 to 28 days; however, in no case may a cycle length be less than 21 days.<br><br>In Arm B, onvansertib will be administered in escalating doses p.o. Day 1 through Day 5 every 21 to 28 days in combination with decitabine, which will be administered consistently in all cohorts as 20 mg/m$^2$ intravenously (IV) over 1 hour on Day 1 through Day 5 every 28 days. Onvansertib administration, in combination with decitabine, will be initiated at a starting dose of 12 mg/m$^2$ p.o. daily for 5 days (Dose Level 0). The daily dose of decitabine will be administered first followed by onvansertib. Investigator assessment of subjects may allow them, at their discretion, to treat more frequently than every 21 to 28 days; however, in no case may a cycle length be less than 21 days.<br><br>The first 3 subjects will be allocated to Arm A (Cohort A1). If Cohort A1 is expanded to 6 subjects prior to the first subject being enrolled in Arm B, then enrollment in Cohort A1 will be completed before enrollment begins in Arm B. After all subjects are enrolled in Cohorts A1 and B1, subjects will enroll in subsequent dose escalation cohorts based on the following decision rules:<br><br>• If Arm A is open for enrollment, subjects will enroll in the open Arm A cohort regardless of dose level<br>• If Arm A is closed to enrollment, subjects will enroll in the open Arm B cohort regardless of dose level<br><br>Dosing in Arms A and B will proceed independently. Each arm will follow a standard 3+3 dose-escalation design in which the onvansertib dose will be escalated by 50% increments in successive cohorts of 3 subjects. If none of the 3 subjects enrolled at any dose level experience a DLT, the dose of onvansertib will be escalated by 1 dose level in each successive cohort. If 1 subject in the first 3 experiences a DLT, up to 3 additional subjects will be enrolled at that dose level. If there are no additional DLTs (ie, ≤1 of 6 subjects with DLT), then dose escalation will again proceed. If there are 2 subjects who experience DLTs among the first 3 subjects enrolled, or there is a second DLT in up to 6 subjects enrolled at any dose level, the MTD will be judged to have been exceeded, and no additional subjects will be started at that dose. The MTD will then be established at a prior dose level or an additional cohort may be enrolled at an intermediate dose level upon agreement with the Sponsor, Medical Monitor, and Principal Investigator.<br><br>The RP2D can be determined based on the assessment of safety, PK, PD, and preliminary efficacy of subjects treated at a dose level that has been cleared for safety, regardless of whether or not an MTD has been reached. In this case, no further dose escalation will be done to determine an MTD.<br><br>Each cohort will be evaluated for toxicity, recovery of blood counts, and PK. DLTs will be evaluated for the first 28 days after initiation of therapy. In the case of pancytopenia present at Day 28 in the absence of other toxicity that |

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| | constitutes a DLT, the duration for DLT evaluation will be extended to 42 days (unless the pancytopenia resolves between Days 28 and 42, or is determined to be due to persistent leukemic involvement of the bone marrow or another cause unrelated to study therapy). Pancytopenia, related to onvansertib in the absence of another cause unrelated to study therapy that persists beyond Day 42, will be considered a DLT. If an Investigator elects to re-treat a subject prior to 28 days (allowed no sooner than on Day 22), the DLT evaluation period will end at the time of initiation of the second cycle of therapy.<br><br>Dose modifications and delays for safety will be performed as described in the protocol. After the first cycle, additional cycles can be administered to individual subjects based on Investigator judgment, if hematopoietic recovery is documented, and may incorporate delays or supportive care until hematopoietic function returns to baseline or Grade ≤1, as long as the subject is receiving clinical benefit without safety or tolerability issues. In the case that failure to achieve hematopoietic recovery is judged to be related to persistent leukemic involvement in the bone marrow, Investigators may re-initiate therapy according to their clinical judgment upon discussion with the Medical Monitor.<br><br>Investigators will also have the option for intra-subject dose escalation in later cycles if safety and tolerability have been demonstrated at higher doses of onvansertib.<br><br>At any time during Phase 1b, the Sponsor, in consultation with the Safety Review Committee (SRC), may elect to discontinue enrollment into either arm of the study based on safety, efficacy, PK, and PD considerations. In this case, enrollment in the other arm will continue as described.<br><br>Following assessment of safety and preliminary efficacy in the first 5 dose level escalation cohorts (0: 12 mg/m$^2$; +1: 18 mg/m$^2$; +2: 27 mg/m$^2$; +3: 40 mg/m$^2$; +4: 60 mg/m$^2$) in both Arm A (onvansertib in combination with low-dose cytarabine) and Arm B (onvansertib in combination with decitabine), the decision was made to discontinue Arm A from further dose escalation and subject enrollment.<br><br>Arm B will continue forward with dose escalation as outlined in the protocol, or until such time as the RP2D is determined at a dose level previously cleared for safety.<br><br>**Phase 2:**<br><br>In Phase 2, a total of 32 subjects will be enrolled at the RP2D to further evaluate safety and preliminary efficacy. Onvansertib will be administered p.o. on Day 1 through Day 5 every 21 to 28 days, in combination with decitabine, administered consistently as 20 mg/m$^2$ IV over 1 hour on Day 1 through Day 5 every 28 days, with treatment modifications or delays based on return of hematopoietic function to baseline or Grade ≤1 toxicity for optimal subject management. The daily dose of decitabine will be |

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| | administered first followed by onvansertib. Investigator assessment of subjects may allow them, at their discretion, to treat more frequently than every 28 days; however, in no case may a cycle length be less than 21 days. Subjects may continue treatment in the study at any dose until clinically significant disease progression or death, unacceptable toxicity, withdrawal of consent, or discontinuation based on Investigator discretion. Any subject becoming pregnant while on the study should be withdrawn from treatment but will remain in the study. After obtaining the subject's consent (or subject and pregnant partner's consent in the case of a male participant), monitoring of the pregnancy should continue until conclusion of the pregnancy. Each subject will be followed for survival for up to 1 year after enrollment.<br><br>AEs and concomitant medication use will be queried, monitored, and recorded throughout the study. Safety evaluations will include: physical examinations, performance status, vital signs, electrocardiograms (ECGs), hematology, and serum chemistry laboratory tests and urinalysis. |
| **Sample Size:** | Phase 1b: up to 84 subjects (42 in each arm), dependent on the number of dose escalation cohorts required to determine the MTD or RP2D<br><br>Phase 2: 32 subjects at the RP2D<br><br>Total: up to 116 subjects |
| **Endpoints:** | Primary safety endpoints:<br><br>1. Characterization of DLTs; characterization of Aes by type, incidence, severity (graded by NCI-CTCAE version 4.03), seriousness, and relationship to treatment effects on vital signs and laboratory parameters; and changes from baseline in ECGs, physical examinations, weight, and ECOG performance status<br><br>Primary efficacy endpoint:<br><br>1. Rate of complete response (CR + Cri) in Phase 2, defined as a morphologic leukemia-free state (MLF; see below) plus:<br><br>For CR:<br><br>a. Subject is independent of transfusions<br><br>b. Absolute neutrophil count (ANC) of >1000/$mm^3$<br><br>c. Platelets of ≥100,000/$mm^3$<br><br>For Cri:<br><br>1. Meets all criteria for CR except for either neutropenia (ANC <1000/$mm^3$) or thrombocytopenia (<100,000/$mm^3$) but must include transfusion independence<br><br>Secondary endpoints: |

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| | 1. Rate of achievement of a MLF in Phase 2, defined as:<br>a. Bone marrow (BM) <5% blasts in an aspirate with spicules (a BM biopsy should be performed if spicules are absent)<br>b. No blasts with Auer rods or persistence of extramedullary disease<br>2. Rate of partial response (PR) in Phase 2: All of the hematologic values for a CR but with a decrease of at least 50% in the percentage of blasts to 5% to 25% in the bone marrow aspirate and a normalization of blood counts as noted above<br>3. Duration of response (DOR) in Phase 2: Time from documentation of response until documentation of recurrence of or progression of disease<br>4. Event-free survival (EFS) in Phase 2: Time from enrollment until disease progression or death from any cause<br>5. Overall survival (OS) in Phase 2: Time from enrollment until death from any cause<br>6. Concentrations of onvansertib in plasma samples collected at pre-specified time points before and after administration of onvansertib, including maximum plasma concentration ($C_{max}$), trough plasma concentration ($C_{min}$), time to maximum plasma concentration ($T_{max}$), area under the plasma concentration versus time curve (AUC), and plasma terminal elimination half-life ($t_{1/2}$)<br>Exploratory endpoints:<br>1. Blood samples for PD and diagnostic biomarker evaluation<br>2. Evaluation of the rate of complete response (CR + CRi), MLF, PR, DOR, EFS and OS in all enrolled subjects (Phases 1b and 2) |
| **Indication:** | Acute myeloid leukemia (AML) |
| **Diagnosis and Main Eligibility Criteria:** | Subjects who meet all of the following inclusion criteria and none of the exclusion criteria will be eligible to be enrolled in the study.<br>Inclusion Criteria:<br>1. Disease Status and Prior Therapy:<br>a. Histologically confirmed diagnosis of AML<br>b. Phase 1b:<br>i. Subjects with relapsed or refractory AML who have received no more than 3 prior treatment regimens for AML. Subjects who have received prior treatment with cytarabine or decitabine are not excluded. Prior treatment with either low-dose cytarabine or decitabine given for MDS will not be considered a prior regimen. For subjects who have undergone hematopoietic stem cell |

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| | transplantation, the preparative (conditioning) regimen and transplant will be considered to be a single line of prior therapy.<br><br>OR<br><br>ii. Subjects who are treatment naïve and are not candidates for or have refused intensive induction therapy.<br><br>c. Phase 2:<br><br>i. Subjects with relapsed or refractory AML who have received no more than one prior treatment regimen for AML. Subjects who have received prior treatment with decitabine are not excluded. Prior treatment with decitabine given for MDS will not be considered a prior regimen.<br><br>OR<br><br>ii. Subjects who are treatment naïve and are not candidates for or have refused intensive induction therapy.<br><br>2. Age ≥18 years<br><br>3. Eastern Cooperative Oncology Group (ECOG) performance status ≤2 (Appendix19.3)<br><br>4. Subjects must be willing and able to review, understand, and provide written consent before starting any study-specific procedures or therapy<br><br>5. All men and women must agree to practice effective contraception during the entire study period and after discontinuing study drug, unless documentation of infertility exists, as follows:<br><br>a. Sexually active, fertile women must use 2 effective forms of contraception (abstinence, intrauterine device, oral contraceptive, or double barrier device) from the time of informed consent and until at least 6 months after discontinuing study drug<br>b. Sexually active men and their sexual partners must use effective contraceptive methods from the time of subject informed consent and until at least 3 months after discontinuing study drug<br><br>Exclusion Criteria:<br><br>1. Treatment-related AML or acute promyelocytic leukemia (APL)<br><br>2. Active malignancies within the last 12 months with the exception of those with a negligible risk of metastasis or death<br><br>3. Clinical evidence of active central nervous system leukemia at the time of screening<br><br>4. Alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) ≥2.5 x upper limit of normal (ULN). |

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| | 5. Total bilirubin >2.0 mg/dL (or >3.0 mg/dL in subjects with documented Gilbert syndrome)<br>6. Serum creatinine ≥2.0 mg/dL<br>7. New York Heart Association (NYHA) Class III or IV heart disease (Appendix 19.2), active ischemia or any other uncontrolled cardiac condition, or hypertensive or metabolic condition<br>8. Myocardial infarction in the previous 12 weeks (from the start of treatment)<br>9. Resting left ventricular ejection fraction <50% at the time of screening<br>10. QT interval with Fridericia's correction [QTcF] [16] >450 milliseconds for men, or >470 milliseconds for women. The QTcF should be calculated as the arithmetic mean of the QTcF on triplicate ECGs. In the case of potentially correctible causes of QT prolongation (eg, medications, hypokalemia), the triplicate ECG may be repeated once during screening and that result may be used to determine eligibility.<br>11. Pregnant or breast feeding<br>12. Active and uncontrolled disease (other than AML) or infection as judged by the treating physician<br>13. Treatment with systemic therapy for the primary disease within 14 days of first dose (except for hydroxyurea or isolated doses of cytarabine or decitabine for white blood cell control)<br>14. Grade 2 or greater toxicities from prior therapy, except for Grade 2 toxicities that are not expected to resolve and that in the judgment of the Investigator do not pose a significant safety risk to subject participation.<br>15. Subjects with any other medical condition, including mental illness or substance abuse, deemed by the Investigator to be likely to interfere with the subject's ability to sign the informed consent form or his/her ability to cooperate and participate in the study, or to interfere with the interpretation of the results. |
| **Test Product, Dose, and Mode of Administration:** | **Onvansertib (PCM-075):** The Phase 1b onvansertib starting dose is 12 mg/m$^2$ (Dose Level 0) administered p.o. on Day 1 through Day 5 every 28 days. Dose escalation is discussed in detail in the protocol. In Phase 2, onvansertib will be administered at the MTD (or RP2D) p.o. on Day 1 through Day 5 every 21 to 28 days. Investigator assessment of subjects may allow them, at their discretion, to treat more frequently than every 28 days; however, in no case may a cycle length be less than 21 days. Day 1 of onvansertib therapy should always be Day 1 of either cytarabine or decitabine therapy in all cycles. |

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| | **Cytarabine:** 20 mg/m$^2$ SC once daily on Day 1 through Day 10 every 28 days in Phase 1b. On days where both agents are administered (Days 1-5), cytarabine will be administered first followed by onvansertib.<br><br>**Decitabine:** 20 mg/m$^2$ IV over 1 hour on Day 1 through Day 5 every 21 to 28 days in Phase 1b. Based on the RP2D combination determined in Phase 1b, decitabine will be given in combination with onvansertib in Phase 2. The daily dose of decitabine will be administered first followed by onvansertib. |
| **Efficacy Evaluation:** | Efficacy Assessments<br><br>All subjects evaluable for anti-leukemic activity will be assessed for response to treatment using the recommendations of the International Working Group (IWG) for standardization of response criteria, treatment outcomes, and reporting for therapeutic trials. [17] The primary efficacy variable is leukemia responses, evaluated by the Investigator based on bone marrow aspirate and peripheral blood examination.<br><br>Efficacy Endpoints [18]:<br><br>1. Morphologic leukemia-free state<br>a. BM <5% blasts in an aspirate with spicules (a BM biopsy should be performed if spicules are absent)<br>b. No blasts with Auer rods or persistence of extramedullary disease<br>2. Complete response (CR):<br>a. Morphologic leukemia-free state plus:<br>i. Subject is independent of transfusions<br>ii. Absolute neutrophil count (ANC) of >1000/mm$^3$<br>iii. Platelets of ≥100,000/mm$^3$<br>3. Complete response with incomplete blood count recovery (CRi) meets all criteria for CR except for either neutropenia (ANC <1000/mm$^3$) or thrombocytopenia (<100,000/mm$^3$) but must include transfusion independence<br>4. Partial response (PR): All of the hematologic values for a CR but with a decrease of at least 50% in the percentage of blasts to 5% to 25% in the bone marrow aspirate and a normalization of blood counts as noted above<br>5. Duration of response (DOR): Time from documentation of response until documentation of recurrence of or progression of disease<br>6. Event-free survival (EFS): Time from enrollment until disease progression or death from any cause |

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| | 7. Overall survival (OS): Time from enrollment until death from any cause |
| **Safety Evaluation:** | Toxicity will be graded using the NCI-CTCAE version 4.03<br>**1.** Safety analyses will be conducted on all subjects who have received at least 1 dose of study drug, and will include the frequency of all AEs and laboratory abnormalities as well as the frequency of dose interruptions, dose reductions, and treatment discontinuations. **All AEs must be attributed to study drugs unless there is a reasonably acceptable alternate cause for the AEs.**<br>2. In each phase of the study, DLTs will be considered to be any non-hematologic Grade 3 abnormalities that persist >7 days without decreasing in severity despite standards of care, are clinically significant, or that are Grade 4 and symptomatic. Exceptions and additional parameters for assessment of non-hematologic DLT are provided in the protocol. For hematologic toxicities, only persistent pancytopenia resistant to current standards of care that continues for ≥42 days and is not related to leukemic infiltration or another cause judged to be unrelated to study therapy will be considered as a DLT, since marrow aplasia is an expected consequence of AML therapy.<br>3. Additional safety assessments will include physical examination; medical history; ECG; ECOG performance status; weight; vital signs measurements; clinical laboratory testing (hematology, clinical chemistry, and urinalysis) and multigated acquisition (MUGA) or echocardiography (ECHO) scans |
| **Safety Monitoring:** | The SRC consisting of the Principal Investigators and Medical Monitor, will monitor subjects for safety and evaluate the efficacy of onvansertib doses to minimize exposure of subjects to a non-efficacious dose level. |
| **Pharmacokinetic Evaluation:** | Blood samples for PK analysis of onvansertib will be collected pre-dose, and 0.5, 1, 2, 3, 4, 8, (±10 minutes) and 24 hours (±1 hour) after administration of onvansertib on Day 1 and Day 5, as well as once each on Days 8, 15, and 22 (Cycle 1 only). For Cycle 2, blood samples for PK analysis should be collected, if feasible, pre-dose, 3 hours, and 24 hours (all ±10 minutes) after administration of onvansertib on Days 1 and 5, and once each on Days 8, 15, and 22. |
| **Pharmacodynamic and Diagnostic Biomarker Evaluation:** | Pharmacodynamic and diagnostic biomarker analysis will be obtained, if feasible, pre-dose, 3 hours (±10 minutes), and 24 hours (±1 hour) after administration of onvansertib on Days 1 and 5, and once each on Days 8, 15, and 22 (Cycles 1-3). For Cycle 4 and beyond, samples will be collected on Days 1 (pre-dose) and 15. The schedule for obtaining these may be amended based on results of prior evaluations. |
| **Statistical Methods:** | **Safety Analysis:** |

