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)

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Statistical Analysis Plan (SAP)

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 Version No./Date:	6.0 Amendment 2/09-Aug-2019
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1.0 Approvals

Sponsor	
Sponsor Name:	Cardiff Oncology, Inc.
Representative/ Title:	[redacted]
Signature /Date:	<Signature of Sponsor Representative /Date> [redacted] This space reserved for eSignature block (if applicable).
PRA	
Biostatistician / Title:	[redacted]
Signature /Date:	<Signature of Biostatistician /Date> [redacted] This space reserved for eSignature block (if applicable).

(NOTE: Electronic Signatures should only be used if all parties have the ability to eSign.)

2.0 Change History

Version/Date	Change Log
0.1	Created as new
1.0	Version reviewed by Trovagene Oncology (2018)
1.1	Updated with comments from Trovagene Oncology
1.2	Updated with protocol amendment (protocol V 6.0)
1.3	Minor changes per [redacted] and [redacted]
1.4	• Updated to reflect PRA current SAP template • Reflect change in name from Trovagene Inc to Cardiff Oncology, Inc • Clarify Cardiff Oncology Inc. responsibility for PD and biomarker data and analysis • Clarify objectives and endpoints • Remove per protocol sensitivity analysis • Cross-checked SAP with current CRF • Remove references to cytarabine arm in Phase 2 where appropriate • Minor wording changes and clarifications • Added deviations from protocol
1.5	• Separate PK analysis by cycle and time point • Update efficacy evaluable definition in PP analysis set • Update PK sections per PK specialist • Added definition of RP2D • Added BOR to a listing • Add PP efficacy listings • Clarify that dose adjustment (increase and decrease) will be summarized separately • Formatting and clarification
1.6	• Change all references to Cytarabine to low-dose Cytarabine • Updated description of summaries to indicate that Phase 1b demographic tables will not be presented by dose level. • Remove AE tables by PT only • Remove reference to tables and listings not reflected in new version of TFL specification • Removed reference to individual PK figures • Clarified wording and minor formatting changes
1.7	• Changed any reference to Cri to Cri • Section 10.6.4 – removed reference to progressive disease in association ith treatment failure to match 10.6.5 and CRF. • Clarified that recurrence and progressive disease will come from the discontinuation CRF page while treatment failure will com from the bone marrow aspirate CRF pages.

3.0 Table of Contents

4.0 Purpose

The Statistical Analysis Plan (SAP) describes the statistical methods to be used during the reporting and analyses of data collected under Cardiff Oncology, Inc. Protocol TROV-052.

5.0 Scope

The Statistical Analysis Plan outlines the following:

- Study Objectives
- Study Design
- Study Endpoints
- Applicable Study Definitions
- Statistical Methods

See Glossary of Abbreviations for a list of abbreviations used throughout this document. The list of the mock tables, figures, and listings (TFLs) depicting the analyses described in this SAP are presented in a separate document.

6.0 Introduction

This SAP describes the statistical methods to be used during the reporting and analyses of data collected under Cardiff Oncology, Inc. Protocol TROV-052.

This SAP should be read in conjunction with the study protocol and case report form (CRF). This version of the plan has been developed using the protocol dated 07-Aug-2019 and CRF dated 31-Jan-2020. Any changes to the protocol or CRF may necessitate updates to the SAP.

Changes following approval of the first draft of the SAP will be tracked in the SAP Change Log; the final version of the SAP will be issued for sponsor approval prior to database lock. Any deviations from the final version of the SAP will be documented in the final Clinical Study Report (CSR).

6.1 Changes from Protocol

The definition of the per protocol analysis set differs from the protocol by requiring at least one post baseline efficacy assessment (bone marrow) and also excluding subjects who have important protocol deviations that have the potential to affect efficacy. Efficacy endpoints from investigator response on bone marrow aspirate response form in CRF differ from the endpoints reflected in the protocol. Additional choices of stable disease and treatment failure are available in the CRF. These efficacy endpoints are incorporated into the statistical sections of this SAP and the TFL shells.

7.0 Study Objectives

Phase 1b:
• 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 acute myeloid leukemia (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.

7.1 Secondary Objectives

Phase 1b:
• 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.
• To analyze the pharmacokinetics (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.

7.2 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.

8.0 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.

This study is being conducted at 8 study centers in the United States, with a total enrollment up to 116 subjects. This study will have 2 arms. In Arm A, onvansertib will be combined with low-dose cytarabine. In Arm B onvansertib will be combined with decitabine. Up to 84 subjects will be enrolled in Phase 1b (42 subjects in each arm), dependent on the number of dose escalation cohorts required to determine MTD or RP2D. Phase 2 will enroll 32 subjects at RP2D identified in Phase 1b.

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.

In Phase 2, subjects must have received no more than one prior regimen for the treatment of their AML.

In both phases, subjects may be treatment naïve as long as they are not candidates for or have refused intensive induction therapy, nor received prior treatment with either low-dose cytarabine or decitabine for myelodysplastic syndromes (MDS). Neither of these circumstances will 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.

Phase 1b
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.

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 low-dose cytarabine which will be administered consistently 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 low-dose 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), low-dose 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 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. 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, at investigator 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 asCohort A1.

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

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 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 subjects 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 preceding lower 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 an onvansertib 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. This may occur 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.

Table 1: Onvansertib 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.

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.

Phase 2

In Phase 2, a total of 32 subjects will be enrolled at the RP2D to further evaluate safety and preliminary efficacy of onvansertib. 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, at investigator discretion, to treat subjects 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 recorded throughout the study. Safety evaluations will include: physical examinations, performance status, vital signs, electrocardiograms (ECGs), hematology and serum chemistry laboratory tests, and urinalysis.

Efficacy evaluations include leukemic response, duration of response, event-free survival and overall survival.

If at any time during Phase 2 more than 33% of subjects develop a DLT, accrual will stop and the RP2D will be reassessed in additional cohorts.