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| | Safety assessment data for all subjects who receive at least one dose of study drug will be listed and summarized and will include data from AEs and concomitant medication queries, physical examination findings, ECOG performance status, weight and vital signs measurements, ECG measurements, and clinical laboratory testing (hematology, clinical chemistry, and urinalysis) values. Descriptive statistics will be generated as appropriate (eg, mean, median, range, and SD for continuous data; and frequency for categorical data).<br><br>**Efficacy Analysis:**<br><br>Data from all subjects who receive at least 1 dose of onvansertib in combination therapy will be included in the intention-to-treat (ITT) efficacy analysis. Subjects completing at least 1 cycle of treatment will be included in the per protocol efficacy analysis.<br><br>Descriptive statistics will be generated as appropriate (ie, mean, median, range, and SD). Median survival statistics will be estimated using the Kaplan-Meier method.<br><br>The primary efficacy endpoint is the rate of CR + CRi in the Phase 2 portion of the study. Based on a population CR + CRi rate of 20% for either the combination of cytarabine plus onvansertib or decitabine plus onvansertib, with 32 evaluable patients in the primary analysis the 90% CI for the CR + CRi rate from the study will have an estimated precision of approximately 58% and width 0.23, and a 95% CI would have an estimated precision of approximately 70% and width 0.28.<br><br>**Pharmacokinetic Analysis:**<br><br>PK parameters of the population defined in the Statistical Analysis Plan will include maximum concentration ($C_{max}$), time of maximum concentration ($T_{max}$), area under the curve over the first 24 hours ($AUC_{0-24}$), and drug elimination half-life ($t_{1/2}$), which will be estimated from plasma concentration data. The geometric mean and 95% CIs will be reported for all evaluable subjects. |
| **Sample Size Rationale:** | Exposure of any subject at the starting dose, based on prior experience with this drug in patients with solid tumors (Section 6.1.3) with exclusively hematologic toxicities that are required in the treatment of patients with AML, is reasonable in Phase 1b for a dose that has the potential for efficacy based on preclinical modeling. The 3+3 design will allow a dose with a ≥50% probability of causing a DLT to have at most a 12.5% chance of satisfying the conditions for dose escalation after the first 3 subjects and a ≥50% chance of stopping at 3. With 6 subjects, there is at most a 17.2% chance of satisfying the conditions for dose escalation after 6 subjects.<br><br>Phase 2 will proceed with a total of 32 subjects at the identified RP2D; however, if at any time during this phase more than 33% of subjects develop |

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| | a DLT-level AE (as per protocol), accrual will stop and the RP2D will be reassessed in additional cohorts. |

# 4 LIST OF ABBREVIATIONS

| Abbreviation | Definition |
|---|---|
| AE | Adverse Event |
| ALP | Alkaline Phosphatase |
| ALT | Alanine Aminotransferase |
| AML | Acute Myeloid Leukemia |
| ANC | Absolute Neutrophil Count |
| APC/C | Anaphase-promoting Complex/Cyclosome |
| APL | Acute Promyelocytic Leukemia |
| ASCO | American Society of Clinical Oncology |
| ASH | American Society of Hematology |
| AST | Aspartate Aminotransferase |
| AUC | Area under the plasma concentration vs time curve |
| BM | Bone Marrow |
| BSA | Body Surface Area |
| BUN | Blood Urea Nitrogen |
| CBC | Complete Blood Count |
| CFR | Code of Federal Regulations |
| $C_{max}$ | Maximum plasma concentration |
| $C_{min}$ | Trough plasma concentration |
| CR | Complete Response |
| CRF | Case Report Form |
| CRi | Complete Response with Incomplete Blood Count Recovery |
| CTCAE | Common Terminology Criteria for Adverse Events |
| DLT | Dose-limiting Toxicity |
| DOR | Duration of Response |
| ECG | Electrocardiogram |
| ECHO | Echocardiography |
| ECOG | Eastern Cooperative Oncology Group |
| eCRF | Electronic CRF |
| EFS | Event-free Survival |
| EOS | End of Study |
| FDA | Food and Drug Administration |

| Abbreviation | Definition |
|---|---|
| GCP | Good Clinical Practice |
| HI | Hematologic Improvement |
| HIPAA | Health Insurance Portability and Accountability Act |
| HMA | Hypomethylating Agent |
| IB | Investigator's Brochure |
| ICF | Informed Consent Form |
| ICH | International Council for Harmonisation |
| IEC | Independent Ethics Committee |
| IND | Investigational New Drug |
| INR | International Normalized Ratio |
| IRB | Institutional Review Board |
| ITT | Intention-to-Treat |
| IV | Intravenous(ly) |
| IWG | International working group |
| LDAC | Low-dose Ara-C |
| LDH | Lactate Dehydrogenase |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MDS | Myelodysplastic Syndromes |
| MLF | Morphologic Leukemia-Free State |
| MTD | Maximum Tolerated Dose |
| MUGA | Multigated Acquisition Scan |
| NCI | National Cancer Institute |
| NYHA | New York Heart Association |
| OS | Overall Survival |
| PD | Pharmacodynamics |
| PHI | Protected Health Information |
| PK | Pharmacokinetics |
| PLK1 | Polo-Like Kinase 1 |
| p.o. | Orally or By Mouth |
| PR | Partial Response |
| RP2D | Recommended Phase 2 Dose |

| Abbreviation | Definition |
|---|---|
| QT | Interval from the beginning of the QRS complex to the end of the T wave on an electrocardiogram |
| QTcF | QT interval with Fridericia's correction |
| SAE | Serious Adverse Event |
| SAP | Statistical Analysis Plan |
| SC | Subcutaneous(ly) |
| SCT | Stem Cell Transplant |
| SEER | Surveillance, Epidemiology, and End Results |
| SRC | Safety Review Committee |
| $t_{1/2}$ | Half-life |
| $T_{max}$ | Time to maximum plasma concentration |
| TdP | Torsade de pointes |
| ULN | Upper Limit of Normal |

# 5 ADMINISTRATIVE STRUCTURE

| | |
|---|---|
| Coordinating Investigator: | [redacted] |
| Contract Research Organization (CRO): | PRA Health Sciences |
| Medical Monitor: | [redacted] |

# 6 INTRODUCTION

## 6.1 Background

### 6.1.1 Acute Myeloid Leukemia

Acute myeloid leukemia (AML) is a hematologic malignancy in which myeloid lineage cells of the bone marrow cease to differentiate appropriately, resulting in a marked increase in the number of circulating immature blast cells. As a consequence, the counts of mature red blood cells, platelets, and normal white blood cells decline, causing fatigue, shortness of breath, bleeding, and increased susceptibility to infection.[1] The Surveillance, Epidemiology, and End Results (SEER) program estimates the annual incidence rate of AML in the US to be approximately 21,000 cases in 2017.[2] Rates of new AML cases have been rising an average of 3.1% each year over the last 10 years. The median age of AML diagnosis is 68 years of age, and approximately 45% of new diagnoses are among patients age 70 years or older. [3]

Treatment options for AML patients are limited and vary depending on the age and fitness of the patient.[4] Typically, patients 60 to 65 years of age or younger undergo induction chemotherapy using a combination of the nucleoside analog cytarabine and an anthracycline (either daunorubicin or idarubicin), a regimen commonly referred to as "7+3" because the administration of the therapies consists of 7 consecutive days of cytarabine intravenous (IV) infusion followed by 3 consecutive days of anthracycline IV bolus; each cycle of 7+3 therapy is 28 days in duration and can be repeated. Complete remission is defined as <5% blast cells in the bone marrow, with recovery of neutrophils to $\geq 10^9$/L and platelets to $\geq 100 \times 10^9$/L within 1 to 2 cycles of induction chemotherapy. Patients then have follow-up consolidation therapy with high-dose cytarabine for 3 to 4 cycles and, when feasible, either an autologous or allogeneic stem cell transplant (SCT). Because of the intensity of this approach, induction therapy as a means to transplant is less frequently adopted for patients over 60 to 65 years of age, although patients over 60 to 65 years of age can be considered for transplant (usually with reduced intensity conditioning regimens) based on other factors suggesting that they will survive the treatment regimen. Thus, despite 7+3 having been the standard first-line treatment for AML for over 30 years, better therapies for all patients are urgently needed, and this need is particularly critical for elderly or frailer patients. [5]

As an alternative to the standard cytotoxic chemotherapy, older patients are most frequently treated with lower-intensity options including hypomethylating agents (HMAs), such as 5'-azacitidine (Vidaza®) and decitabine (Dacogen™) or antimetabolites such as cytosine arabinoside (also referred to as cytarabine or Ara-C) given at a low-dose commonly known as low-dose Ara-C (LDAC). These agents have demonstrated a survival benefit compared to best supportive care in elderly AML patients. However, when these drugs are used as single-agents, AML relapses are inevitable and generally occur within 12 months.

Clearly, new and better therapeutic options are urgently required for AML, supporting the current study exploring onvansertib (PCM-075), a polo-like kinase 1 (PLK1) inhibitor, in patients with refractory or relapsed AML.

### 6.1.2 Polo-like Kinase 1

Polo-like kinase 1 is the most well characterized member of the 5 members of the family of serine/threonine protein kinases and strongly promotes the progression of cells through mitosis. PLK1 performs several important functions throughout mitotic (M) phase of the cell cycle, including the regulation of centrosome maturation and spindle assembly, the removal of cohesins from chromosome arms, the inactivation of anaphase-promoting complex/cyclosome (APC/C) inhibitors, and the regulation of mitotic exit and cytokinesis. [6] It plays a key role in centrosome functions and the assembly of bipolar spindles. It also acts as a negative regulator of p53 family members leading to ubiquitination and subsequent degradation of p53/TP53, inhibition of the p73/TP73 mediated pro-apoptotic functions and phosphorylation/degradation of bora, a cofactor of Aurora kinase A. During the various stages of mitosis, PLK1 localizes to the centrosomes, kinetochores, and central spindle. PLK1 is aberrantly overexpressed in a variety of human cancers including AML and is correlated with cellular proliferation and poor prognosis. [7] The first PLK1 inhibitor, BI 2536, showed interesting clinical activity in patients with relapsed and treatment refractory AML in an early clinical study, and its successor volasertib (also known as BI 6727) demonstrated a more favorable toxicity profile, as well as potent anti-leukemic activity as monotherapy and in combination with LDAC in heavily pretreated AML patients. [8, 9, 10] In 2013, volasertib received a Breakthrough Therapy designation from the Food and Drug Administration (FDA) for its potential as a treatment for patients with untreated AML who are ineligible for intensive remission induction therapy.

### 6.1.3 Onvansertib (PCM-075)

Onvansertib (also known as PCM-075 and NMS-1286937) is the first PLK1-specific ATP competitive inhibitor administered by oral route to enter clinical trials with proven antitumor activity in different preclinical models. [11, 12, 13, 14, 15] The compound shows high potency in proliferation assays having low nanomolar activity on a large number of cell lines, both from solid as well as hematologic tumors. Onvansertib potently causes a mitotic cell-cycle arrest followed by apoptosis in cancer cell lines and inhibits xenograft tumor growth with a clear PLK1-related mechanism of action at well tolerated doses in mice after oral administration. In addition, onvansertib shows activity in combination therapy with approved cytotoxic drugs, such as irinotecan, in which there is enhanced tumor regression in HT29 human colon adenocarcinoma xenografts compared to each agent alone, and shows prolonged survival of animals in a disseminated model of AML in combination therapy with cytarabine. Onvansertib has favorable pharmacologic parameters and good oral bioavailability in rodent and nonrodent species, as well as proven antitumor activity in different nonclinical models using a variety of dosing regimens, which may potentially provide a high degree of flexibility in dosing schedules, warranting investigation in clinical settings. Onvansertib has several advantages over volasertib, including a higher degree of potency and specificity for the PLK1 isozyme, and oral bioavailability.

To date, a single Phase 1 dose-escalation safety study with onvansertib has been completed in adult subjects with advanced/metastatic solid tumors at a single study site in the US. The

primary objective of that study was to determine first-cycle dose-limiting toxicities (DLT) and maximum tolerated dose (MTD) of onvansertib administered p.o. for 5 consecutive days every 3 weeks (ie, 21-day treatment cycle) in adult subjects with advanced/metastatic solid tumors. Secondary objectives of the study were to define the safety profile of onvansertib, determine the pharmacokinetics (PK) of onvansertib in plasma (at the MTD), and document any antitumor activity.

A total of 21 subjects were enrolled in the Phase 1 study, and 19 subjects were treated. Four dose levels were explored: 6 mg/m$^2$/day (4 subjects enrolled, 3 treated), 12 mg/m$^2$/day (3 subjects treated), 24 mg/m$^2$/day (6 subjects treated), 48 mg/m$^2$/day (4 subjects enrolled, 3 subjects treated), and 36 mg/m$^2$/day (4 subjects treated).

The PK parameters of onvansertib showed that the systemic exposure to onvansertib was generally higher on Day 5 than after the first administration on Day 1, with a terminal half-life ranging between 20 to 30 hours. Following the second cycle of treatment, the systemic exposure appeared to be similar to that in the first cycle, suggesting comparable exposure to the onvansertib in the 2 treatment cycles.

In onvansertib subjects with ≥1 on-treatment safety assessment (as of the cut-off date of 18 Dec 2013), no DLT occurred at the first 3 dose levels of 6, 12, and 24 mg/m$^2$/day. No patients experienced myelosuppression of any grade, defined as thrombocytopenia, leukopenia, neutropenia, or thrombocytopenia, at the 6 mg/m$^2$ or 12 mg/m$^2$ dose levels, and a single patient (1/6) developed thrombocytopenia at the 24 mg/m$^2$ dose level. At the subsequent dose level of 48 mg/m$^2$/day, 2 of the 3 subjects treated developed a first-cycle DLT: in 1 subject, a decrease in platelets to Grade 4 and an absolute neutrophil count (ANC) to Grade 4 lasted >7 days, and both events were considered by the Investigator to be not related to onvansertib; in the second subject, who was also receiving opiates, Grade 3 constipation was judged by the Investigator to be possibly related to onvansertib. At the 48 mg/m$^2$/day dose level, the MTD was considered to have been exceeded and an intermediate dose level of 36 mg/m$^2$/day was investigated.

Four subjects were treated at the 36 mg/m$^2$/day dose level. Two of the 4 subjects had DLT following 5 days of treatment with onvansertib:

- One subject had DLT of thrombocytopenia Grade 4 (platelet count <25,000/mm$^3$) and neutropenia Grade 4 (ANC <500/mm$^3$ for >7 days). Vitamin K and platelet transfusions were given to treat thrombocytopenia, and granulocyte colony-stimulating factor was administered for neutropenia. The subject demonstrated complete recovery of neutrophil and platelet counts to within normal limits within 10 days.
- In a second subject, a DLT of thrombocytopenia Grade 4 (platelet count <25,000/mm$^3$) was observed. Following platelet transfusion, the subject's platelet level recovered to Grade 1.

Treatment-emergent abnormalities in hematology tests included lymphopenia (84.2%, 36.8%; Grade 3-4), neutropenia (52.6%, 21%; Grade 3-4), anemia (36.8%, 10.5%; Grade 3-4), thrombocytopenia (31.6%, 15.8%; Grade 3-4) and leukopenia (26.3%, 21.0%; Grade 3-4).

Treatment-emergent abnormalities were dose-dependent and mostly mild to moderate in severity except for 4 cases of neutropenia and leukopenia Grade 4, 3 cases of thrombocytopenia Grade 4, and 4 cases of lymphopenia Grade 4. At baseline all of these patients had Grade 1 to 2 hematological toxicities with the exception of 2 patients with lymphopenia Grade 3. During Cycle 1, median time to anemia, thrombocytopenia, leukopenia, neutropenia, and lymphocytopenia nadir was 10, 14.5, 15, 15, and 13 days, respectively. Median time to recovery from nadir was 3.5 days for hemoglobin, 7 days for platelets, 7 days for white blood cells, 6.5 days for neutrophils, and 7.5 days for lymphocytes. Some of the hematological abnormalities detected were also reported as adverse events (AEs) related to study medication, in particular: thrombocytopenia (4 patients, 21.1%, Grade 4 in 3 cases), neutropenia (3 patients, 15.8% all Grade 4), anemia and leukopenia (2 patients each, 10.5%, Grade 3 in both cases).

Treatment-emergent abnormalities of blood chemistry parameters were mostly of Grade ≤2 severity. Grade 3 abnormalities included: 2 cases of hypoalbuminemia in patients with renal metastases and a Grade 1 or Grade 2 value at baseline; 2 cases of increase in alkaline phosphatase (ALP) in 2 patients who already had a Grade 2 value at baseline; 1 case of hyponatremia in one patient with a borderline Grade 3 value (129 mmol/L); 1 case of increase in aspartate aminotransferase (AST) and alanine aminotransferase (ALT), 1 case of increase in lipase and 1 case of hypophosphatemia in one patient each. Only 1 case of increase in ALP Grade 4 was recorded in 1 patient, who had already presented with a Grade 3 value at baseline, likely tumor-related. Only ALT Grade 3 and AST Grade 3, recorded in 1 patient treated at 12 mg/m$^2$, were judged drug related by the Investigator.

Hematological toxicity was dose-limiting at doses of 48 mg/m$^2$/day for 5 consecutive days every 3 weeks. At the 48 mg/m$^2$/day dose level, serious adverse events (SAEs) of thrombocytopenia Grade 4 and leukopenia Grade 4 occurred in 1 subject and at 36 mg/m$^2$/day, thrombocytopenia Grade 4 and neutropenia Grade 4 occurred in 1 subject. No other relevant toxicities were observed during the study. Recovery for both platelets and ANC (even without colony-stimulating factors support) was prompt, being generally achieved in 1 to 2 weeks.

A summary of Drug-related Treatment-emergent AEs by dose level is provided in

Table 6-1 below.

## Table 6-1: Drug-related Treatment-emergent AEs

| MS-1286937H PO, Days 1-5, q 3 weeks | | Assigned Dose Level (mg/m²/day) | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Any Dose Level (N=19) | | 6 (N=3) | | 12 (N=3) | | 24 (N=6) | | 36 (N=4) | | 48 (n=3) | |
| | | n | % | n | % | n | % | n | % | n | % | n | % |
| **Preferred Term** | **CTC Grade** | | | | | | | | | | | | |
| Any Term | 1–4 | 11 | 57.9 | 2 | 66.7 | 2 | 66.7 | 2 | 33.3 | 3 | 75.0 | 2 | 66.7 |
| | 3–4 | 7 | 36.8 | | | 1 | 33.3 | 1 | 16.7 | 3 | 75.0 | 2 | 66.7 |
| Thrombocytopenia | 1–4 | 4 | 21.1 | | | | | 1 | 16.7 | 2 | 50.0 | 1 | 33.3 |
| | 3–4 | 3 | 15.8 | | | | | | | 2 | 50.0 | 1 | 33.3 |
| Hypokalemia | 1–4 | 3 | 15.8 | 1 | 33.3 | 1 | 33.3 | | | | | 1 | 33.3 |
| Neutropenia | 1–4 | 3 | 15.8 | | | | | | | 2 | 50.0 | 1 | 33.3 |
| | 3–4 | 3 | 15.8 | | | | | | | 2 | 50.0 | 1 | 33.3 |
| Anemia NOS | 1–4 | 2 | 10.5 | | | | | | | 1 | 25.0 | 1 | 33.3 |
| | 3–4 | 2 | 10.5 | | | | | | | 1 | 25.0 | 1 | 33.3 |
| **MS-1286937H PO, Days 1-5 q 3 weeks** | | **Assigned Dose Level (mg/m²/day)** | | | | | | | | | | | |
| | | **Any Dose Level (N=19)** | | **6 (N=3)** | | **12 (N=3)** | | **24 (N=6)** | | **36 (N=4)** | | **48 (n=3)** | |
| | | **n** | **%** | **n** | **%** | **n** | **%** | **n** | **%** | **n** | **%** | **n** | **%** |
| **Preferred Term** | **CTC Grade** | | | | | | | | | | | | |
| Aspartate aminotransferase elevation | 1–4 | 2 | 10.5 | 1 | 33.3 | 1 | 33.3 | | | | | | |
| | 3–4 | 1 | 5.3 | | | 1 | 33.3 | | | | | | |
| Hypocalcemia | 1–4 | 2 | 10.5 | 1 | 33.3 | | | | | | | 1 | 33.3 |
| Hypophosphataemia | 1–4 | 2 | 10.5 | | | 1 | 33.3 | 1 | 16.7 | | | | |
| | 3–4 | 1 | 5.3 | | | | | 1 | 16.7 | | | | |
| Leukopenia NOS | 1–4 | 2 | 10.5 | | | | | | | 1 | 25.0 | 1 | 33.3 |
| | 3–4 | 2 | 10.5 | | | | | | | 1 | 25.0 | 1 | 33.3 |
| Nausea | 1–4 | 2 | 10.5 | 1 | 33.3 | | | | | | | 1 | 33.3 |
| Alanine aminotransferase elevation | 1–4 | 1 | 5.3 | | | 1 | 33.3 | | | | | | |
| | 3–4 | 1 | 5.3 | | | 1 | 33.3 | | | | | | |
| Cholecystitis NOS | 1–4 | 1 | 5.3 | | | | | | | | | 1 | 33.3 |
| | 3–4 | 1 | 5.3 | | | | | | | | | 1 | 33.3 |
| Constipation | 1–4 | 1 | 5.3 | | | | | | | | | 1 | 33.3 |
| | 3–4 | 1 | 5.3 | | | | | | | | | 1 | 33.3 |
| Hyponatremia | 1–4 | 1 | 5.3 | 1 | 33.3 | | | | | | | | |
| Hypoxia | 1–4 | 1 | 5.3 | | | | | | | 1 | 25.0 | | |
| | 3–4 | 1 | 5.3 | | | | | | | 1 | 25.0 | | |
| Lymphocyte percentage elevation | 1–4 | 1 | 5.3 | | | | | | | | | 1 | 33.3 |
| | 3–4 | 1 | 5.3 | | | | | | | | | 1 | 33.3 |
| Pneumonia NOS | 1–4 | 1 | 5.3 | | | | | | | | | 1 | 33.3 |
| | 3–4 | 1 | 5.3 | | | | | | | | | 1 | 33.3 |
| White blood cell decrease | 1–4 | 1 | 5.3 | | | | | | | | | 1 | 33.3 |
| | 3–4 | 1 | 5.3 | | | | | | | | | 1 | 33.3 |

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| White blood cell count elevation | 1–4 | 1 | 5.3 | | | | | | | | | 1 | 33.3 |
| | 3–4 | 1 | 5.3 | | | | | | | | | 1 | 33.3 |

Source: CSR PLKA-937-001 (Appendix 19.5)

Further details regarding the nonclinical and clinical studies of onvansertib are provided in the onvansertib Investigator's Brochure (IB). In addition, the current cytarabine and decitabine package inserts provide a description of the AEs that can be expected with their administration (Appendix 19.4).

## 6.2 Study and Dose Rationale

There is an urgent unmet medical need of subjects who have relapsed after or not responded to therapy for AML. Based on the body of data with therapies targeting PLK, there appears to be potential clinical benefit for subjects with AML. The aim of this study is to explore treatment with onvansertib in combination with either low-dose cytarabine or decitabine in subjects with AML. The onvansertib starting dose will be 12 mg/m$^2$ based on results from the Phase 1 study PLKA-937-001. In that study, a dose of 12 mg/m$^2$ p.o. daily for 5 days was evaluated during dose escalation, and was not associated with myelosuppression of any grade.

## 6.3 Risks and Benefits for Subjects

The current safety clinical profile of onvansertib in treated subjects indicates that hematological toxicity (thrombocytopenia and neutropenia) is the most relevant toxicity of treatment. Recovery from hematologic toxicity was prompt in all reported subject cases, occurring in 1 to 2 weeks from the onset, even without colony-stimulating factor support. Therefore, the toxicity of onvansertib appears to be manageable with conventional treatments. No other relevant toxicities were observed during the study

Clinical data with a compound similar to onvansertib (ie, volasertib) in combination therapy produced promising results for subjects with AML. Onvansertib has several advantages over volasertib, including oral bioavailability and a higher degree of potency and specificity for the PLK1 isozyme. In a Phase 1 clinical study, onvansertib demonstrated a safety profile that was manageable, with transient AEs that were related to the drug's mechanism of action.

# 7 STUDY OBJECTIVES

## 7.1 Primary Objectives

Phase 1b:

- To evaluate the DLTs and MTD, or Recommended Phase 2 Dose (RP2D), of onvansertib (PCM-075) in combination with either low-dose cytarabine or decitabine in subjects with AML

Phase 2:

- To assess the safety and tolerability of the combination of onvansertib (PCM-075) at the MTD (or RP2D) and low-dose cytarabine, or the combination of onvansertib (PCM-075) at the MTD (or RP2D) and decitabine in subjects with AML
- To evaluate the preliminary anti-leukemic activity of the combination of onvansertib (PCM-075) at the MTD (or RP2D) and low-dose cytarabine, or the combination of onvansertib (PCM-075) at the MTD (or RP2D) and decitabine in subjects with AML

## 7.2 Secondary Objectives

Phase 1b:

- To assess the incidence and severity of AEs according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE, version 4.03) of onvansertib (PCM-075) in combination with either low-dose cytarabine or decitabine in subjects with AML
- To analyze the PK of onvansertib (PCM-075) when given in combination with either low-dose cytarabine or decitabine in subjects with AML

Phase 2:

- To assess the incidence and severity of AEs according to the NCI-CTCAE version 4.03 of onvansertib (PCM-075) in combination with either low-dose cytarabine or decitabine in subjects with AML
- To analyze the PK of onvansertib (PCM-075) when given in combination with either low-dose cytarabine or decitabine in subjects with AML

## 7.3 Exploratory Objectives

Phase 1b and Phase 2:

- To explore additional analyses evaluating potential pharmacodynamic (PD) and diagnostic biomarkers of onvansertib (PCM-075) in subjects with AML

# 8 INVESTIGATIONAL PLAN

## 8.1 Overall Study Design and Plan

This is a Phase 1b/2, open-label study of the safety and anti-leukemic activity of onvansertib in combination with either low-dose cytarabine or decitabine in subjects with AML.

In Phase 1b, subjects will have relapsed or refractory disease and must have received no more than 3 prior regimens for the treatment of their AML. Subjects may be treatment naïve as long as they are not candidates for or have refused intensive induction therapy.

In Phase 2, subjects must have received no more than one prior regimen for the treatment of their AML. Subjects may be treatment naïve as long as they are not candidates for or have refused intensive induction therapy.

In both phases, prior treatment with either low-dose cytarabine or decitabine for myelodysplastic syndromes (MDS) will not be considered a prior regimen. For subjects who have undergone hematopoietic stem cell transplantation, the preparative (conditioning) regimen and transplant will be considered to be a single line of prior therapy.

### 8.1.1 Phase 1b

Phase 1b will be conducted in 2 arms of subjects allocated to receive either a combination of onvansertib and low-dose cytarabine, or a combination of onvansertib and decitabine.

#### *8.1.1.1 Combination Treatment Arms*

In Arm A, onvansertib will be administered p.o. Day 1 through Day 5 every 21 to 28 days in combination with cytarabine which will be administered in all cohorts as 20 mg/m$^2$ subcutaneously (SC) once daily on Day 1 through Day 10 every 28 days. The starting dose of onvansertib in combination with cytarabine, will be 12 mg/m$^2$ p.o. daily for 5 days (Dose Level 0). On days where both agents are administered (Days 1-5), cytarabine will be administered first followed by onvansertib. Investigator assessment of subjects may allow them, at their discretion, to treat more frequently than every 28 days; however, in no case may a cycle length be less than 21 days.

In Arm B, onvansertib will be administered orally (p.o.) Day 1 through Day 5 every 21 to 28 days in combination with decitabine, which will be administered consistently in all cohorts as 20 mg/m$^2$ IV over 1 hour on Day 1 through Day 5 every 28 days. Onvansertib administration, in combination with decitabine, will be initiated at a starting dose of 12 mg/m$^2$ (Dose Level 0). The daily dose of decitabine will be administered first followed by onvansertib. Investigator assessment of subjects may allow them, at their discretion, to treat more frequently than every 28 days; however, in no case may a cycle length be less than 21 days.

The first 3 subjects will be allocated to Arm A (Cohort A1). If Cohort A1 is expanded to 6 subjects prior to the first subject being enrolled in Arm B, then enrollment in Cohort A1 will be completed before enrollment begins in Arm B.

After all subjects are enrolled in Cohorts A1 and B1, subjects will enroll in subsequent cohorts based on the following decision rules:

- If Arm A is open for enrollment, subjects will enroll in the open Arm A cohort regardless of dose level
- If Arm A is closed to enrollment, subjects will enroll in the open Arm B cohort regardless of dose level

#### *8.1.1.2 Dose Escalation*

Dosing in each arm will proceed independently. Each arm will follow a standard 3+3 dose-escalation design in which the onvansertib dose will be escalated by 50% increments in successive cohorts of 3 subjects (Table 8-1). If none of the 3 subjects enrolled at any dose level experience a DLT, the dose of onvansertib will be escalated by 1 dose level in each successive cohort. If 1 subject in the first 3 experiences a DLT, up to 3 additional subjects will be enrolled at that dose level. If there are no additional DLTs (ie, ≤1 of 6 subjects with DLT), then dose escalation will again proceed. If there are 2 subjects who experience DLTs among the first 3 subjects enrolled, or there is a second DLT in up to 6 subjects enrolled at any dose level, the MTD will be judged to have been exceeded and no additional subjects will be started at that dose. The MTD will then be established at a prior dose level or an additional cohort may be enrolled at an intermediate dose level upon agreement with the Sponsor, Medical Monitor, and Principal Investigator.

The RP2D can be determined based on the assessment of safety, PK, PD, and preliminary efficacy of subjects treated at a dose level that has been cleared for safety, regardless of whether or not an MTD has been reached. In this case, no further dose escalation will be done to determine an MTD.

Each cohort will be evaluated for toxicity, recovery of blood counts, and PK. DLTs will be evaluated for the first 28 days after initiation of therapy. In the case of pancytopenia present at Day 28 in the absence of other toxicity that constitutes a DLT, the duration for DLT evaluation will be extended to 42 days (unless the pancytopenia resolves between Days 28 and 42, or is determined to be due to persistent leukemic involvement of the bone marrow or another cause unrelated to study therapy). Pancytopenia in the absence of another cause unrelated to study therapy that persists beyond Day 42 will be considered a DLT. If an Investigator elects to re-treat a subject prior to 28 days (allowed no sooner than on Day 22), the DLT evaluation period will end at the time of initiation of the second cycle therapy. Dose modifications and delays for safety will be performed as described in the protocol. After the first cycle, additional cycles can be administered to individual subjects based on Investigator judgment if hematopoietic recovery is documented, and may incorporate delays or supportive care until hematopoietic function returns to baseline or Grade ≤1, as long as the subject is receiving clinical benefit without safety or tolerability issues. In the case that failure to achieve hematopoietic recovery is judged to be related to persistent leukemic involvement in the bone marrow, Investigators may re-initiate therapy according to their clinical judgment upon discussion with the Medical Monitor.

Investigators will also have the option for intra-subject dose escalation in later cycles if safety and tolerability have been demonstrated at higher doses of onvansertib.

At any time during Phase 1b, the Sponsor, in consultation with the Safety Review Committee (SRC), may elect to discontinue enrollment into either arm of the study based on safety, efficacy, PK, and PD considerations. In this case, enrollment in the other arm will continue as described.

**Table 8-1: Onvansertib (PCM-075) Dose and Dosing Levels**

| Dose Level | Dose* |
|---|---|
| -1 | 6 mg/m$^2$ |
| **0 (Initial dose)** | **12 mg/m$^2$** |
| +1 | 18 mg/m$^2$ |
| +2 | 27 mg/m$^2$ |
| +3 | 40 mg/m$^2$ |
| +4 | 60 mg/m$^2$ |
| +5 | 90 mg/m$^2$ |
| +6 | 135 mg/m$^2$ |

*Initial starting dose is Dose Level 0. If there are >1 DLTs at a dose level and the prior dose level was associated with 1 or fewer DLTs, an additional cohort may be enrolled at an intermediate dose level upon agreement with the Sponsor, Medical Monitor, and Principal Investigator.