8.1 Sample Size Considerations

The planned sample size in the Phase 1b portion of the study is up to 84 subjects (42 in each arm; combination of onvansertib and low-dose cytarabine, combination of onvansertib and decitabine), 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 standard 3+3 design 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:

- If 0 out of 3 subjects experience DLT (as defined in Section 10.1.4 of the protocol) during the first cycle of therapy, the next cohort of 3 subjects will be treated at the next higher dose level.
- 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.
- 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 are dosed and a ≥50% chance of stopping with 3 subjects. With 6 subjects, there is at most a 17.2% chance of satisfying the conditions for dose escalation after 6 subjects have been dosed. 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.

8.2 Randomization

This is an open-label, non-randomized study.

9.0 Study Endpoints

9.1 Primary Endpoints

Phase 1b

- Characterization of DLTs
- MTD or RP2D dose of onvansertib in combination with either low-dose cytarabine or decitabine
- Characterization of AEs by incidence and severity (graded by NCI-CTCAE version 4.03)

Phase 2

- Safety And Tolerability
    - 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

- Frequency of dose interruptions, dose reductions, and treatment discontinuation
- Frequency of lab abnormalities
- Medical history
- Changes from baseline in ECGs, physicalexaminations, weight, and ECOG performance, echocardiograph (ECHO)/ multigated acquisition scan (MUGA)

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

    For CR:
    - Subject is independent of transfusions
    - Absolute neutrophil count (ANC) of >1000/mm^3
    - Number of platelets of ≥100,000/mm^3

    For complete response with incomplete blood count recovery (CRi):
    - Meets all criteria for CR except for neutropenia (ANC<1000/mm^3) or thrombocytopenia (<100,000/mm^3) but must include transfusion independence

9.2 Secondary Endpoints

Phase 1b

- Characterization of AEs by incidence and severity (graded by NCI-CTCAE version 4.03)
- Concentrations of onvansertib in plasma samples collected at prespecified time points before and after administration of onvansertib, including maximum plasma concentration (Cmax), trough plasma concentration (Ctrough), time to maximum plasma concentration (Tmax), area under the concentration-time curve from 0 to time of last quantifiable concentration (AUClast), and plasma terminal elimination half-life (T-HALF)

Phase 2

- Note that Phase 2 analysis will only include onvansertib in combination with decitabine
- Characterization of AEs by incidence and severity (graded by NCI-CTCAE version 4.03)
- Concentrations of onvansertib in plasma samples collected at prespecified time points before and after administration of onvansertib, including maximum plasma concentration (Cmax), trough plasma concentration (Ctrough), time to maximum plasma concentration (Tmax), area under the concentration-time curve from 0 to time of last quantifiable concentration (AUClast), and plasma terminal elimination half-life (T-HALF)
- Efficacy
  - Rate of MLF in Phase 2, defined as:
    - Bone marrow (BM) <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
  - 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
  - Duration of response (DOR) in Phase 2: Time from documentation of response until documentation of recurrence of or progression of disease
  - Event-free survival (EFS) in Phase 2: Time from enrollment until disease

progression or death from any cause

- Overall survival (OS) in Phase 2: Time from enrollment until death from any cause

9.3 Exploratory Endpoints

- Blood samples for PD and diagnostic biomarker evaluation
- Evaluation of the rate of complete response (CR + CRi), MLF state, PR, DOR, EFS and OS in all enrolled subjects (Phases 1b and 2)
- Note that PRA will not receive PD or biomarker data and will not provide this evaluation

10.0 Conventions and Derivations

10.1 Study Day

Study day is defined as:

(study date – Cycle 1/Day 1 date +1)

Cycle 1/Day 1 is the start date of study treatment. Study days before the first administration of study treatment will be calculated as date of assessment minus date of first administration of study treatment. Every effort will be made to avoid missing and/or incomplete dates. In case of missing and/or incomplete dates no study days will be calculated.

10.2 Baseline

The baseline value is defined as the last measurement prior to the first dose of study drug on Day 1 of Cycle 1 (the earliest of onvansertib, plus low-dose cytarabine or decitabine). If assessment time is missing and there is no way to determine if the assessment occurred pre-dose, Cycle 1/Day 1 assessments will be considered for baseline, including for assessments occurring on Cycle 1/Day 1.

10.3 Change from Baseline

Change from baseline is defined as:

(value at post-baseline visit – value at baseline)

In summary tabulations over time, unscheduled post-baseline values will be excluded.

10.4 Past and Current Medical History

Past medical histories are those with a stop date prior to the first administration of study treatment.

Current medical histories are those which started prior to enrollment in the study but which are ongoing at the start date on or after the first administration of study treatment.

10.5 Prior and Concomitant Medications

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 end of study treatment. Use of all concomitant medications, including any change in therapy, will be recorded, categorized and summarized according to WHO Drug Global B3 SEP2017. Prior medications are medications that end prior to a subject's first dose of study drug. Prior and concomitant medications are medications that begin prior to a subject's first dose of study drugRefer to Section 10.11.1 for rules of imputing partial/missing concomitant medications start and stop dates.

10.6 Derivation of Efficacy Variables

The primary efficacy measure is leukemia response in Phase 2, which is evaluated at the timepoints indicated in the schedule of events in the clinical protocol (tables 9-1, 9-2, and 9-3) and is based on BM aspirate results and peripheral blood examinations. Response criteria will be based on the International Working Group for AML (Cheson et. al. 2003). Baseline efficacy assessments are required to be completed within 14 days of enrollment.