#### *8.1.1.3 Preliminary Safety and Efficacy Assessment*

Following assessment of safety and preliminary efficacy in the first 5 dose level escalation cohorts (0: 12 mg/m$^2$; +1: 18 mg/m$^2$; +2: 27 mg/m$^2$; +3: 40 mg/m$^2$; +4: 60 mg/m$^2$) in both Arm A (onvansertib plus low-dose cytarabine) and Arm B (onvansertib plus decitabine), the decision was made to discontinue Arm A from further dose escalation and subject enrollment.

Arm B will continue forward with dose escalation as outlined in the protocol or until such time as the RP2D is determined at a dose level previously cleared for safety.

The RP2D can be determined based on the assessment of safety, PK, PD, and preliminary efficacy of subjects treated at a dose level that has been cleared for safety. In this case, no further dose escalation will be done to determine an MTD.

### 8.1.2 Phase 2

In Phase 2, a total of 32 subjects will be enrolled at the RP2D to further evaluate safety and preliminary efficacy. Onvansertib will be administered p.o. on Day 1 through Day 5 every 21 to 28 days, in combination with decitabine, administered consistently as 20 mg/m$^2$ IV over 1 hour on Day 1 through Day 5 every 28 days, with treatment modifications or delays based on return of hematopoietic function to baseline or Grade ≤1 toxicity for optimal subject management. The daily dose of decitabine will be administered first followed by onvansertib. Investigator assessment of subjects may allow them, at their discretion, to treat more frequently than every 28 days; however, in no case may a cycle length be less than 21 days.

Subjects may continue treatment in the study at any dose until clinically significant disease progression or death, unacceptable toxicity, withdrawal of consent, or discontinuation based on Investigator discretion. Subjects will be followed for survival for up to 1 year after enrollment.

AEs and concomitant medication use will be queried, monitored, and recorded throughout the study. Safety evaluations will include: physical examinations, performance status, vital signs, electrocardiograms (ECGs), hematology and serum chemistry laboratory tests, and urinalysis.

### 8.1.3 Study Endpoints

Primary safety endpoints:

1. Characterization of DLTs; characterization of AEs by type, incidence, severity (graded by NCI-CTCAE version 4.03), seriousness, and relationship to treatment; effects on vital signs and laboratory parameters; and changes from baseline in ECGs, physical examinations, weight, and ECOG performance

Primary efficacy endpoint:

1. Rate of complete response (CR + CRi) in Phase 2, defined as a morphologic leukemia-free state (MLF; defined below) plus:

   For CR:

   a. Subject is independent of transfusions

   b. Absolute neutrophil count (ANC) of >1000/mm$^3$

   c. Platelets of ≥100,000/mm$^3$

   For CRi:

   a. Meets all criteria for CR except for either neutropenia (ANC <1000/mm$^3$) or thrombocytopenia (<100,000/mm$^3$) but must include transfusion independence

Secondary endpoints:

1. Rate of achievement of a MLF in Phase 2, defined as:
    a. Bone marrow (BM) <5% blasts in an aspirate with spicules (a BM biopsy should be performed if spicules are absent)
    b. No blasts with Auer rods or persistence of extramedullary disease
2. Rate of partial response (PR) in Phase 2: All of the hematologic values for a CR but with a decrease of at least 50% in the percentage of blasts to 5% to 25% in the bone marrow aspirate and a normalization of blood counts as noted above
3. Duration of response (DOR) in Phase 2: Time from documentation of response until documentation of recurrence of or progression of disease
4. Event-free survival (EFS) in Phase 2: Time from enrollment until disease progression or death from any cause
5. Overall survival (OS) in Phase 2: Time from enrollment until death from any cause
6. Concentrations of onvansertib in plasma samples collected at pre-specified time points before and after administration of onvansertib, including maximum plasma concentration ($C_{max}$), trough plasma concentration ($C_{min}$), time to maximum plasma concentration ($T_{max}$), area under the plasma concentration versus time curve (AUC), and plasma terminal elimination half-life ($t_{1/2}$)

Exploratory endpoints:

1. Blood samples for PD and diagnostic biomarker evaluation
2. Rate of complete response (CR+CRi), MLF, PR, DOR, EFS and OS in all enrolled subjects (Phases 1b and 2)

## 8.2 Study Duration

The screening period will be up to 28 days prior to enrollment. Onvansertib administration in both phases can continue for as long as the subject has documented hematopoietic recovery and for as long as the Investigator considers that the subject is receiving clinical benefit without safety or tolerability issues. In addition, subjects may be escalated or de-escalated to doses or schedules that are considered safe and well tolerated, and in the best interest of the subject. Subjects will be followed for survival for up to 1 year after enrollment.

## 8.3 Eligibility Criteria

Subjects who meet all of the following inclusion criteria and none of the exclusion criteria will be eligible to be enrolled in the study.

### 8.3.1 Inclusion Criteria

1. Disease Status and Prior Therapy:
    a. Histologically confirmed diagnosis of AML
    b. Phase 1b:
        i. Subjects with relapsed or refractory AML who have received no more than 3 prior treatment regimens for AML. Subjects who have received prior treatment with cytarabine or decitabine are not excluded. Prior treatment with either low-dose cytarabine or decitabine given for MDS will not be considered a prior regimen. For subjects who have undergone hematopoietic stem cell transplantation, the preparative (conditioning) regimen and transplant will be considered to be a single line of prior therapy.

            OR

        ii. Subjects who are treatment naïve and are not candidates for or have refused intensive induction therapy.
    c. Phase 2:
        i. Subjects with relapsed or refractory AML who have received no more than 1 prior treatment regimen for AML. Subjects who have received prior treatment with cytarabine or decitabine are not excluded. Prior treatment with either low-dose cytarabine or decitabine given for MDS will not be considered a prior regimen.

            OR

        ii. Subjects who are treatment naïve and are not candidates for or have refused intensive induction therapy.
2. Age ≥18 years
3. ECOG performance status ≤2 (Appendix 19.3)
4. Subjects must be willing and able to review, understand, and provide written consent before starting any study-specific procedures or therapy.
5. All men and women must agree to practice effective contraception during the entire study period and after discontinuing study drug, unless documentation of infertility exists
    a. Sexually active, fertile women must use 2 effective forms of contraception (abstinence, intrauterine device, oral contraceptive, or double barrier device) from the time of informed consent and until at least 6 months after discontinuing study drug

b. Sexually active men and their sexual partners must use effective contraceptive methods from the time of subject informed consent and until at least 3 months after discontinuing study drug

### 8.3.2 Exclusion Criteria

Subjects must not meet any of the following exclusion criteria:

1. Treatment-related AML or acute promyelocytic leukemia (APL)
2. Active malignancies within 12 months with the exception of those with a negligible risk of metastasis or death
3. Clinical evidence of active central nervous system leukemia at the time of screening
4. ALT and/or AST ≥2.5 x upper limit of normal (ULN)
5. Total bilirubin >2.0 mg/dL (or >3.0 mg/dL in subjects with documented Gilbert syndrome)
6. Serum creatinine ≥2.0 mg/dL
7. NYHA Class III or IV heart disease (Appendix 19.2), active ischemia or any other uncontrolled cardiac condition, or hypertensive or metabolic condition
8. Myocardial infarction in the previous 12 weeks (from the start of treatment)
9. Resting left ventricular ejection fraction <50% at the time of screening
10. QT interval with Fridericia's correction [QTcF] [16] >450 milliseconds for men, or >470 milliseconds for women. The QTcF should be calculated as the arithmetic mean of the QTcF on triplicate ECGs. In the case of potentially correctible causes of QT prolongation (eg, medications, hypokalemia), the triplicate ECG may be repeated once during screening and that result may be used to determine eligibility.
11. Pregnant or breast feeding
12. Active and uncontrolled disease (other than AML) or infection as judged by the treating physician
13. Treatment with systemic therapy for the primary disease within 14 days of first dose (except for hydroxyurea or isolated doses of cytarabine or decitabine for WBC control)
14. Grade 2 or greater toxicities from prior therapy, except for Grade 2 toxicities that are not expected to resolve and that in the judgment of the Investigator do not pose a significant safety risk to subject participation.
15. Subjects with any other medical condition, including mental illness or substance abuse, deemed by the Investigator to be likely to interfere with the subject's ability to sign the informed consent form (ICF) or his/her ability to cooperate and participate in the study, or to interfere with the interpretation of the results

### 8.3.3 Removal of Subjects from Therapy or Assessment

Subjects will be discontinued from further study drug administration in the event of any of the following:

- Intolerable toxicity as determined by the Investigator
- Progression of disease requiring an alternate therapy, in the opinion of Investigator
- Entry into another therapeutic clinical study or start of additional anticancer therapy
- Significant deviation from the protocol or eligibility criteria, in the opinion of the Medical Monitor or Investigator
- Noncompliance with study or follow-up procedures
- Pregnancy
- Subject withdrawal of consent and decision to discontinue participation
- Termination of the study by the Sponsor
- Any other reason that, in the opinion of the Investigator, would justify removal of the subject from the study.

In the event that a subject is withdrawn from the study every effort will be made by the Investigator to document and report the reasons for withdrawal as thoroughly as possible. The reason(s) for withdrawal must be clearly reported on the appropriate page of the subject's electronic case report form (eCRF). An eCRF must be completed for any subject who receives study drug. An End-of-Treatment reason must be recorded for any subject who receives study drug. The requirement for subject replacement is outlined in Section 11.

If a subject is discontinued from the study for any reason, every effort must be made to perform all end of study (EOS) assessments (Section 9.1). In the event that the subject fails to return for the necessary visit(s), an effort must be made to contact the subject to determine the reason, and this information should be recorded in the appropriate source record and reported as a deviation.

## 8.4 STUDY DRUG TREATMENT

### 8.4.1 Description of Study Treatments

#### *8.4.1.1 Onvansertib (PCM-075)*

The chemical name of onvansertib is 1-(2-hydroxyethyl)-8-{[5-(4-methylpiperazin-1-yl)-2-(trifluoromethoxy) phenyl] amino}- 4,5-dihydro-1H-pyrazolo[4,3-h] quinazoline-3-carboxamide fumarate salt.

Onvansertib will be supplied as 5 mg and 20 mg (as free base) hard gelatin capsules that will be administered p.o.

- A Size 4 opaque caramel body and Swedish orange cap hard gelatin capsule contains 6.09 mg of onvansertib corresponding to 5 mg as free base, lactose monohydrate, pregelatinized starch, and glyceryl behenate. The capsule body shell contains gelatin, black iron oxide, red iron oxide, yellow iron oxide, and titanium dioxide; the capsule cap shell contains gelatin, red iron oxide, and titanium dioxide.
- A Size 4 opaque Swedish orange body and cap hard gelatin capsule contains 24.36 mg of onvansertib corresponding to 20 mg as free base, lactose monohydrate, pregelatinized starch, and glyceryl behenate. The capsule shell contains gelatin, red iron oxide, and titanium dioxide.

#### 8.4.1.1.1 Storage Conditions

Onvansertib is to be stored under refrigerated conditions (5°C ± 3°C; 36°F to 46°F) in the original packaging.

#### 8.4.1.1.2 Shelf-life

When onvansertib is stored at 5°C±3°C (36°F to 46°F), on the basis of the available stability information, a shelf-life of 48 months is currently assigned to the 5 mg and 20 mg (as free base) hard gelatin capsules.

Concurrent stability studies on the clinical batches are being conducted with 5 mg and 20 mg (as free base) hard gelatin capsules in order to evaluate the chemical, physical, and microbiological parameters. The onvansertib expiry date will be extended accordingly with the stability results. Any unexpected findings will be promptly communicated to study Investigators and to the applicable regulatory authorities.

#### 8.4.1.1.3 Dose Levels

The Phase 1b onvansertib starting dose is 12 mg/m$^2$ (Dose Level 0). The dose of onvansertib will be escalated in sequential dose cohorts as described (Section 8.1.1). Subjects will be assigned to a given dose regimen by the Principal Investigator based on prior dose levels tested and cohorts available. A subject will not be enrolled in the study until they complete all Screening evaluations, all eligibility criteria are met based on screening evaluations, and the eligibility criteria continues to be met following all baseline assessments on Day 1 of Cycle 1. Onvansertib will be administered p.o. on Day 1 through Day 5 every 21 to 28 days. Investigator assessment of subjects may allow them, at their discretion, to treat more frequently than every 28 days; however, in no case may a cycle length be less than 21 days.

Note that additional dosing regimens and doses may be explored if, after review of the safety, PK/PD, and efficacy data for the Phase 1b and Phase 2, alternative dosing schedules and doses are deemed to be in the best interest of understanding the safety and efficacy of the drug, and agreed upon by the Sponsor, Medical Monitor, and Principal Investigator.

8.4.1.1.4 Dose Delays

Subjects who experience any AE considered related to the study drug (ie, adverse reaction or suspected adverse reaction per criteria in Section 10.1) will have their next dose of onvansertib held until all study drug-related toxicities have reverted to Grade 1 or to Baseline. All AEs must be attributed to study drugs unless there is a reasonably acceptable alternate cause for the AEs.

8.4.1.1.5 Dose Reduction

Subjects who experience AEs of Grade ≥3 that is considered related to the study drug (ie, adverse reaction or suspected adverse reaction per criteria in Section 10.1) that do not show resolution with standard medical intervention by 7 days will have their next dose of onvansertib and all subsequent doses reduced by 1 dose level. If a second study drug-related toxicity such as this is encountered, the subject's next dose will be further reduced by 1 dose level, to an intermediate dose level, or subject may be discontinued from the study, based on the Investigator's discretion. All AEs must be attributed to study drugs unless there is a reasonably acceptable alternate cause for the AEs.

#### *8.4.1.2 Cytarabine*

The cytarabine dose will be 20 mg/m$^2$ SC daily on Day 1 through Day 10 every 28 days in Phase 1b. The dose of cytarabine will not be modified. On days where both agents are administered (Days 1-5), cytarabine will be administered first followed by onvansertib. Investigator assessment of subjects may allow them, at their discretion, to treat more frequently than every 28 days; however, in no case may a cycle length be less than 21 days.

Storage of cytarabine should be in accordance with the product package insert (Appendix 19.4).

#### *8.4.1.3 Decitabine*

The decitabine dose will be 20 mg/m$^2$ IV over 1 hour on Day 1 through Day 5 every 28 days in Phase 1b and Phase 2. The dose of decitabine will not be modified. The daily dose of decitabine will be administered first followed by onvansertib. Investigator assessment of subjects may allow them, at their discretion, to treat more frequently than every 28 days; however, in no case may a cycle length be less than 21 days.

Storage of decitabine should be in accordance with the product package insert (Appendix 19.4).

### 8.4.2 Dosing Schedule

Subjects will receive study drugs according to the dosing schedule outlined in tables in Section 9.1.

After review of the safety, PK, PD, and efficacy data from the Phase 1b portion of the study, and during the Phase 2 portion of the study, additional dosing schedules and doses (eg, fewer

days with higher doses and shorter treatment cycles) in a given cohort may be explored if agreed upon by the Sponsor, Medical Monitor, and Investigators, and are deemed to be important for the development of the study drug.

### 8.4.3 Study Drug Inventory and Accountability

In accordance with current Good Clinical Practice (GCP), each study site will keep an accounting of all study drug supplies. Details of receipt, storage, administration, and return or destruction will be recorded in the study drug accountability record according to the standard operating procedure of the study site. Copies of the study drug accountability record will be provided to the Sponsor.

Study drug must only be dispensed to subjects enrolled in the study and only as directed by this protocol. Administration of study drugs will be accurately recorded in each subject's source documents and case report form.

### 8.4.4 Treatment Compliance

The study drug will be administered p.o. as 5 mg and 20 mg hard gelatin capsules. Compliance will be ascertained by Investigational Site staff by individual subject assessment and monitoring/accounting for return of 5 mg and 20 mg hard gelatin capsules.

### 8.4.5 Concomitant Medications and Treatments

Concomitant medications are all medications (or treatments) other than study drugs that are taken or received by the subject at any time during the study starting at the time that the first dose of study drug was administered through the final study visit assessment. Use of all concomitant medications, including any change in therapy, must be recorded and updated in the source documentation and on the case report form.

All inter-current medical conditions will be treated at the discretion of the Investigator according to acceptable community and/or institutional standards of medical care.