10.6.1 Rate of Complete Response

The primary efficacy variable is the rate of complete response (CR + CRi), where complete response is defined as follows:

CR

subject has MLF, plus:

- subject is independent of transfusions
- has an absolute neutrophil count (ANC) >1000/mm^3, and
- platelets ≥ 100,000/mm^3

or

CRi

- subject meets all criteria for CR except for either neutropenia (ANC<1000/mm^3) or thrombocytopenia (platelets<100,000/mm^3) but also must include transfusion independence

CR or CRi are indicated on the Bone Marrow Aspirate Response CRFs as an Investigator Response of "Morphologic complete remission (CR)" or "Morphologic complete remission with incomplete blood count recovery (CRi)", respectively. The rate of complete response is defined as the proportion of subjects where best overall response (BOR) is CR or CRi at the 14 to 21 days post-treatment assessment.

10.6.2 Rate of Achievement of a Morphologic Leukemia-Free State

Achievement of MLF is indicated by a 'Y' response to the "Morphologic leukemia-free state present?" field of the Bone Marrow Aspirate Response CRFs. The rate of achievement of MLF is defined as the proportion of subjects with MLF indicated at the 14 to 21 days post-treatment assessment.

10.6.3 Rate of Partial Response

A Partial Response (PR) is indicated on the Bone Marrow Aspirate Response CRFs as an Investigator Response of "Partial response (PR)". The rate of partial response is defined as the proportion of subjects with a response of PR at the 14 to 21 days post-treatment assessment.

10.6.4 Best Overall (Leukemic) Response

The Best Overall (Leukemic) Response (BOR) for each subject is defined as the best response per Investigator assessment among all responses recorded after start of treatment through to disease progression or end of treatment, whichever comes first, with a decreasing response ranking of CR, CRi, MLF state, PR, stable disease, then Treatment Failure. Stable disease and treatment failure are indicated as Investigator Responses on the Bone Marrow Aspirate Response CRFs.

10.6.5 Duration of Response

The Duration fo Response (DOR) is defined as the time in months from documentation of response until documentation of recurrence of or progression of disease, i.e.:

(date of documentation of recurrence or progression of disease – date of first observation of CR, CRi, MLF state, or PR + 1)/30.4375

Disease progression is captured on the Discontinuation CRF as a Reason for Discontinuation of "Progressive Disease" along with the Date of Discontinuation (progression of disease).

Recurrent disease is captured on the Discontinuation CRF as an Reason for Discontinuation of "Recurrent Disease" along with the Date of Discontinuation (progression of disease).

The DOR will only be calculated for the subgroup of subjects achieving CR, CRi, MLF state, or PR at the 14 to 21 days post-treatment assessment. Event times will be censored either on the date of the last evaluable assessment documenting response and recurrence-free or progression-free at the time of analysis or on date of death.

10.6.6 Event-free Survival

Event-free Survival (EFS) is defined as the time in months from enrollment until disease progression or death from any cause, i.e.:

(earlier of date of documentation of progression of disease or death – date of enrollment + 1)/30.4375

Disease progression is captured on the Discontinuation CRF as a Reason for Discontinuation of "Progressive Disease" along with the Date of Discontinuation (progression of disease). Deaths are captured on the Adverse Events or Survival Status CRFs. Event times will be censored on the date of the last evaluable assessment documenting response and progression-free at the time of analysis.

10.6.7 Overall Survival

Overall Survival (OS) is defined as the time in months from enrollment until death from any cause, i.e.:

(date of death – date of enrollment + 1)/30.4375

Deaths are captured on the Adverse Events or Survival Status CRFs. Event times will be censored on the date last known to be alive at the time of analysis for subjects who do not have death documented. Last alive dates will come from the Survival Status CRFs.

10.7 Study Drug Exposure Variables

10.7.1 Duration of Exposure

Duration of exposure (months) is defined as (last dose date – first dose date +1)/30.4375 and will be computed for each study treatment. Treatment free periods within cycles are included.

10.7.2 Number of Cycles

The number of cycles, regardless of length, initiated where a dose was administered > 0 mg. This is defined for each study treatment.

10.7.3 Dose Interruption

A dose interruption is defined for decitabine only as any interruption during the administration (infusion) of a dose. Dose interruptions of decitabine are recorded on the Decitabine Administration CRF page as a 'Y' response to "Was the treatment administration interrupted?" The duration and units of the duration of the interruptions are also recorded in the EXINTRP and EXINTRPU fields, respectively. Duration will be

summarized in minutes. A dose interruption recorded in hours or days will be transformed to minutes using the following calculations:

Recorded in hours: (dose interruption (hours))/60
Recorded in days: (dose interruption (days))/(60*24)

10.7.4 Dose Adjustment

A dose adjustment is defined for onvansertib only as any change in the dose assigned for ingestion. Dose adjustments of onvansertib are captured as a 'Y' response in the EXDPSADJ field (Was the dose level adjusted from planned?) along with the adjusted dose (mg) in the EXDSADJ field of the Onvansertib Administration CRF pages.

10.7.5 Total Dose Administered

Total dose administered (mg/m^2) is defined as the total amount of study drug received as recorded in the EXDSTXT field on the Onvansertib Administration, Decitabine Administration, and the low-dose Cytarabine Administration CRF pages, i.e., the sum of all doses (mg/m^2) administered. This is computed separately for each study treatment.

10.7.6 Missed Doses

A missed dose is defined as any planned dose not administered and is captured as a 'N' response in the EXADM field (Was dose administered?) on the Onvansertib Administration, Decitabine Administration, and the low-dose Cytarabine Administration CRF pages. Treatment free periods within cycles are not considered in this definition.

10.8 Safety Variables

10.8.1 Adverse Events

An Adverse Event (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 can be any unfavorable and unintended sign (e.g., 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 (e.g., off-label use, use in combination with another drug) and with any route of administration, formulation, or dose, including an overdose.

All reported AEs will be mapped to standard coding terms using Medical Dictionary for Regulatory Activities (MedDRA) version 20.1, and grouped by system organ class (SOC) and preferred term (PT).

10.8.1.1 Serious Adverse Events (SAEs)

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
- Is life-threatening
- 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 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 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.

10.8.1.2 Severity of Adverse Events

Each AE will be graded according to the NCI-CTCAE version 4.03. 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 SOC and graded according to the general CTCAE severity guidelines (see protocol, Appendix 1).

10.8.1.3 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 the onvansertib, decitabine, or low-dose cytarabine. All AEs must be attributed to study drugs unless there is a reasonably acceptable alternate cause for the adverse events. 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 meiecondition 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.

10.8.1.4 Treatment-Emergent Adverse Events (TEAEs)

AEs that occur or start, or increase in severity on or after the first dose of study drug and no later than 30 days after the last dose of study drug will be considered treatment-emergent. See Section 10.11.1 for imputation rules for AE dates.

The earliest date of the first dose of onvansertib, low-dose cytarabine or decitabine will be considered the first study drug dose date; the latest date of the last dose of onvansertib, low-dose cytarabine or decitabine will be considered the last dose of study drug date.

10.8.1.5 Treatment-Related Adverse Events

All AEs for which the relationship to study treatment is classified as “possibly”, “probably” or “definitely” related will be classified as treatment-related. If the relationship to study treatment is missing, the relationship will be assumed to be treatment-related.

10.8.2 Dose Limiting Toxicities

Dose-limiting toxicities (DLTs) are defined as events related to onvansertib that are considered an adverse reaction or suspected adverse reaction occurring during the first cycle of therapy, per criteria outlined in protocol Section 10.1.4. 4An AE with a response ‘Y’ to the question “Was the AE classified as Dose Limiting Toxicity (DLT)?” on the AE CRF page will be classified as a DLT. An AE with a missing response to the question “Was the AE classified as Dose Limiting Toxicity (DLT)?” will be classified as a DLT.

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.

10.8.3 Maximum Tolerated Dose

The maximum tolerated dose (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.

10.8.4 Recommended Phase 2 Dose

The Recommended Phase 2 Dose (RP2D) may be as high as the MTD and will 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.

10.8.5 Clinical Laboratory Parameters

Clinical laboratory parameters to be collected routinely on study are listed in Table 2 below. All parameters will be tested by local laboratories. Clinical laboratory data will be entered into the electronic data capture (EDC) system and converted to International System (SI) units for analysis. Normal ranges will be merged in during dataset programming. Baseline laboratory parameters are the last collected any time prior to start of treatment on Cycle 1 Day 1 in each phase.

Table 2: Laboratory Safety Parameters

Hematology Panel	**Blood Chemistry Panel**
Hematocrit (HCT)	Alkaline Phosphatase (ALP)
Hemoglobin (HGB)	Alanine aminotransferase (ALT)
Red Blood Cell Count (RBCC)	Aspartate aminotransferase (AST)
Platelet Count	Total Bilirubin
White blood cell count (WBC) with Differential (absolute and %)	Lactate Dehydrogenase (LDH)
Basophils	Total Protein
Eosinophils	Albumin

Lymphocytes	Bicarbonate
Monocytes	Calcium
Neutrophils	Sodium
Immature cells	Potassium
	Magnesium
Urinalysis (only at baseline)	Phosphorus
Specific Gravity	Glucose
pH	Chloride
Leukocyte Esterase	Creatinine
Nitrite	Blood Urea Nitrogen (BUN)
Protein	Urea
Glucose	Uric acid
Ketones	
Urobilinogen	
Bilirubin	
Blood	

10.8.6 Physical Examination and Vital Signs

Abnormal results of physical examinations of body systems will be captured on the Medical History CRFs (screening examinations) and the Adverse Events CRFs (after screening examinations). The vital signs collected on this study are height (cm), weight (kg), body temperature (°C), systolic and diastolic blood pressure (mmHg), pulse (beats/min), and respiratory rate (breaths/min). These will be entered on the Vital Signs – Screening and Vital Signs CRFs. Baseline vital signs are the last collected any time prior to start of treatment on Cycle 1 Day 1 in each phase.

10.8.7 Electrocardiograms

Twelve-Lead electrocardiograms (ECGs) will periodically be performed in triplicate and the following information entered on the EGLR1 and EGLR2 CRFs for analysis:

- mean heart rate (beats/min)
- mean P-R interval (msec)
- mean QRS interval (msec)
- mean QT interval (msec)
- mean R-R interval (msec)
- mean QTc (msec) by the Fridericia's formula, QTcF
- indicator of clinically significant ECG

Categories for QTcF are described as follows:

- ≤ 450 msec

- > 450 to ≤ 480 msec
- > 480 to ≤ 500 msec
- > 500 msec

Categories for change from baseline in QTcF as described as follows:

- ≤ 30 msec
- > 30 to ≤ 60 msec
- > 60 msec

Baseline values are reported any time prior to start of treatment on Cycle 1 Day 1 in each phase.

10.8.8 Echocardiography or Multigated Acquisition Scans

In Phase 1b and Phase 2, electrocardiography (ECHO) or multigated acquisition (MUGA) scans will be performed at screening and the end -of -study visit (1 to 2 weeks after discontinuation). Indications of abnormal or clinically significant scan results are reported on the ECHO/MUGA CRFs.

10.8.9 Eastern Cooperative Oncology Group Performance Status

Eastern Cooperative Oncology Group (ECOG) performance status (grade or score ranging from 0-5; Appendix 19.3 of the protocol) will be collected at baseline and within 1 to 2 weeks after study treatment discontinuation and reported on the ECOG CRF.

10.9 Other Derived Variables

10.9.1 Body Mass Index

Body mass index (BMI) will be calculated based on baseline weight and baseline height using the following formula:

$$BMI = Weight\ (kg) / Height^2\ (m)$$

10.9.2 Age

Besides being analyzed as a continuous variable, baseline age, from Demography CRF page, will be categorized into the following groups:

- < 65 years old
- 65 to 75 years old
- > 75 years old

10.9.3 Differentials

When both absolute and % differentials are collected for a particular visit then data will be handled as follows:

- If absolute reported (or absolute and %) then report absolute
- If only % reported then calculate absolute from % and total WBC count with the following formula

Absolute differential= % differential * total WBC count

10.10 Partial Dates

For diagnosis and prior therapy dates, if day is missing and month is non-missing, the first day of the month with be assumed. If day and month are missing, the missing day and month will be set to 01 January.