Concomitant use of drugs with a known high risk of TdP should be avoided. For a list of drugs known to increase the risk of TdP, please refer to the published list of drugs at www.crediblemeds.org. Specific exception is allowed for the use of ciprofloxacin, which is commonly used in patients with AML and carries a low risk of TdP. Unplanned use of drugs known to increase the risk of TdP or the QTc interval should only occur during the conduct of the study with full consideration of the risks and benefits. Investigators should consult the TdP risk QT interval normogram included in Appendix 19.6.

Prophylactic filgrastim, pegfilgrastim, or oprelvekin, or other drugs of this class will be allowed if clinically indicated; the subject may receive growth factor support if needed and according to American Society of Clinical Oncology/American Society of Hematology (ASCO/ASH) guidelines. Erythropoietin, blood products, anti-emetics, antimicrobials, and steroids may be given at the discretion of the Investigator based on established criteria.

No other anti-leukemia treatments are allowed in subjects while the subject is participating in this study.

Subjects receiving warfarin or other coumarin-derivative anticoagulant should be monitored regularly for changes in prothrombin time or international normalized ratio (INR).

# 9 ASSESSMENTS

## 9.1 Schedule of Assessments

The schedule of events for Phase 1b Cycle 1, Phase 1b Cycle 2 and higher, and Phase 2 are provided in Table 9-1, Table 9-2, and Table 9-3, respectively.

Every attempt should be made to have each subject attend each visit as scheduled. Per protocol blood collection time points for determination of PK parameters should be adhered to as closely as possible.

## Table 9-1: Schedule of Events: Phase 1b Cycle 1

| Event | Screening | | Baseline | On Treatment | | | | | | | | | | | | Follow-up/EOS |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | ≤28 days prior to enrollment | ≤14 days prior to enrollment | Days -2 to 1 | Days | | | | | | | | | | | | (1-2 wks after Discontinuation) |
| | | | | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 15[k] | 22[k, l] | |
| Informed consent | X | | | | | | | | | | | | | | | |
| Relapsed/refractory AML: confirmation of diagnosis and cytogenetic analysis and molecular characterization obtained at diagnosis | X | | | | | | | | | | | | | | | |
| ECOG performance status | X | | X | | | | | | | | | | | | | X |
| History and physical examination[a] | X | | X | | | | | | | | | | | | | X |
| Triplicate ECG[b] | | X | | X | | | | X | | | X | | | | | |
| Blood chemistry[c] | | X | X | | | | | | | | X | | | X | X | X |
| CBC, including differential, and platelet count[d] | | X | | X | | | | X | | | X | | | X | X | X |
| Urinalysis | | X | | | | | | | | | | | | | | |
| Pregnancy test[e] | | X | X | | | | | | | | | | | | | X |
| Confirmation of all eligibility criteria | | X | | | | | | | | | | | | | | |

| | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| ECHO or MUGA scan | | X | | | | | | | | | | | | | | X |
| Bone marrow aspirate & peripheral blood for measuring status of disease and diagnostic biomarker evaluation[f] | | X | | | | | | | | | | | | X | | |
| Blood samples for PK analysis[g] | | | | X | | | | X | | | X | | | X | X | |
| Blood samples for pharmacodynamic and biomarker analysis[h] | | X | | X | | | | X | | | X | | | X | X | |
| Onvansertib (PCM-075) administration | | | | X | X | X | X | X | | | | | | | | |
| Cytarabine administration[i] | | | | X | X | X | X | X | X | X | X | X | X | | | |
| Decitabine administration[i] | | | | X | X | X | X | X | | | | | | | | |
| AE recording | | | | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Concomitant medication recording | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Survival[j] | | | | | | | | | | | | | | | | X |

**Footnotes for Table 9-1:**

Abbreviations: AE=adverse event; ALT=alanine aminotransferase; AML=acute myeloid leukemia; AST=aspartate aminotransferase; BUN=blood urea nitrogen; CBC=complete blood count; ECG=electrocardiogram; ECHO=echocardiogram; ECOG=Eastern Cooperative Oncology Group (performance score); EOS=end of study; LDH=lactate dehydrogenase; MUGA=multigated acquisition scan; PK=pharmacokinetics

[a] Including height, weight, vital signs, and general physical exam
[b] Triplicate ECGs should be collected at pre-dose and 3 hours (±15 minutes) after dosing of onvansertib (PCM-075) on Days 1 and 5 and once on Day 8.
[c] Sodium, potassium, chloride, bicarbonate, calcium, magnesium, phosphorus, BUN, creatinine, glucose, albumin, total protein, alkaline phosphatase, total bilirubin, AST, ALT, LDH, and uric acid
[d] CBC, to include differential and platelet count should be repeated as clinically indicated

[e] A serum or urine pregnancy test should be performed for women of childbearing potential at least once per cycle prior to dosing, as well as during Screening and at the Follow-up/EOS visit.

[f] Bone marrow aspirate and peripheral blood (complete blood count, differential, and platelet count; flow cytometry is optional) should be performed within 15 days prior to the first dose of study drug to document disease. If clinically appropriate, a bone marrow aspirate (or biopsy if necessary) should be performed 14-21 days after the start of therapy to document disease status. If hypoplasia is present, then a repeat aspirate/biopsy at the time of hematologic recovery based on peripheral blood counts should be obtained to document remission. If hypoplasia is not documented or is indeterminate, a repeat biopsy should be obtained, if clinically appropriate, in another 7-14 days to clarify the persistence of leukemia. If cytogenetics were initially abnormal, include cytogenetics as part of the remission documentation. For peripheral blood, include CBC, including differential and platelet count.

[g] Blood samples for PK analysis will be collected predose, and 0.5, 1, 2, 3, 4, 8 (all ±10 minutes), and 24 hours (±1 hour) after administration of onvansertib on Days 1 and 5, as well as once each on Days 8, 15, and 22.

[h] Blood samples for pharmacodynamic and diagnostic biomarker analysis will be obtained at screening in conjunction with the bone marrow aspirate; on Day 1 predose, 3 hours (±10 minutes) and 24 hours (±1 hour) after administration of onvansertib; on Day 5 predose, 3 hours (±10 minutes) after administration of onvansertib in conjunction with the PK sample being obtained at those time points, as well as once each on Days 8, 15, and 22.

[i] Subjects will receive either cytarabine or decitabine based on the arm in which they are enrolled (Section 8.1.1). On days where both agents are administered (Days 1-5), cytarabine will be administered first followed by onvansertib. For patients receiving decitabine, the decitabine will be administered first followed by onvansertib.

[j] After cessation of study treatment, subjects will be followed for survival every 2 months for 1 year (may be by telephone).

[k] Visits on Days 15 and 22 may occur ±1 day for subject convenience.

[l] Investigator assessment of subjects may allow them, at their discretion, to treat more frequently than every 28 days; however, in no case may a cycle length be less than 21 days. If an Investigator elects to re-treat a subject prior to 28 days (allowed no sooner than on Day 22), the DLT evaluation period will end at the time of initiation of the second cycle therapy.

## Table 9-2: Schedule of Events: Phase 1b Cycle ≥2

| Event | On Treatment | | | | | | | | | | | | Follow-up/EOS |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Days | | | | | | | | | | | | (1-2 wks after Discontinuation) |
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 15[k] | 22[k, j, l] | |
| ECOG performance status | X | | | | | | | | | | | | X |
| History and physical examination[a] | X | | | | | | | | | | | | X |
| Triplicate ECG[b] | X | | | | X | | | | | | | | |
| Blood chemistry[c] | X | | | | | | | X | | | X | X | X |
| CBC, including differential, and platelet count[d] | X | | | | X | | | X | | | X | X | X |
| Urinalysis[d] | X | | | | | | | | | | | | |
| Pregnancy test[e] | X | | | | | | | | | | | | |
| ECHO or MUGA scan | | | | | | | | | | | | | X |
| Bone marrow aspirate & peripheral blood for measuring status of disease and diagnostic biomarker evaluation[f] | | | | | | | | | | | X | | |
| Blood samples for PK evaluation[g] | X | | | | X | | | X | | | X | X | |
| Blood samples for pharmacodynamic and diagnostic biomarker evaluation[h] | X | | | | X | | | X | | | X | X | |

| Event | On Treatment | | | | | | | | | | | | Follow-up/EOS |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Days | | | | | | | | | | | | (1-2 wks after Discontinuation) |
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 15[k] | 22[k, j, l] | |
| Onvansertib (PCM-075) administration | X | X | X | X | X | | | | | | | | |
| Cytarabine administration[i] | X | X | X | X | X | X | X | X | X | X | | | |
| Decitabine administration[i] | X | X | X | X | X | | | | | | | | |
| AE recording | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Concomitant medication recording | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Survival[j] | | | | | | | | | | | | | X |

**Footnotes for Table 9-2:**

Abbreviations: AE=adverse event; BUN=blood urea nitrogen; ALT= alanine aminotransferase; AST= aspartate aminotransferase; CBC=complete blood count; ECG=electrocardiogram; ECHO=echocardiogram; ECOG=Eastern Cooperative Oncology Group (performance score); EOS=end of study; LDH=lactate dehydrogenase; MUGA=multigated acquisition scan; PK=pharmacokinetics; TBD=timing based on prior marrow and blood counts, as specified in (f).

[a] Physical examination should include weight, vital signs, and general physical exam.
[b] Triplicate ECGs will also be collected pre-dose and 3 hours (±15 minutes) after dosing of onvansertib on Days 1 and 5 (Cycle 2 only). ECGs are not required after Cycle 2.
[c] Sodium, potassium, chloride, bicarbonate, calcium, magnesium, phosphorus, BUN, creatinine, glucose, albumin, total protein, alkaline phosphatase, total bilirubin, AST, ALT, LDH, and uric acid. Day 1 chemistry values may be obtained up to 3 days prior.
[d] CBC, to include differential and platelet count may be repeated as clinically indicated. A serum or urine pregnancy test should be performed for women of childbearing potential at least once per cycle prior to dosing, as well as at the Follow-up/EOS visit. Day 1 urinalysis and pregnancy tests may be obtained up to 3 days prior.
[e] A serum or urine pregnancy test should be performed for women of childbearing potential at least once per cycle prior to dosing.

[f] Bone marrow aspirate (and biopsy if necessary) should be obtained to document remission status prior to Cycle 3 and every other cycle thereafter, which may be obtained at any time within 10 days to cycle Day 1. If cytogenetics were initially abnormal, include cytogenetics as part of the remission documentation. For peripheral blood, include CBC, differential & platelet count.

[g] Blood samples for PK evaluation of onvansertib should be collected at Cycle 2 only, if feasible, on Days 1 and 5 at predose, 3 hours (±10 minutes), and 24 hours (±1 hour) after administration of onvansertib, as well as once each on Days 8, 15, and 22.

[h] Blood samples for pharmacodynamic and biomarker evaluation of onvansertib should be collected, if feasible, at Cycles 2 and 3 on Days 1 and 5 at pre-dose and 3 hours (±10 minutes) after administration of onvansertib, as well as once each on Days 8, 15, and 22. For Cycle 4 and beyond, blood samples should be collected pre-dose on Days 1 and 15.

[i] Subjects will receive either cytarabine or decitabine based on the arm in which they are enrolled (Section 8.1.1). On days where both agents are administered (Days 1-5), cytarabine will be administered first followed by onvansertib. For patients receiving decitabine, the decitabine will be administered first followed by onvansertib.

[j] After cessation of study treatment, subjects will be followed for survival every 2 months for 1 year (may be by telephone).

[k] Visits on Days 15 and 22 may occur ±1 day for subject convenience.

[l] Investigator assessment of subjects may allow them, at their discretion, to treat more frequently than every 28 days; however, in no case may a cycle length be less than 21 days.

## Table 9-3: Schedule of Events: Phase 2 (all cycles)

| Event | Screening | | Baseline | On Treatment | | | | | | | | | | | | Follow-up/EOS |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | ≤28 days prior to enrollment | ≤14 days prior to enrollment | Days -2 to 1 | Days | | | | | | | | | | | | (1-2 wks after Discontinuation) |
| | | | | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 15[k] | 22[k, l] | |
| Informed consent | X | | | | | | | | | | | | | | | |
| Confirmation of AML and prior therapy, either relapsed/refractory or newly diagnosed, cytogenetic analysis, and molecular characterization obtained at diagnosis | X | | | | | | | | | | | | | | | |
| ECOG performance status | X | | X | | | | | | | | | | | | | X |
| History and physical examination[a] | X | | X | | | | | | | | | | | | | X |
| Triplicate ECG[b] | | X | | X | | | | X | | | X | | | | | |
| Blood chemistry[c] | | X | X | | | | | | | | X | | | X | X | X |
| CBC, including differential, and platelet count[d] | | X | | X | | | | X | | | X | | | X | X | X |
| Urinalysis[e] | | X | X | | | | | | | | | | | | | |
| Pregnancy test[e] | | X | X | | | | | | | | | | | | | |

| Event | Screening | | Baseline | On Treatment | | | | | | | | | | | | Follow-up/EOS |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | ≤28 days prior to enrollment | ≤14 days prior to enrollment | Days -2 to 1 | Days | | | | | | | | | | | | (1-2 wks after Discontinuation) |
| | | | | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 15[k] | 22[k, l] | |
| Confirmation of all eligibility criteria | | X | | | | | | | | | | | | | | |
| ECHO or MUGA scan | | X | | | | | | | | | | | | | | X |
| Bone marrow aspirate & peripheral blood for measuring status of disease and diagnostic biomarker evaluation[f] | | X | | | | | | | | | | | | X | | |
| Blood samples for PK analysis[g] | | | | X | | | | X | | | X | | | X | X | |
| Blood samples for pharmacodynamic and diagnostic biomarker evaluation[h] | | X | | X | | | | X | | | X | | | X | X | |
| Onvansertib (PCM-075) administration | | | | X | X | X | X | X | | | | | | | | |
| Decitabine administration[i] | | | | X | X | X | X | X | | | | | | | | |
| AE recording | | | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Concomitant medication recording | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |

| Event | Screening | | Baseline | On Treatment | | | | | | | | | | | | Follow-up/EOS |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | ≤28 days prior to enrollment | ≤14 days prior to enrollment | Days -2 to 1 | Days | | | | | | | | | | | | (1-2 wks after Discontinuation) |
| | | | | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 15[k] | 22[k, l] | |
| Survival[j] | | | | | | | | | | | | | | | | X |

**Footnotes for Table 9-3:**

Abbreviations: AE=adverse event; ALT=alanine aminotransferase; AML=acute myeloid leukemia; AST=aspartate aminotransferase; BUN=blood urea nitrogen; CBC=complete blood count; ECG=electrocardiogram; ECHO=echocardiogram; ECOG=Eastern Cooperative Oncology Group (performance score); EOS=end of study; LDH=lactate dehydrogenase; MUGA=multigated acquisition scan; PK=pharmacokinetics

[a] Physical examination should include height (screening only), weight, vital signs, and general physical exam. History and physical should be repeated prior to each cycle of therapy.

[b] Triplicate ECGs should also be collected at pre-dose and 3 hours after dosing on Days 1 and 5 and on Day 8 during Cycle 1. Triplicate ECGs should also be collected at pre-dose and 3 hours after dosing on Days 1 and 5 during Cycle 2 (Day 8 not required for Cycle 2). ECGs are not required after Cycle 2.

[c] Sodium, potassium, chloride, bicarbonate, calcium, magnesium, phosphorus, BUN, creatinine, glucose, albumin, total protein, alkaline phosphatase, total bilirubin, AST, ALT, LDH, and uric acid. Day 1 chemistry values may be obtained up to 3 days prior.

[d] CBC, to include differential and platelet count should be repeated as clinically indicated.

[e] A serum or urine pregnancy test should be performed for women of childbearing potential at least once per cycle prior to dosing, as well as at the Follow-up/EOS visit. Day 1 urinalysis and pregnancy test may be obtained up to 3 days prior.

[f] Bone marrow aspirate and peripheral blood (complete blood count, differential, and platelet count; flow cytometry is optional) should be performed within 15 days prior to the first dose of study drug to document disease. If clinically appropriate, a bone marrow aspirate (or biopsy if necessary) should be performed 14 to 21 days after the start of therapy to document disease status. If hypoplasia is present, then a repeat aspirate/biopsy at the time of hematologic recovery based on peripheral blood counts should be obtained to document remission. If hypoplasia is not documented or is indeterminate, a repeat biopsy should be obtained in clinically appropriate in another 7-14 days to clarify the persistence of leukemia. If cytogenetics were initially abnormal, include cytogenetics as part of the remission documentation. Bone marrow aspirate (and biopsy if necessary) should also be obtained to document remission status prior to Cycle 3 and every other cycle thereafter, which may be obtained at any time within 10 days prior to Cycle Day 1. If

cytogenetics were initially abnormal, include cytogenetics as part of the remission documentation. For peripheral blood, include CBC, differential & platelet count.