If a death date is missing month or day, the following imputation method will be used:

- If only the death year is known and the last date the subject was known to be alive is in the same year, the subject's last alive date will be used as the death date. If the last alive date occurs in a previous year, the missing death month and day will be imputed as the first day and month of the year (01JAN).
- If the year and month are known and the last alive date is in the same year and month as the death date, then the last alive date will be used. If the last alive date is in a month prior to the death month, then the death day will be imputed as the first day of the month.

10.10.1 AE and Concomitant Medication Start and Stop Dates

Start Date: If only 'day' is missing, and the month and year are not the same as the month and year of the first dose, then day will be imputed with '01'. Otherwise, if the month and year are the same as first dose date, first dose date will be used. If 'day' and 'month' are missing, and 'year' is not missing, then month and day will be imputed with month and day of first dose date (assuming same 'year'). If the start date is completely missing, then the first dose date will be used. If the stop date is complete and the imputed start date is after the stop date, then the imputed start date will be set to the stop date. The original, non-imputed, dates will be retained in the clinical trial database and will be included in subject listings.

Stop Date: If only 'day' is missing, day will be imputed with last day of the month. If 'day' and 'month' are missing, and 'year' is not missing, then month will be imputed with '12' and day will be imputed with '31' (or date of study discontinuation/completion if earlier than Dec-31 and year is the same as the year of discontinuation). If the stop date is completely missing, it will be set to the date of study discontinuation/completion. A stop date will not be applied to ongoing AEs. If the imputed stop date is greater than the last contact date, then the imputed stop date will be set to last contact date. The original, non-imputed, dates will be retained in the clinical trial database and will be included in subject listings.

10.11 Missing Data

10.11.1 Missing Neutrophils

When a neutrophil value is missing, if values for segmented cells (SEGS) and bands (BANDS) are available, neutrophils will be calculated as:

SEGS+BANDS

If the neutrophil value is missing and either SEGS or BANDS are available, the neutrophil value will be the non-missing value of SEGS or BANDS.

10.11.2 Missing Absolute Differential

See section 10.10.3 Differential above.

10.12 Completed Trial

All subjects who remain on trial through their End of Study Visit and listed as "Subject Completed Study" will be considered as having completed the trial.

11.0 Analysis Sets

In all analysis sets, individual subjects will be grouped by dose according to the initial dose assigned.

11.1 Safety

The safety analysis set comprises all subjects who receive at least one dose of onvansertib and will be used in the analysis of safety variables.

11.2 Intention-to-Treat

The Intention to Treat (ITT) analysis set comprises all subjects who received at least one dose of study treatment (onvansertib and at least one dose of either low-dose cytarabine or decitabine) These subjects will be used in the analysis of efficacy variables.

11.3 Per Protocol

Subjects in the ITT analysis set who complete at least one cycle of study treatment, have had ≥1 evaluable post-baseline tumor assessment (BM) and have no important protocol deviations that have the potential to affect efficacy will be included in the PP analysis set.

11.4 Pharmacokinetics

The PK analysis set will consist of all subjects in the safety analysis set who have adequate plasma onvansertib concentration data as determined by the PK scientist.

12.0 Interim Analyses

Not applicable. There is no formal interim analysis planned for this study. However, the Safety Review Committee, 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.

13.0 Statistical Methods

All statistical analyses will be performed using SAS® Version 9.4 or higher.

Summaries will be presented by dose level and total within each combination (onvansertib + decitabine or onvansertib + low-dose cytarabine) at each dose enrolled, except for demographic data which will be presented by Phase but not individual dose levels. PK summaries will not include totals combining dose levels.

Subjects who have intra-subject dose escalation will be summarized in their initial dose group.

Categorical variables will be summarized using counts and percentages. Percentages will be rounded to one decimal place except 100% will be displayed without any decimal places and percentages will not be displayed for zero counts.

Continuous variables will be summarized using the number of observations (n), mean, standard deviation, median, minimum, maximum, 25th and 75th percentiles. The mean, median, and quantiles will be presented to one more and the standard deviation to 2 more decimal places than the precision of the original variable, while the minimum and miaximum will be presented at the same precision as the original variable.

13.1 Subject Disposition

The count and percentage of subjects screened, enrolled and treated in the study will be presented, along with the count and percentage of subjects included in each analysis set. The count of subjects who discontinue the study along with a breakdown of the corresponding reasons for discontinuation will also

be summarized in the safety analysis set. The count and percentage of subjects enrolled at each site will also be summarized based on all subjects enrolled. All visits and treatment assignments of the safety set will presented in the listings. Discontinuations from study will be presented in listings.

13.2 Demographic and Baseline Characteristics

Demographics including age (years), age categories, sex, race, ethnicity, height (cm), weight (kg) and BMI (kg/m^2) will be summarized at baseline using the safety analysis set. An additional demographics table will be generated for the PP analysis set

The number of weeks from AML diagnosis to the first dose of study drug, prior therapy use (yes/no), weeks from last prior AML therapy to the first dose of study drug, relapse status (yes/no), weeks from relapse to first dose, weeks from last AML therapy to relapse, and progression status (yes/no) will be summarized for the safety analysis set. Additionally, ECOG PS will be summarized. Prior AML therapy data will be listed by subject.

Medical history and physical examination results will be presented in listings in the safety analysis set.

13.3 Treatments

13.3.1 Extent of Study Drug Exposure

Study drug exposure will be summarized descriptively based on the safety analysis set for the following variables:

- Duration of exposure (months)
- Number of cycles administered for each study treatment
- Total dose administered (mg/m^2) calculated for each study treatment
- Number of dose adjustments (increase and decrease) per subject (onvansertib) with reason for dose adjustment
- Number of dose interruptions per subject (decitabine)
- Duration of dose interruptions per subject (minutes) (decitabine)
- Number of missed doses per subject for each study drug.

A listing will present exposure data by subject for onvansertib administration for the safety analysis set. Separate listings will present exposure data for low-dose cytarabine and decitabine administration based on the safety analysis set.

13.3.2 Concomitant Medications

Using the safety analysis set, the count and percentage of subjects using at least one concomitant medication overall will be summarized along with the count and percentage of subjects using at least one concomitant medication for each PT.

All medications will also be listed for the safety set. In the listing, medications will be classified as prior, prior and concomitant or concomitant.

13.4 Important Protocol Deviations

Protocol deviations will be identified, including, but not limited to, subjects that 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 an incorrect dose. The reason for each protocol deviation will also be identified.

Per PRA processes, important protocol deviations data will be entered into our Clinical Trials Management System (CTMS). The study team and the Sponsor will conduct ongoing reviews of the deviation data from CTMS and the resulting set of PP subjects throughout the study, adjusting the deviation criteria as appropriate. The PP analysis set must be finalized at the post-freeze data review meeting (or earlier), prior to database lock.

For each study phase, important protocol deviations for subjects in the safety analysis set will be summarized by deviation category. Important protocol deviations will also be listed. A Data listing will also present all protocol deviations by subject including whether deviation is an important protocol deviation resulting in exclusion from PP analysis set.

13.5 Efficacy Analyses

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

Subjects from the ITT analysis set will be included in the efficacy analyses. Similar summaries will also be generated for the PP analysis set.

Primary efficacy summaries will be generated for Phase 2 subjects. Derived efficacy data for Phase 1b and Phase 2 subjects will be presented in Subject listings.

13.5.1 Leukemic Response

The primary efficacy variable is leukemia response in Phase 2 subjects as evaluated by the Investigator at the end of each induction cycle, as indicated by the Investigaor, and at the end of -study visit based on BM aspirate and peripheral blood examination results.

Responders are subjects with a CR or CRi accompanied by MLF state. Subjects without efficacy evaluable assessments will be considered non-responders in the ITT analysis population.

The count and proportion of Phase 2 subjects achieving CR, CRi, MLF state, PR, Stable Disease, or Treatment Failure as the best overall leukemic response will be summarized based on the ITT analysis set using counts and percentages.

Rate of complete response (CR+CRi) will be summarized for the ITT analysis set and exact 95% binomial confidence intervals generated.

The count of subjects with MLF state and PR will be summarized based on counts and percentages for the ITT analysis set. All efficacy tables will also be presented for the PP analysis set. Ninety-Five% exact CIs will be presented for the percentages. Similar summaries will be generated based on extramedullary disease.

BOR data will be provided in a listing.

13.5.2 Duration of Response

DOR will be summarized using Kaplan-Meier (KM; Kaplan and Meier 1958) estimates for the ITT and PP analysis set in Phase 2 subjects who have had a response (CR, CRi, MLF state, or PR). The min, max, 25%, 50%, and 75% quartiles will be calculated and corresponding 95% CIs for the quartiles by the KM method. A KM plot for DOR will be presented. The count and percentage of responding subjects who have an event or are censored will be summarized.

DOR data will be provided in a listing.

13.5.3 Event-Free Survival

EFS will be summarized using KM estimates for the ITT and PP analysis set in Phase 2 subjects. The min, max, 25%, 50%, and 75% quartiles will be calculated and corresponding 95% CIs for the quartiles by the KM method. A KM plot of EFS will be presented. The count and percentage of those who have an event or are censored will be summarized. The EFS rate at 12 months and corresponding 95% CIs by the KM method will be presented.

EFS data will be provided in a listing.

13.5.4 Overall Survival

Overall Survival (OS) will be summarized using KM estimates for the ITT and PP analysis sets in Phase 2 subjects. The min, max, 25%, 50%, and 75% quartiles will be calculated. A KM plot of OS will be presented. The count and percentage of subjects who have an event or are censored will be summarized. The OS rate at 12 months and corresponding 95% CIs will be presented by the KM method.

OS data will be provided in a listing.

13.5.5 Exploratory Efficacy Analyses

Select individual components from BM aspirate results, BM aspirate response, and other parameters used to assess disease response will be listed for the ITT analysis set and the PP set.

13.6 Safety Analyses

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

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

13.6.1 Adverse Events

Safety will be assessed primarily based on AEs. All summaries of AEs will be based on treatment-emergent AEs unless otherwise indicated.
Counting of AEs will be by subject, not by event; subjects will be counted only once within each SOC or PT.

The count and percentage of subjects who report AEs will be summarized by phase and dose cohort for the safety analysis set as follows:

- AEs that are DLTs
- AEs by SOC and PT
- AEs by SOC, PT, and maximum NCI-CTCAE grade
- NCI-CTCAE Grade ≥ 3 AEs by PT
- Serious AEs by SOC and PT
- AEs related to onvansertib by SOC, PT, and maximum NCI-CTCAE grade
- NCI-CTCAE Grade ≥ 3 AEs related to onvansertib by PT
- Serious AEs related to onvansertib by SOC and PT
- AEs leading to discontinuation of study medication
- AEs with an outcome of death

For grade summaries, subjects with multiple events within a particular SOC or PT will be counted under the category of their most severe event within that SOC or PT. Events will be sorted by descending frequency of the total across all dose cohorts by SOC, and by PT within SOC for summaries.

AEs and TEAEs will be listed for individual subjects, including information regarding onset, duration, severity, seriousness, outcome and relationship to study drug.

13.6.2 Deaths

AEs with an outcome of death will be listed. In addition, death data from the survival status CRF will be presented in a listing. Causes of death will be included.