[g] Blood samples for PK analysis will be collected at Cycle 1 at pre-dose, and 0.5, 1, 2, 3, 4, 8 (all ± 10 minutes), and 24 hours (± 1 hour) after administration of onvansertib on Days 1 and 5, as well as once each on Days 8, 15, and 22. At Cycle 2, blood samples should be collected, if feasible, pre-dose, 3 hours (± 10 minutes) and 24 hours (± 1 hour) after administration of onvansertib on Days 1 and 5, and once each on Days 8, 15, and 22.

[h] Blood samples for pharmacodynamic and diagnostic biomarker analysis will be obtained at screening in conjunction with the bone marrow aspirate; at Cycle 1: on Day 1 pre-dose, 3 hours (±10 minutes) and 24 hours (±1 hour) after administration of onvansertib; on Day 5 pre-dose, 3 hours (±10 minutes) after administration of onvansertib in conjunction with the PK sample being obtained at those time points, as well as once each on Days 8, 15, and 22. At Cycles 2 and 3, blood samples should be collected, if feasible on Days 1 and 5 at pre-dose, 3 hours (± 10 minutes) after administration of onvansertib, and once each on Days 8, 15, and 22. For Cycle 4 and beyond, blood samples should be collected, if feasible, on Days 1 (pre-dose) and 15. The schedule for obtaining these may be amended based on results of prior evaluations.

[i] Decitabine will be administered first followed by onvansertib.

[j] After cessation of study treatment, subjects will be followed for survival every 2 months for 1 year (may be by telephone).

[k] Visits on Days 15 and 22 may occur ±1 day for subject convenience.

[l] Investigator assessment of subjects may allow them, at their discretion, to treat more frequently than every 28 days; however, in no case may a cycle length be less than 21 days.

## 9.2 Study Visits

The following sections describe the pretreatment, treatment, and post-treatment evaluations in this study.

### 9.2.1 Phase 1b

#### *9.2.1.1 Pretreatment Evaluations (Screening and Baseline)*

The Investigator is responsible for keeping a record of all subjects screened for entry into the study and those that are subsequently excluded. The reason(s) for subject exclusion from the study must also be recorded.

Each subject (or subject's legal representative if applicable) must provide written informed consent before any study-specific assessments may be performed.

The following screening procedures must be performed within 28 days prior to the first dose of study drug:

1. Complete history of AML, to include date and confirmation of diagnosis; dates of prior therapies as well as date of documented recurrence/progression are required for Phase 1b only. Cytogenetic analysis and molecular characterization obtained at diagnosis will be recorded.
2. Record ECOG performance status.
3. Complete medical history to include pertinent medical conditions and a careful history of all prior medical treatments.
4. Physical examination, including height (at screening only), weight, and vital signs.

The following screening procedures must be performed within 14 days prior to the first dose of study drug:

1. Perform triplicate ECG
2. Blood sample collection for clinical chemistry laboratory testing
3. Blood sample collection for hematology laboratory testing
4. Blood sample collection for PD and diagnostic biomarker evaluation
5. Urine sample collection
6. Pregnancy test for women of childbearing potential within 72 hours prior to first dose of study drug.
7. Recording of concomitant medication use
8. Perform an echocardiography (ECHO) or multigated acquisition (MUGA) scan
9. Confirmation of all eligibility criteria
10. Bone marrow aspirate and peripheral blood sample for measuring status of disease and performing biomarker analysis

The following baseline procedures must be performed within 2 days prior to the first dose of study drug:

1. Record ECOG performance status

2. Interval medical history to update pertinent medical conditions
3. Physical examination, including weight and vital signs
4. Blood sample collection for clinical chemistry laboratory testing
5. Blood sample collection for hematology laboratory testing
6. Recording of concomitant medication use

#### *9.2.1.2 Evaluations During Treatment*

Day 1 through Day 28 procedures:

1. Study drug administration:
    a. Onvansertib on Day 1 through Day 5
        i. Cytarabine on Day 1 through Day 10, or
        ii. Decitabine on Day 1 through Day 5
    b. On days where both agents are administered (Days 1-5), cytarabine will be administered first followed by onvansertib. For patients receiving decitabine, the decitabine will be administered first followed by onvansertib.
    c. Investigator assessment of subjects may allow them, at their discretion, to treat more frequently than every 28 days; however, in no case may a cycle length be less than 21 days.
2. Triplicate ECGs will be collected at pre-dose and 3 hours (± 15 minutes) after dosing of onvansertib on Days 1 and 5 (Cycles 1 and 2) and once on Day 8 (Cycle 1 only)
3. Pregnancy testing for women of childbearing potential will be performed prior to each cycle of therapy
4. If clinically appropriate, a bone marrow aspirate (or biopsy if necessary) should be performed 14 to 21 days after the start of therapy to document disease status. If hypoplasia is present, then a repeat aspirate/biopsy at the time of hematologic recovery based on peripheral blood counts should be obtained to document remission. If hypoplasia is not documented or is indeterminate, a repeat biopsy should be obtained in clinically appropriate in another 7 to 14 days to clarify the persistence of leukemia. If cytogenetics were initially abnormal, include cytogenetics as part of the remission documentation. For peripheral blood, include complete blood count (CBC), including differential and platelet count. A repeat bone marrow aspirate (or biopsy if necessary) will be obtained prior to Cycle 3 and every other cycle thereafter or as clinically indicated
5. Blood samples for PK analysis will be collected on Days 1 and 5 of the first cycle pre-dose and at 0.5, 1, 2, 3, 4, 8, and 24 hours after administration of onvansertib. Blood samples for PD and diagnostic biomarker evaluation of onvansertib will be collected on Day 1 of the first cycle at pre-dose, 3 hours, and 24 hours, and on Day 5 at pre-dose and 3 hours after administration of onvansertib. Blood samples for PK, PD, and diagnostic biomarker analysis will also be obtained for the first cycle weekly on Days 8, 15, and 22. For Cycle 2 (only), blood samples for PK analysis will be collected on Days 1 and 5 at pre-dose, 3 hours, and 24 hours post dose, and weekly on Days 8, 15, and 22. Blood samples for PD and diagnostic biomarker will be collected for Cycles 2 and 3 on Days 1 and 5 at pre-dose, 3 hours after administration of onvansertib, and weekly on Days 8, 15,

and 22; for Cycle 4 and beyond on Day 1 at pre-dose and Day 15. Visits on Days 15 and 22 may occur ±1 day for subject convenience.
6. Blood sample collection for CBC, including differential and platelet count, and blood chemistry will be performed on Days 1 and 5 and weekly after the start of the cycle (Days 8, 15, and 22) and as clinically indicated.
7. Urine sample collection (once per cycle pre-dose)
8. AE and concomitant medication recording daily during dosing and then weekly

#### *9.2.1.3 Post-Treatment Evaluations (Follow-up/End of Study)*

Within 14 days after decision to discontinue patient from further treatment, the following evaluations will be conducted:

1. Record ECOG performance status
2. Physical examination
3. Pregnancy test for women of childbearing potential
4. Blood sample collection for clinical chemistry laboratory testing
5. Blood sample collection for hematology laboratory testing
6. Perform ECHO or MUGA scan
7. AE recording
8. Recording of concomitant medication use

Any subject with a suspected study drug-related toxicity at the last follow-up visit must be followed until resolution or until the event is considered irreversible. This may require additional clinical assessments and laboratory tests. The follow-up results will be recorded on the appropriate page of the case report form, as well as in the subject's source documentation.

### 9.2.2 Phase 2

#### *9.2.2.1 Pretreatment Evaluations (Screening and Baseline)*

The Investigator is responsible for keeping a record of all subjects screened for entry into the study and those that are subsequently excluded. The reason(s) for subject exclusion from the study must also be recorded.

Each subject (or subject’s legal representative if applicable) must provide written informed consent before any study-specific assessments may be performed.

The following screening procedures must be performed within 28 days prior to the first dose of study drug:

1. Complete history of AML, to include date and confirmation of diagnosis and prior therapy, and cytogenetic analysis and molecular characterization obtained at diagnosis
2. Record ECOG performance status
3. Complete medical history to include pertinent medical conditions and a careful history of all prior medical treatments
4. Physical examination, including height (at screening only), weight, and vital signs
5. Recording of concomitant medication use

The following screening procedures must be performed within 14 days prior to the first dose of study drug:

1. Perform triplicate ECG
2. Blood sample collection for clinical chemistry laboratory testing
3. Blood sample collection for hematology laboratory testing
4. Blood sample collection for PD and diagnostic biomarker evaluation
5. Urine sample collection
6. Pregnancy test for women of childbearing potential within 72 hours prior to first dose of study drug
7. Confirmation of all eligibility criteria
8. Record concomitant medication use
9. Perform ECHO or MUGA scan
10. Bone marrow aspirate and peripheral blood sample for measuring status of disease and performing biomarker analysis

The following baseline procedures must be performed within 2 days prior to the first dose of study drug:

1. Record ECOG performance status
2. Complete medical history to include pertinent medical conditions and a careful history of all prior medical treatments
3. Physical examination, including weight and vital signs
4. Blood sample collection for clinical chemistry laboratory testing
5. Blood sample collection for hematology laboratory testing
6. Recording of concomitant medication use

#### *9.2.2.2 Evaluations During Treatment*

Day 1 through Day 28 procedures:

1. Study drug administration:
    a. Onvansertib at the RP2D on Day 1 through Day 5
        i. Decitabine on Day 1 through Day 5
    b. On days where both agents are administered (Days 1-5), decitabine will be administered first followed by onvansertib.
    c. Dosing of onvansertib may be delayed for safety if any hematologic toxicity and/or toxicity determined to be related to drug administration remains >Grade 2
    d. Investigator assessment of subjects may allow them, at their discretion, to treat more frequently than every 28 days; however, in no case may a cycle length be less than 21 days.
2. Triplicate ECGs will be collected at pre-dose and 3 hours after dosing on Days 1 and 5 (Cycles 1 and 2), and once on Day 8 (Cycle 1 only). ECGs are not required after Cycle 2
3. Pregnancy testing for women of childbearing potential will be performed prior to each cycle of therapy

4. If clinically appropriate, a bone marrow aspirate (or biopsy if necessary) should be performed 14 to 21 days after the start of therapy to document disease status. If hypoplasia is present, then a repeat aspirate/biopsy at the time of hematologic recovery based on peripheral blood counts should be obtained to document remission. If hypoplasia is not documented or is indeterminate, a repeat biopsy should be obtained in clinically appropriate in another 7 to 14 days to clarify the persistence of leukemia. If cytogenetics were initially abnormal, include cytogenetics as part of the remission documentation. For peripheral blood, include CBC, including differential and platelet count. A repeat bone marrow aspirate (or biopsy if necessary) will be obtained prior to Cycle 3 and every other cycle thereafter or as clinically indicated
5. Blood samples for PK analysis will be collected on Days 1 and 5 of the first cycle pre-dose and at 0.5, 1, 2, 3, 4, 8, and 24 hours after administration of onvansertib. Blood samples for PD and diagnostic biomarker evaluation of onvansertib will be collected on Day 1 of the first cycle at pre-dose, 3 hours, and 24 hours and on Day 5 at pre-dose, 3 hours after administration of onvansertib. Blood samples for PK, PD and diagnostic biomarker analysis will also be obtained for the first cycle weekly on Days 8, 15, and 22. For Cycle 2 (only), blood samples for PK analysis will be collected on Day 1 and Day 5 at pre-dose, 3 hours and 24 hours post dose and weekly on Days 8, 15, and 22. Blood samples for PD and diagnostic biomarker will be collected for Cycles 2 and 3 on Day 1 and 5 at pre-dose, 3 hours after administration of onvansertib and weekly on Days 8, 15, 22; for Cycles 4 and beyond on Day 1 at pre-dose and Day 15. Visits on Days 15 and 22 may occur ±1 day for subject convenience.
6. Blood sample collection for CBC, including differential and platelet count, and blood chemistry will be performed on Day 5 and weekly after the start of the cycle (Days 8, 15, and 22) and as clinically indicated.
7. Urine sample collection (once per cycle, pre-dose)
8. AE and concomitant medication recording daily during dosing and then weekly

#### *9.2.2.3 Post-treatment Evaluations (Follow-up/End of Study)*

Within 14 days after the decision to discontinue the patient from further treatment, the following evaluations will be conducted:

1. Record ECOG performance status
2. Physical examination
3. Pregnancy test for women of childbearing potential
4. Blood sample collection for clinical chemistry laboratory testing
5. Blood sample collection for hematology laboratory testing
6. Perform ECHO or MUGA scan
7. AE recording
8. Recording of concomitant medication use

Any subject with a suspected study drug-related toxicity at the last follow-up visit must be followed until resolution or until the event is considered irreversible. This may require additional

clinical assessments and laboratory tests. The follow-up results will be recorded on the appropriate page of the CRF, as well as in the subject's source documentation.

After completion of treatment, subjects will be followed every 2 months for survival for 1 year. Survival follow-up may be obtained by telephone.

## 9.3 Efficacy Assessments

All subjects evaluable for anti-leukemic activity will be assessed for response to treatment using the recommendations of the International Working Group (IWG) for standardization of response criteria, treatment outcomes, and reporting for therapeutic studies. [17]

### 9.3.1 Efficacy Variables

Response criteria will be based on the International Working Group for AML. [17] The primary efficacy variable is leukemia responses, evaluated by the Investigator based on bone marrow aspirate and peripheral blood examination.

Efficacy endpoints are per NCCN. [18] Responders are subjects who obtain a complete response (CR), CR with incomplete blood count recovery (CRi), or partial response (PR), with or without cytogenetic response, hematologic improvements (HI), and morphologic leukemia-free (MLF) state. Other criteria include DOR, EFS, and OS. Briefly, criteria are defined as follows:

#### *9.3.1.1 Morphologic Leukemia-free State*

- Bone marrow <5% blasts in an aspirate with spicules (a BM biopsy should be performed if spicules are absent)
- No blasts with Auer rods or persistence of extramedullary disease

#### *9.3.1.2 Complete Response*

Complete response is defined by the following criteria:

- Morphologic leukemia-free state plus:
  - Subject is independent of transfusions
  - Absolute neutrophil count of >1000/$mm^3$
  - Platelets of ≥100,000/$mm^3$

#### *9.3.1.3 Complete Response with Incomplete Blood Count Recovery*

- Complete response with incomplete blood count recovery meets all criteria for CR except for either neutropenia (ANC <1000/$mm^3$) or thrombocytopenia (<100,000/$mm^3$) but must include transfusion independence

#### *9.3.1.4 Partial Response*

- All of the hematologic values for a CR but with a decrease of at least 50% in the percentage of blasts to 5% to 25% in the bone marrow aspirate and a normalization of blood counts as noted above.

#### *9.3.1.5 Duration of Response*

- Time from documentation of response until documentation of recurrence of or progression of disease.

#### *9.3.1.6 Event-free Survival*

- Time from enrollment until disease progression or death from any cause

#### *9.3.1.7 Overall Survival*

- Time from enrollment until death from any cause.

## 9.4 Safety Assessments

Toxicity will be graded using the National Cancer Institute Common Terminology Criteria (NCI-CTCAE version 4.03).

- Safety analysis will be conducted on all subjects who have received at least one dose of study drug, and will include the frequency of all AEs and laboratory abnormalities as well as the frequency of dose interruptions, dose reductions, and treatment discontinuation.
- In Phase 1b, DLTs will be considered to be any non-hematologic Grade 3 abnormalities that persist >7 days without decreasing in severity despite standards of care, are clinically significant, or that are Grade 4 and symptomatic. Exceptions and additional parameters for assessment of non-hematologic DLTs are provided in the protocol. For hematologic toxicities, only persistent pancytopenia resistant to current standards of care that continues for ≥42 days and is not related to leukemic infiltration or another cause unrelated to study therapy will be considered as a DLT, since marrow aplasia is an expected consequence of AML therapy.
- Any subject that has not completed a full initial cycle and received at least 80% of study drug due to issues other than DLTs, including disease progression, will be replaced.

Additional safety assessments will include physical examination; medical history; ECG; ECOG performance status; weight; vital signs measurements; clinical laboratory testing (hematology, clinical chemistry, and urinalysis) and MUGA or ECHO scans.

Safety assessments will be performed as per the Schedule of Assessments (Section 9.1). Safety assessment may be performed at additional time points during the study at the discretion of the Investigator in the interest of subject safety.

The SRC, consisting of the Principal Investigators and Medical Monitor, will monitor subjects for safety and to evaluate efficacy of onvansertib doses to minimize exposure of subjects to a non-efficacious dose level.