13.6.3 Laboratory Data

All laboratory results (hematology, clinical serum chemistry and urinalysis) will be presented in listings.

Shift tables for some hematology and chemistry tests will be provided for the maximum post-baseline grade including data from any unscheduled post-baseline timepoint, and the last study assessment while on study treatment. These tables will compare the NCI-CTCAE grade for the baseline value relative to each post-baseline time point value for all non-missing post-baseline data.

13.6.4 Vital Signs

A summary of abnormal vital signs by time point will be presented, where abnormal vital signs are systolic blood pressure >140 mmHg, diastolic blood pressure >90 mmHg, heart rate <60 beats/min or >100 beats/min, or temperature >37.5°C.

Vital sign results will be provided in data listings.

13.6.5 Physical Examinations, ECGs, and Other Observations Related to Safety

Additional safety assessments include physical examinations, ECG measurements, ECOG performance status, pregnancy tests and multigated acquisition (MUGA) or echocardiography (ECHO) scans.

Summaries of the above safety assessments are described below. Only listings will be generated for physical examination and pregnancy test results.

13.6.5.1 ECG

A summary of average of triplicate ECG parameters, heart rate, P-R interval, QRS interval, QT interval, QTcF interval and RR interval and change from baseline will be presented for each planned visit.

The count and percentage of subjects who have abnormal QTcF during the study will be summarized by the following International Conference on Harmonization (ICH) E14 categories:

Male:
QTc interval > 450 ms
QTc interval > 480 ms
QTc interval > 500 ms

Female:
QTc interval > 480 ms
QTc interval > 500 ms

Change from baseline in QTc interval:
QTc interval increases from baseline > 30 ms
QTc interval increases from baseline > 60 ms

All triplicate and average ECG data will be provided in data listings.

13.6.5.2 ECOG Performance Status

For Phase 1b and Phase 2, shift tables comparing ECOG data from baseline to post-treatment follow up/EOS ECOG score will be generated.

All ECOG data will be provided in data listings.

13.6.5.3 ECHO/MUGA

ECHO/MUGA results will be summarized based on shifts between screening and post-treatment follow up/EOS, with shift tables generated using normal/abnormal categories and normal/abnormal non-clinically significant abnormal/abnormal clinically significant categories.

ECHO/MUGA results will be presented in a listing.

13.7 Pharmacokinetic Analyses (PK)

13.7.1 Pharmacokinetic Variables

Concentrations of onvansertib will be collected in plasma.

PK parameters of onvansertib will be calculated for plasma.

13.7.2 Plasma Pharmacokinetic Summaries

13.7.2.1 Plasma Concentrations

The lower limit of quantification (LLOQ) of onvansertib is 0.100ng/mL. Plasma concentrations onvansertib below the quantifiable limit (BQL) will be set to 0 in the computation of mean concentration values. Descriptive statistics (number of subjects, mean, geometric mean, standard deviation (SD), coefficient of variation [%CV], median, min, and max) will be used to summarize the plasma concentrations by phase, cycle, combination drug and dose at each scheduled time point.

Semi-logarithmic (+SD) plots of the arithmetic mean plasma concentration by scheduled sampling time will be provided by phase, cycle, combination drug and dose. These plots will show time in hours. The plots will present all calculated means and will include a reference line for LLOQ.

All individual subject plasma concentration data will be listed by subject, by phase, combination drug and dose.

13.7.2.2 Plasma Pharmacokinetic Parameters

Plasma PK parameters for onvansertib will be estimated using non-compartmental methods with WinNonlin® version 8.1 using Best Fit regression. The PK parameters will be estimated from the concentration-time profiles, and AUCs will be calculated using linear up / log down method. In estimating the PK parameters, BQL values will be set to zero. Actual sampling times, rather than scheduled sampling times, will be used in all computations involving sampling times. If the actual time is missing, the scheduled time will be substituted and flagged.

In estimating the PK parameters, BLQ values at the beginning of the profile will be set to 0. BLQ values that occur after the first quantifiable point will be considered missing. Values that are embedded between BLQs, or quantifiable values occurring after two or more BLQs, will be set to missing at the discretion of the PK specialist

The following flags will be used to include parameters that meet the predefined criteria for summary and analysis:

Criteria Name	Analysis Flag	Criteria
Regression	ANL02FL	Adj Rsq >= 0.8

Note: Flags will be applied to parameters prior to derivation of additional parameters in SAS and will be used to include derived parameters as well.

The plasma concentration of onvansertib administered in combination with low-dose cytarabine or decitabine will be collected at specified study timepoints measured according to the schedule outlined in Tables 9-1, 9-2, and 9-3 of the protocol and reported by timepoint for onvansertib. The following PK parameters will be calculated as applicable for each subject:

Table 3. PK Parameters

Parameter	Description	Cycle, Day	SAS Programming Notes
Cmax	Maximum plasma concentration. Observed peak analyte concentration obtained directly from the experimental data without interpolation, expressed in concentration units	Cycle 1, Day 1, Cycle 1, Day 5, Cycle 2, Day 1, Cycle 2, Day 5	Cmax from WNL
Ctrough	Observed plasma concentration at the end of each dosing interval	Cycle 1, Day 5, Cycle 1, Day 8, Cycle 1 Day 15, Cycle 1, Day 22, Cycle 2 Day 5, Cycle 2 Day 8, Cycle 2 Day 15, Cycle 2 Day 22	Pre-dose concentration on for Cycle 1 on Day 5, 8, 15 and 22 and Cycle 2 on Day 5, 8, 15 and 22 from ADPC. Calculated in SAS.
Tmax	Time to maximum plasma concentration. First observed time to reach peak analyte concentration obtained directly from the experimental data without interpolation, expressed in time units.	Cycle 1, Day 1, Cycle 1, Day 5, Cycle 2, Day 1, Cycle 2, Day 5	Tmax from WNL
AUClast	Area under the concentration-time curve (time 0 to time of last quantifiable concentration).	Cycle 1, Day 5, Cycle 2, Day 5	AUClast from WNL
AUCtau	Area under the concentration-time curve over the dosing interval (time 0 to 24hr). If the nominal 24hr concentration was taken at or after 24hr postdose then AUCtau will be calculated by WNL to 24hr. If the nominal 24hr concentration was taken before 24hr post-dose and a valid λz is available then the data will be extrapolated to 24hr. If the nominal 24hr concentration was taken before 24hr post-dose and a valid λz is not available then AUC0-24 calculated to actual time will be used for AUCtau.	Cycle 1, Day 1, Cycle 1, Day 5, Cycle 2, Day 1, Cycle 2, Day 5	AUClast from WNL for Cycle 1 Day 1 and Cycle 2 Day 1 AUCtau from WNL Cycle 1 Day 5 and Cycle 2 Day 5 In case when AUCtau might not be available in WNL file, summary file might be used to extract the parameters for 24h nominal sampling time
T-HALF	Terminal phase half-life expressed in time units	Cycle 1, Day 5	HL_Lambda_z from WNL
CLss/F	Apparent clearance at steady state	Cycle 1, Day 5	CLss_F from WNL
Vss/F	The apparent volume of distribution during the terminal phase is calculated by dividing Dose by the product of AUCtau and Lz.	Cycle 1, Day 5	Vz_F from WNL

Descriptive statistics (number of subjects, mean, geometric mean, SD, %CV, median, min, and max) will be used to summarize the calculated PK parameters by phase, cycle, combination drug and dose. For Tmax, only median, min and max will be presented.

All parameters will be listed by subject, by phase, cycle, combination drug and dose; parameters that meet the inclusion criteria will be accompanied by an indication that each is criteria met.

The following parameters will be used for diagnostics and thus listed but not summarized.

Parameter	Description	SAS Programming Notes
Adj Rsq	Goodness of fit statistic for the log-linear terminal elimination phase of the concentration-time profile identified by least-squares linear regression and adjusted for the number of points (minimum of 3) used in the estimation of Lz.	Rsq_adjusted from WNL
Lz	Terminal phase rate constant calculated by linear regression of the terminal log-linear portion of the concentration vs. time curve. Using no weighting factor, the terminal log- linear phase of the concentration-time curve is identified by least-square linear regression of at least 3 data points that yielded a maximum G criteria, which is also referred to as adjusted R2. Lz is the absolute value of the slope of the terminal log-linear phase. Note: In Phoenix, use Best Fit method to determine regression.	Lambda_z from WNL

13.8 Pharmacodynamic and Diagnostic Biomarkers

Polo-like kinase 1, % blasts (serum and BM), and tumor gene expressions will be measured periodically during the study. Results will not be transferred to PRA and will not be included in the TFL deliveries.

13.9 Methods for Handling Dropouts and Missing Data

In Phase 1b, 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 without experiencing a DLT will be replaced. Data for subjects who are replaced will not be included in the summary analyses; data for replaced subjects will be presented in separate data listings. Sensitivity analyses of response parameters including all subjects (with replaced subjects analyzed as non-responders) may be generated as deemed appropriate per study results. Censoring rules for time to event endpoints are specified in Sections 10.6.5 to 10.6.7. Rules for imputation of missing/partial dates and other missing data are specified in Sections 10.10 and 10.11.

13.10 Multiplicity

There will be no adjustment made for multiplicity.

14.0 References

1. Cheson BD, Bennett JM, Kopecky KJ, et al. Revised recommendations of the International Working Group for Diagnosis, standardization of response criteria, treatment outcomes, and reporting standards for therapeutic trials in acute myeloid leukemia. J Clin Oncol. 2003; 21:4642-9.
2. Kaplan, E.L., and Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc. 1958; 53:457-481.

15.0 Glossary of Abbreviations

Glossary of Abbreviations:	
AE	Adverse event
AML	Acute Myeloid Leukemia
ANC	Absolute Neutrophil Count

AUC	Area under the plasma concentration-time curve
AUClast	Area under the concentration-time curve (time 0 to time of last quantifiable concentration)
AUCtau	Area under the serum concentration-time curve over the dosing interval (time 0 to 24hr)
BM	Bone marrow
BMI	Body Mass Index
BOR	Best Overall Response
BQL	Below the Limit of Quantification
CI	Confidence Interval
CLss/F	Apparent clearance at steady state
Cmax	Maximum plasma concentration
CR	Complete Response
CRF	Case Report Form
CRi	Complete Response with Incomplete Blood Count Recovery
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
CTMS	Clinical Trials Management System
Ctrough	Observed plasma concentration at the end of each dosing interval
DLT	Dose-Limiting Toxicity
DOR	Duration of Response
EDC	Electronic Data Capture
ECG	Electrocardiogram
ECHO	Echocardiography
ECOG PS	Easter Cooperative Oncology Group Performance Score
EFS	Event-free Survival
EOS	End of Study
EOT	End of Treatment
ITT	Intention-to-Treat
IV	Intravenously
LLOQ	Lower Limit of Quantification
KM	Kaplan-Meier
MLF	Morphologic Leukemia-Free
MTD	Maximum Tolerated Dose
MUGA	Multigated acquisition scan

NCI	National Cancer Institute
OS	Overall Survival
PD	Pharmacodynamics
PK	Pharmacokinetics
p.o.	Taken orally
PP	Per Protocol
PR	Partial Response
PT	Preferred Term
RP2D	Recommended Phase 2 Dose
SAP	Statistical Analysis Plan
SAE	Serious Adverse Event
SC	Subcutaneously
SD	Standard Deviation
SOC	System Organ Class
TEAE	Treatment-Emergent Adverse Event
TFL	Table, figure, and listing.
T-HALF	Terminal phase half-life expressed in time units
Tmax	Time to maximum plasma concentration
Vss/F	The apparent volume of distribution