## 9.5 Pharmacokinetic Assessments

Pharmacokinetic analysis will be obtained as outlined in Section 9.2.1 and Section 9.2.2.

Pharmacokinetic parameters to be determined will include:

- Maximum concentration ($C_{max}$)

- Time of maximum concentration ($T_{max}$)
- Area under the curve over the first 24 hours ($AUC_{0-24}$)
- Drug elimination half-life ($t_{1/2}$)

### 9.6 Pharmacodynamic and Biomarker Evaluation

Pharmacodynamic and biomarker evaluation will be obtained as outlined in Section 9.2.1 and Section 9.2.2. Details of the PD and biomarker evaluations will be included in the laboratory manual.

## 10 ADVERSE EVENT REPORTING

### 10.1 Definitions

#### 10.1.1 Adverse Event

An AE is defined in Title 21 Code of Federal Regulations (CFR) 312.32(a) as follows:

- Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

An AE (also referred to as an adverse experience) can be any unfavorable and unintended sign (eg, an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, and does not imply any judgment about causality. An AE can arise with any use of the drug (eg, off-label use, use in combination with another drug) and with any route of administration, formulation, or dose, including an overdose.

#### 10.1.2 Unexpected Adverse Events

An unexpected AE is defined in 21 CFR 312.32(a) as follows:

- An AE or suspected adverse reaction is considered "unexpected" if it is not listed in the IB or is not listed at the specificity or severity that has been observed; or, if an IB is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended.

#### 10.1.3 Serious Adverse Event

An SAE is defined in 21 CFR 312.32(a) as follows:

An AE or suspected adverse reaction is considered "serious" if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- Death
- A life-threatening AE
- Subject hospitalization or prolongation of existing hospitalization

- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect

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

An AE or suspected adverse reaction is considered "life-threatening" if, in the view of either the Investigator or Sponsor, its occurrence places the subject or subject at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

### 10.1.4 Definition of Dose-limiting Toxicities

Dose-limiting toxicities are defined as events related to onvansertib that are considered an adverse reaction or suspected adverse reaction (per criteria in Section 10.1), during the first cycle of therapy and that fulfills at least one of the criteria listed below. Further information on the grading of AEs is presented in Section 10.2.

Hematologic

- Since marrow aplasia is an expected consequence of AML therapy, only persistent pancytopenia resistant to current standards of care that continues for ≥42 days and is not related to leukemic infiltration or another cause unrelated to study therapy will be considered as a DLT. Bone marrow evaluation may be required.

Non-Hematologic

- Any Grade 3 abnormalities that persist >7 days without decreasing in severity despite standards of care, are clinically significant, or that are Grade 4 and symptomatic. The following will also be considered DLTs:
  - Aminotransferase abnormality ≥Grade 3 in the presence of elevated total bilirubin to >2× ULN (at least a Grade 2) with no other reason that can be found to explain the combination of increased ALT and total bilirubin, such as viral hepatitis A, B, or C; preexisting or acute liver disease; or another drug capable of causing the observed injury (Hy's Law)
  - Nausea, vomiting or diarrhea Grade ≥3 persisting for >2 days without evidence of decreased severity (to at least Grade 2) despite maximal medical intervention
  - Serum amylase or lipase ≥Grade 3 accompanied by symptoms consistent with pancreatic injury
  - Neurologic toxicity ≥Grade 3 persisting for >2 days and not attributable to central nervous system leukemic infiltrate, external causes or concomitant medications

### 10.1.5 Determination of the Maximum Tolerated Dose

The planned dose-escalation strategy for onvansertib in combination with either cytarabine or decitabine is presented in Section 8.1.1.

In Phase 1b, the dose of onvansertib will be escalated in sequential dose cohorts, while the dose of either cytarabine or decitabine will be administered in the doses and regimens as per product insert. The onvansertib starting dose will be 12 mg/m$^2$ (Dose Level 0), and escalated or reduced in dosing cohorts based on criteria outlined in Section 8.1.1. Dose modifications, delays and reductions for individual subjects will be performed as described in Sections 8.4.1.1.3, 8.4.1.1.4, and 8.4.1.1.5, respectively. DLTs will be recorded for 28 days after initiation of therapy; however, if an Investigator elects to re-treat a subject prior to 28 days (allowed no sooner than on Day 22), the DLT evaluation period will end at the time of initiation of the second cycle therapy. Subjects may continue with additional cycles as long as the subject is receiving clinical benefit and there are no safety or tolerability issues.

Subjects who have not received at least 80% of the dose of study drug(s) during the first cycle or who are discontinued for any reason other than DLT will be replaced.

The MTD of onvansertib in combination with either low-dose cytarabine or decitabine in subjects with AML will be defined as the highest dose level achieved at which no more than 1 out of 6 subjects experienced a DLT during the first cycle of therapy in Phase 1b.

## 10.2 Severity of Adverse Events

Each AE will be graded according to the NCI-CTCAE version 4.03 (Appendix 19.1). In most cases AE terms will be listed in the CTCAE, with grading criteria specific to that term. If the AE is not specifically defined in the CTCAE, it is to be reported using the "Other, specify" term under the appropriate system organ class and graded according to the general CTCAE severity guidelines.

## 10.3 Relationship of Adverse Events to the Study Drug

The Investigator must attempt to determine if an AE is in some way related to the use of onvansertib, the study drug. All AEs must be attributed to study drugs unless there is a reasonably acceptable alternate cause for the AEs. This relationship should be described as follows:

- **Unrelated:** The event has no temporal relationship to study drug administration (too early or late or study drug not taken), or there is a reasonable causal relationship between the AE and another drug, concurrent disease, or circumstance.
- **Unlikely:** The event with a temporal relationship to drug administration which makes a causal relationship improbable, and in which other drugs, chemicals, or underlying disease provide plausible explanations.
- **Possibly:** The event follows a reasonable temporal sequence from administration of the study drug and the event follows a known response pattern to the study drug BUT the event could have been produced by an intercurrent medical condition which, based on the

pathophysiology of the condition, and the pharmacology of the study drug, would be unlikely related to the use of the study drug or the event could be the effect of a concomitant medication.

- **Probably:** The event follows a reasonable temporal sequence from administration of the study drug and the event follows a known response pattern to the study drug AND the event cannot have been reasonably explained by an intercurrent medical condition or the event cannot be the effect of a concomitant medication.
- **Definitely:** The event follows a reasonable temporal sequence from administration of the study drug, the event follows a known response pattern to the study drug and based on the known pharmacology of the study drug, the event is clearly related to the effect of the study drug.

## 10.4 Monitoring of Adverse Events

AEs will be monitored continuously during the study starting immediately after the first dose of study drug is administered. Subjects will be instructed to report all AEs experienced during the study, and subjects will be assessed for the occurrence of AEs throughout the study.

All AEs will be followed until resolution or stabilization of the event. This may require additional clinical assessments and laboratory tests.

## 10.5 Reporting Procedures

### 10.5.1 Routine Reporting of Adverse Events

AEs, whether or not associated with study drug administration, will be recorded on the AE form of the CRF and will be submitted to the Sponsor at regularly scheduled intervals.

The information to be entered in the CRF will include:

1. Time of onset of any new AE or the worsening of a previously observed AE. In most cases, date of onset will be adequate; however, for days when the subject is in the clinic and receives study drug(s), the time (based on a 24-hour clock) of onset should also be recorded
2. Specific type of reaction in standard medical terminology
3. Time of resolution of the event (or confirmation ongoing). In most cases, date of resolution will be adequate; however, for events that initiate and resolve on days where the subject is in the clinic and receives study drug(s), the time (based on a 24-hour clock) of resolution should also be recorded
4. Severity/grade of AE. The severity should be rated according to NCI-CTCAE version 4.03 (Appendix 19.1)
5. An assessment should be made of the relationship of the AE to the study drug according to the definitions outlined in Section 10.3.
6. Description of action taken in treating the AE and/or change in study drug administration or dose

Follow-up assessments should be repeated to document return of any abnormalities to normal, or to document other outcome of the AE.

### 10.5.2 Reporting of Serious Adverse Events, Including Death

SAEs, including death due to any cause, which occur during this study or within 30 days following the last dose of the study drugs, whether or not related to the administration of study drugs, must be reported to the Medical Monitor by telephone or email **within 24 hours of learning of the event**.

SAE Forms will be provided by the Sponsor or Sponsor designated CRO. The study site should send the SAE Form to the Medical Monitor as soon as possible so that the tracking procedure can begin immediately upon receipt of the information. Once the Medical Monitor is informed of an SAE with preliminary information obtained, the study site will be instructed to update the SAE Form with additional information, as per the following guidelines.

If all information is not known at the time of the incident, an initial report should still be made. In the event there is a question as to whether the event is serious, the information should be forwarded to the Medical Monitor for review. The Investigator is responsible for following up on completion of the SAE Form. The Investigator will submit substantiating data in hard copy form, such as diagnostic test reports and progress notes, to the Medical Monitor. In the case of fatality, autopsy reports will be furnished to the Medical Monitor as soon as available.

During the initial communication, the Medical Monitor will require the following information about the subject and the reported SAE:

1. Subject identification including subject number, initials, and date of birth
2. Date of first dose of study drugs and details of administration, including study drug names (including labeled strength and manufacturer), lot number, expiration date, and dose
3. Date of last dose of study drugs (ie, prior to onset of SAE) and details of administration, including study drug names (including labeled strength and manufacturer, lot number, expiration date, and dose)
4. Medical diagnosis of the event in standard medical terminology (if a medical diagnosis cannot be determined, a description of each sign or symptom characterizing the event)
5. Date of onset of the AE
6. Date of resolution of the AE (or confirmation ongoing)
7. Severity of the AE (see Section 10.2)
8. Assessment of the attribution of the AE to the study drug (see Section 10.3)
9. Reason AE is considered serious (per definition in Section 10.1.3)
10. Whether the AE is expected (see Section 10.1)
11. Action taken in treating the AE and/or change in study drug administration or dose (including concomitant medications or therapies administered, whether hospitalization or prolongation of hospitalization was required, diagnostic procedures performed, and whether the subject was discontinued from the study)
12. All concomitant medications (including doses, routes, regimens, and indications)

13. Pertinent clinical laboratory testing data
14. Medical history

The Investigator and the Medical Monitor will review each SAE report and evaluate the relationship of the adverse experience to study drugs and to underlying disease. Based on the Investigator's and Medical Monitor's assessment of the adverse experience, a decision will be made concerning the need for further action. The primary consideration governing further action is whether new findings affect the safety of subjects participating in the clinical study. If the discovery of a new adverse experience related to the study drug raises concern over the safety of continued administration of study drug, the Sponsor will take immediate steps to notify the regulatory authorities.

Further action that may be required includes the following:

1. Alteration of existing research by modification of the protocol
2. Discontinuation or suspension of the study
3. Alteration of the informed consent process by modification of the existing consent form and informing current study participants of new findings
4. Modification of previously identified expected adverse experiences to include adverse experiences newly identified as study medication-related.

Any SAE that is determined by the Sponsor to be reportable to FDA as an Investigational New Drug (IND) Safety Report [as defined in 21 CFR 312.32] will be reported to FDA by the Sponsor within the specified time frame. All IND Safety Reports will also be promptly provided to the Investigator for submission to his or her Institutional Review Board (IRB)/Independent Ethics Committee (IEC). Similarly, any SAE that is determined by the Sponsor to require expedited reporting to other regulatory authorities will be reported to the appropriate authorities by the Sponsor within the specified time frames, and will be provided to the Investigator for submission to his or her IRB/IEC.

### 10.5.3 Other Events Requiring Immediate Reporting

#### *10.5.3.1 Overdose*

An overdose is defined as a subject receiving a dose of investigational product in excess of that specified in the IB, unless otherwise specified in this protocol. Any overdose of a study subject with the investigational product, with or without associated AEs/SAEs, is required to be reported to the Medical Monitor within 24 hours of knowledge of the event. Overdose does not automatically make an AE serious, but if the consequences of the overdose are serious, for example death or hospitalization, the event is serious and must be reported as an SAE.

#### *10.5.3.2 Pregnancy*

Pregnancy in a female subject who has received investigational product is required to be reported within 24 hours of knowledge of the event. Should the Investigator become aware of a pregnancy of a female partner of a male participant, the pregnancy should be reported within 24 hours of knowledge of the event. The information should be captured on the Initial Pregnancy Report

Form (Please refer to the Site Operations Manual). After obtaining the subject's consent (or subject and pregnant partner's consent in the case of a male participant), monitoring of the pregnancy should continue until conclusion of the pregnancy whereby the Investigator will notify PRA of the outcome on the Pregnancy Outcome Report Form (Please refer to the Site Operations Manual).

Subjects who become pregnant during the study period must not receive additional doses of investigational product but will not be withdrawn from the study.

# 11 SUBJECT DISCONTINUATION AND TRIAL DISCONTINUATION

## 11.1 Subject Discontinuation

A subject may choose to withdraw from this study at any time for any reason without penalty of jeopardizing their health care or loss of benefits to which the subject is otherwise entitled.

Subjects will be discontinued from study drug (onvansertib) treatment if one or more of the following events occur:

1. Clinically significant progressive disease
2. Subject refusal to remain on study
3. Pregnancy
4. Non-compliance or inability to comply with protocol requirements by subject
5. Development of unacceptable toxicity (regardless of study drug relationship)
6. Determination by the Investigator that it is no longer safe for the subject to continue therapy.

Subjects who have an ongoing AE at the time of discontinuation will continue to be followed until resolution of the event to Grade ≤1 or baseline, or until the event is considered irreversible.

Subjects who are discontinued prior to completing the first treatment cycle for any reason other than toxicity, or who have not received at least 80% of the intended doses, will be replaced.

## 11.2 Study Discontinuation

Treatment may be continued longer at the discretion of the treating physician if there is no evidence of disease progression and the subject is not experiencing unacceptable toxicity, and if both the subject and physician agree that further therapy is in the subject's best interest.

The Sponsor has the right to terminate this study, and the Investigator/Investigational Site has the right to close the site, at any time, although this should occur only after consultation between involved parties. The Investigator must notify the IRB/IEC in writing of a premature termination of a study or closure of Investigational Site, and must send a copy of the notification to the Sponsor.

Events that may trigger premature termination of a study or closure of an Investigational Site include, but are not limited to, a new toxicity finding, a request to discontinue the study from a regulatory authority, non-compliance with the protocol, slow recruitment, or change in development plans for the study drug.

# 12 STATISTICAL METHODS

## 12.1 Dosing Algorithm and Determination of Sample Size

The planned sample size in the Phase 1b portion of the study is up to 84 subjects (42 in each arm), which is considered sufficient for the determination of safety and PK parameters for the study drug.

This study is a dose-escalation study that initially utilizes a 3+3 design [19] with a starting dose of onvansertib of 12 mg/m$^2$ (Dose Level 0) administered Day 1 through Day 5 every 21 to 28 days. If an Investigator elects to re-treat a subject prior to 28 days (allowed no sooner than on Day 22), the DLT evaluation period will end at the time of initiation of the second cycle of therapy. The sample size is anticipated to be up to 84 subjects (42 per arm) in Phase 1b, depending on the dose level at which toxicity is observed. The 3+3 dose-escalation algorithm is as follows:

1. If 0 out of 3 subjects experience DLT (as defined in Section 10.1.4) during the first cycle of therapy, the next cohort of 3 subjects will be treated at the next higher dose level.
2. If 1 out of 3 subjects develop DLT during the first cycle of therapy (ie, 28 days from start of therapy), an additional 3 subjects will be treated at the same dose level. If no additional DLTs occur during the first cycle of therapy for the additional 3 subjects treated (ie, 1 out of a total of 6 subjects develops DLT that initiates within the specified period), the dose escalation continues to next higher level for a cohort of 3 subjects.
3. If at any time there are 2 or more subjects who experience DLTs in the 3 to 6 subjects at a given dose, the next cohort will receive a prior dose level or an intermediate dose level, agreed upon by the Sponsor, Medical Monitor, and Principal Investigator.

With this 3+3 design, a dose with a ≥ 50% probability of causing a DLT has at most a 12.5% chance of satisfying the conditions for dose escalation after the first 3 subjects and a ≥50% chance of stopping at 3. With 6 subjects, there is at most a 17.2% chance of satisfying the conditions for dose escalation after 6 subjects. Phase 2 will proceed with a total of 32 subjects at the identified RP2D; however, if at any time during this phase more than 33% of subjects develop a DLT-level AE (as per protocol), accrual will stop, and the RP2D will be reassessed in additional cohorts.

Subjects who are discontinued prior to completing the first cycle for any reason other than toxicity or who have not received at least 80% of the intended doses, without experiencing DLT will be replaced.

## 12.2 Statistical Analysis of Safety Data

Data from all subjects who receive at least one dose of study drug (onvansertib) will be included in the safety analysis.

Safety will be assessed primarily based on AEs. The severity of AEs will be graded as mild, moderate, severe, or life-threatening according to NCI-CTCAE version 4.03 (Appendix 19.1). AEs will be tabulated by system organ class and preferred term (per Medical Dictionary for

Regulatory Activities [MedDRA]), and will be further categorized by onvansertib dose level, severity, and assigned relationship to study drug. The incidence for each AE will be provided as the total number of subjects who experienced the AE, as well as the percentage of the population that this represents. If an AE is reported more than once during treatment for a given subject, the greatest severity and the worst-case attribution will be presented in the AE summary tables.

AEs will also be listed for individual subjects, along with information regarding onset, duration, severity, relationship to study drug, and outcome. AEs that lead to withdrawal from the study will be listed and summarized. A separate tabulation and listing of SAEs will also be generated.

Secondary safety assessments, including physical examination, ECOG performance status, weight (for body surface area [BSA] calculation), vital signs, ECG measurements and clinical laboratory testing (hematology, clinical chemistry, and urinalysis) will be listed and summarized. Descriptive statistics will be generated as appropriate (ie, mean, median, range, and SD for continuous data and frequency for categorical data).

Inferential statistical analysis comparing the safety data among onvansertib dose levels or historical data is not planned.

## 12.3 Statistical Analysis of Efficacy Data

Data from all subjects who receive at least one dose of onvansertib in combination with either cytarabine or decitabine will be included in the intention-to-treat (ITT) efficacy analysis. Subjects completing at least one cycle of treatment will be included in the per protocol efficacy analysis.

The efficacy endpoints for this study include CR, CRi, PR, MLF, DOR, and OS. Further description of the efficacy measurements and response criteria for this study is presented in Section 9.3.1.

Descriptive statistics will be generated as appropriate (ie, mean, median, range, and SD). Median survival statistics will be estimated using the Kaplan-Meier Time-to-Event.

Inferential statistical analysis comparing efficacy data among onvansertib dose levels or historical data is not planned.

The primary efficacy endpoint is the rate of CR + CRi in the Phase 2 portion of the study. Based on a population CR + CRi rate of 20% for either the combination of cytarabine plus onvansertib or decitabine plus onvansertib, with 32 evaluable patients in the primary analysis the 90% CI for the CR + CRi rate from the study will have an estimated precision of approximately 58% and width 0.23, and a 95% CI would have an estimated precision of approximately 70% and width 0.28.

PK parameters to be determined will include $C_{max}$, $T_{max}$, $AUC_{0-24}$, and $t_{1/2}$, which will be estimated from plasma concentration data. The geometric mean and 95% CIs will be reported for all evaluable subjects.

# 13 ACCESS TO SOURCE DOCUMENTS AND RETENTION OF RECORDS

The Investigator will make the source documents for this study available for monitoring by the Sponsor or its representatives, or by regulatory authorities or health authority inspectors.

Subject medical information obtained as a result of this study is considered confidential and disclosure to third parties other than those noted below is prohibited. All reports and communications relating to subjects in this study will identify each subject only by their initials and number. Medical information resulting from a subject's participation in this study may be given to the subject's personal physician or to the appropriate medical personnel responsible for the subject's welfare. Data generated as a result of this study are to be available for inspection on request by FDA or other government regulatory agency auditors, the Sponsor (or designee), and the IRB/IEC.

The information developed in this clinical study will be used by the Sponsor in the clinical development of the study drug and therefore may be disclosed by the Sponsor as required for disclosure as a public company to other clinical Investigators, to other pharmaceutical companies, to the FDA, and to other government agencies.

Any information, inventions, or discoveries (whether patentable or not), innovations, suggestions, ideas, and reports made or developed by the Investigator(s) as a result of conducting this study shall be promptly disclosed to the Sponsor and shall be the sole property of the Sponsor. The Investigator agrees, upon the Sponsor's request and at the Sponsor's expense, to execute such documents and to take such other actions as the Sponsor deems necessary or appropriate to obtain patents in the Sponsor's name covering any of the foregoing.

The Investigator will retain all study documents for at least 2 years after the last approval of a marketing application in an International Council for Harmonisation (ICH) region (ie, US, Europe, or Japan), and until there are no pending or contemplated marketing applications in an ICH region. If no application is filed or if the application is not approved for such indication, the Investigator will retain all study documents for at least 2 years after the Investigation is discontinued and regulatory authorities have been notified.

The Investigator will notify the Sponsor prior to destroying any study records. Should the Investigator wish to assign the study records to another party or move them to another location, the Sponsor must be notified in writing in advance.

If the Investigator cannot guarantee this archiving requirement at the study site for any or all of the documents, special arrangements will be made between the Investigator and the Sponsor for storage. If source documents are required for continued care of the subject, appropriate copies for storage off-site will be made.

# 14 QUALITY CONTROL AND QUALITY ASSURANCE

## 14.1 Data Collection

All data required by the study protocol will be entered onto case report forms and must be verifiable against source documents. Case report forms will be completed for every subject who is enrolled in this study.

Only authorized Investigational Site personnel will enter data on the case report forms. Any corrections to data entered into the case report form will be made in such a way that the original entry is not obscured. The date of the correction and the initials of the person making the correction will be documented.

The case report forms will be kept up-to-date by the Investigator and the research staff at the Investigational Site. The Investigator will be responsible for reviewing all data and case report form entries and will sign and date each subject's case report form, verifying that the information is true and correct.

## 14.2 Study Monitoring

The study will be monitored to evaluate the progress of the study, to verify the accuracy and completeness of the case report forms, to assure that all protocol requirements, applicable laws and/or regulations, and Investigator's obligations are being fulfilled, and to resolve any inconsistencies in the study records.

The Investigator will allow the study monitor to periodically review, at mutually convenient times during the study and after the study has been completed, all case report forms and office, hospital, and laboratory records supporting the participation of each subject in the study.

The study monitor will compare the case report form data against source documentation in order to verify its accuracy and completeness. The Investigator and research staff will collaborate with the study monitor to resolve any identified data discrepancies in a timely manner.

The study monitor will record any protocol deviations identified, including, but not limited to, subjects who were enrolled even though they did not meet all eligibility criteria, subjects who took concomitant medications specifically prohibited by the protocol, and subjects who received the wrong study drug or incorrect dose. The Investigator and research staff will collaborate with the study monitor to identify the reason for each protocol deviation.

The study monitor will compare the Investigational Site study drug accountability record against the study drug inventory (unused and used) at the site. The Investigator and research staff will collaborate with the study monitor to resolve any identified discrepancies in a timely manner.

Each issue identified during study monitoring visits will be documented and reported to both the Sponsor and the Investigator.

## 14.3 Data Management

After the case report forms have been reviewed by the study monitor and all identified discrepancies have been identified, the Investigator signed copy of the case report forms will be forwarded to Data Management. Queries generated by Data Management will be sent to the study site for resolution. The Investigator is responsible for the review and approval of all responses.

All case report form data will be entered into a validated database and an electronic audit study of edits maintained. Laboratory data may be imported to the database electronically.

The database will be authorized for lock once no data queries are outstanding, all study data are considered clean, and all defined procedures completed.

## 14.4 Sponsor Audits

At some point during the study, individuals from the Sponsor's Quality Assurance group or their authorized representative may visit the Investigator's site to conduct an audit of the study. The purpose of this visit will be to determine the Investigator's adherence to the protocol, applicable regulations, and the Sponsor's procedures, in addition to assessing the accuracy of the study data. Prior to initiating this audit, the Investigator will be contacted by the Sponsor to arrange a convenient time for this visit. The Investigator and staff will cooperate with the auditors and allow access to all subject records supporting the case report forms and other study-related documents.

## 14.5 Inspection by Regulatory Authorities

At some point during the study, a regulatory authority may visit the Investigator to conduct an inspection of the study. The Investigator and staff will cooperate with the inspectors and allow access to all source documents supporting the case report forms and other study-related documents. The Investigator will immediately notify the Sponsor when contacted by any regulatory authority for purposes of conducting an inspection.

# 15 ETHICS

## 15.1 Declaration of Helsinki

The study will be conducted in accordance with the Declaration of Helsinki. [20]

## 15.2 Good Clinical Practice and Regulatory Compliance

This study will be conducted in accordance with the principles of GCP (current ICH guideline) and the requirements of all local regulatory authorities regarding the conduct of clinical studies and the protection of human subjects.

## 15.3 Institutional Review Board/Independent Ethics Committee

The protocol, ICF, IB, and any materials (such as advertisements, subject information sheets, or descriptions of the study used to obtain informed consent) for this study will be reviewed and approved by a duly constituted IRB/IEC.

The Investigator will ensure that all aspects of the IRB/IEC review are conducted in accordance with current institutional, local, and national regulations. A letter documenting the IRB/IEC approval will be provided to the Sponsor prior to initiation of the study.

Amendments to the protocol will be subject to the same requirements as the original protocol. A letter documenting the IRB/IEC approval will be provided to the Sponsor prior to implementation of the changes described in the protocol amendment.

Revisions to the ICF will be reviewed and approved by the IRB/IEC prior to use in the study. The Investigator will inform the IRB/IEC of all reportable AEs. IND Safety Reports provided by the Sponsor to the Investigator will be promptly forwarded to the IRB/IEC by the Investigator. Updates to the IB provided by the Sponsor to the Investigator will be submitted to the IRB/IEC by the Investigator.

The Investigator will submit all periodic reports and updates that the IRB/IEC may require. After completion or termination of the study, the Investigator will submit a final report to the IRB/IEC. The structure and content of the report will meet that described in Structure and Content of Clinical Study Reports E3 (ICH Harmonized Tripartite Guideline, dated 30 Nov 1995).

## 15.4 Informed Consent

No study-related procedures, including screening evaluations, will be performed until the subject has given written informed consent.

The ICF will clearly describe the nature, scope, and potential risks and benefits of the study, in a language that the subject understands. The ICF will conform to all the requirements for informed consent according to ICH GCP and US FDA guidelines (21 CFR 50) and any additional elements required by the Investigator's institution or local regulatory authorities. The Investigator will submit the ICF to the IRB/IEC for review, and will provide the Sponsor with a letter documenting the IRB/IEC approval prior to initiation of the study.

The IRB/IEC approved ICF will be given to each prospective participant. The subjects will be given adequate time to discuss the study with the Investigator or site staff and to decide whether or not to participate. Each subject who agrees to participate in the study and who signs the ICF will be given a copy of the signed, dated, and witnessed document. The original signed ICF will be retained by the Investigator in the study files.

The Investigator will also obtain authorization from the subject to use and/or disclose Protected Health Information (PHI) in compliance with Health Insurance Portability and Accountability Act (HIPAA) or equivalent. Written HIPAA authorization may be obtained as part of the informed consent process.

If a protocol amendment substantially alters the study design or increases the potential risk to the subject, or the known risks of the study drug change over the course of the study, the ICF will be revised and submitted to the IRB/IEC for review and approval. The revised ICF must be used to obtain consent from subjects currently enrolled in the study if they are affected by the amendment and to obtain consent from new subjects prior to enrollment.

## 15.5 Emergency Departure from Protocol

When an emergency occurs that requires a departure from the protocol for an individual, a departure will be only for that subject. The Investigator or other physician in attendance in such an emergency will, if circumstances and time permit, contact the Sponsor's Medical Monitor immediately by telephone. Such contacts will be made as soon as possible to permit a decision as to whether or not the subject (for whom the departure from protocol was affected) is to continue in the study. The case report form and source documents will completely describe the departure from the protocol and state the reasons for such departure. In addition, the IRB/IEC will be notified in writing of such departure from protocol.

# 16 PUBLICATION POLICY

All information and data obtained in the course of the study are the property of the Sponsor and are considered confidential. To avoid disclosures that could jeopardize proprietary rights, the institution and/or the Investigator agree to certain restrictions on publications (eg, abstracts, speeches, posters, manuscripts, and electronic communications), as detailed in the clinical study agreement.

The publication or presentation of any study results shall comply with all applicable privacy laws, including, but not limited to, HIPAA or equivalent.

# 17 PROTOCOL AMENDMENTS AND MODIFICATIONS

The Investigator will ensure that the study is conducted in accordance with the procedures and evaluations described in this protocol. The Investigator will not modify the protocol without first receiving Sponsor authorization to do so, except in those cases intended to reduce immediate risk of the subjects. The Sponsor is responsible for submitting protocol amendments to the appropriate governing regulatory authorities. The Investigator is responsible for submitting protocol amendments to the appropriate IRB/IEC. Approval by the IRB/IEC will be obtained before protocol modifications are implemented, except in those cases intended to reduce immediate risk to subjects.

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# 19 APPENDICES:

## 19.1 Appendix 1: National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03

NCI-CTCAE version 4.03 will be used in this study for AE reporting.

A copy of CTCAE version 4.03 can be downloaded from the Cancer Therapy Evaluation Program (CTEP).

https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

## 19.2 Appendix 2: New York Heart Association Functional Classification

The New York Heart Association (NYHA) Functional Classification [21] provides a simple way of classifying the extent of heart failure. It places subjects in one of 4 categories based on how much they are limited during physical activity; the limitations/symptoms are in regards to normal breathing and varying degrees in shortness of breath and or angina pain:

| **Functional Capacity** | | **Objective Assessment** |
|---|---|---|
| **Class I** | Subjects with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain. | No objective evidence of cardiovascular disease |
| **Class II** | Subjects with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain. | Objective evidence of minimal cardiovascular disease |
| **Class III** | Subjects with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain. | Objective evidence of moderately severe cardiovascular disease |
| **Class IV** | Subjects with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If | Objective evidence of severe cardiovascular disease |

| | | |
|---|---|---|
| | any physical activity is undertaken, discomfort increases. | |

## 19.3 Appendix 3: ECOG Performance Status

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

Note: As previously published. [22]

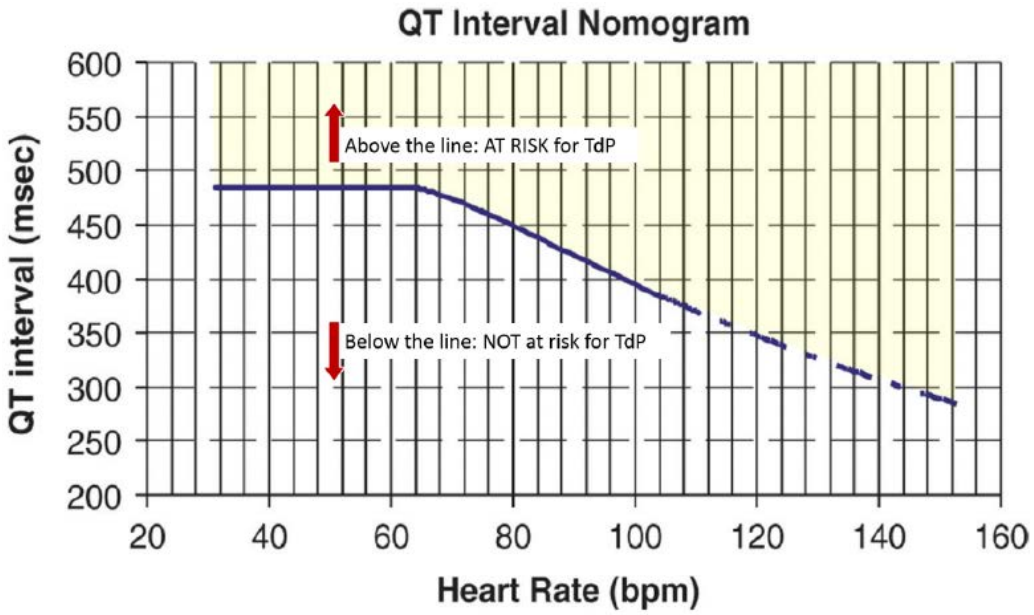
## 19.4 Appendix 4: Package Insert for Cytarabine and Dacogen™ (Decitabine)

- Conventional cytarabine is no longer a branded product in the US. A copy of the product insert for generic cytarabine can be downloaded from the following link:
  https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=34803a0e-f54d-4147-8f9f-7d0e3a007756
- A copy of the Package Insert for Dacogen (decitabine) can be downloaded from the following link:
  https://www.otsuka-us.com/media/static/DACOGEN-PI.pdf
  Note that generic equivalents are available.

## 19.5 Appendix 5: Clinical Study Report PLKA-937-001

A Phase 1 Dose Escalation Study of NMS-1286937 Administered to Adult Patients with Advanced/Metastatic Solid Tumors, dated 06 Apr 2016

## 19.6 Appendix 6: Torsades de Pointes Risk QT Interval Normogram




Derived from: https://missouripoisoncenter.org/qt-nomogram-assessing-risk-torsades-de-pointes/