Statistical Analysis Plan

NCT Number: NCT04266795

Title: A Randomized, Open-label, Controlled, Phase 2 Study of Pevonedistat, Venetoclax, and Azacitidine Versus Venetoclax Plus Azacitidine in Adults With Newly Diagnosed Acute Myeloid Leukemia Who Are Unfit for Intensive Chemotherapy

Study Number: Pevonedistat-2002

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STATISTICAL ANALYSIS PLAN

STUDY NUMBER: Pevonedistat-2002

A Randomized, Open-label, Controlled, Phase 2 Study of Pevonedistat, Venetoclax, and Azacitidine Versus Venetoclax Plus Azacitidine in Adults With Newly Diagnosed Acute Myeloid Leukemia Who Are Unfit for Intensive Chemotherapy

PHASE 2

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1.1 Approval Signatures

Study Title: A Randomized, Open-label, Controlled, Phase 2 Study of Pevonedistat, Venetoclax, and Azacitidine Versus Venetoclax Plus Azacitidine in Adults With Newly Diagnosed Acute Myeloid Leukemia Who Are Unfit for Intensive Chemotherapy

Approvals:

[redacted] MD, PhD
[redacted] Statistical and Quantitative Sciences

Date

2.0 TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

3.0 LIST OF ABBREVIATIONS

Abbreviation	Term
AE	adverse event
ALT	alanine aminotransferase
AML	acute myeloid leukemia
ANC	absolute neutrophil count
AST	aspartate aminotransferase
BSA	body surface area
BMA	bone marrow aspirate
CMH	Cochran-Mantel-Haenszel
CMML	chronic myelomonocytic leukemias
CR	complete remission
CRi	complete remission with incomplete blood count recovery
CCR	composite complete remission
CRh	complete remission + partial recovery of blood cells
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EFS	event-free survival
EOT	end of treatment
EU	European Union
FA	final analysis
HI	hematologic improvement
HR MDS	higher-risk myelodysplastic syndromes
HRQOL	health-related quality of life
IA	interim analysis
ITT	intent-to-treat
ITD	internal tandem duplication
IV	intravenous(ly)
IWG	International Working Group
IWRS	interactive web response system
K-M	Kaplan-Meier
LFT	liver function test
MDS	myelodysplastic syndromes
MedDRA	Medical Dictionary for Regulatory Activities
MLFS	morphological leukemia-free state
MRD	minimal residual disease
MPN	myeloproliferative neoplasm
mCR	marrow CR
NAE	NEDD8-activating enzyme
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events

Abbreviation	Term
ORR	overall response rate
OS	overall survival
PD	progressive disease; disease progression
PK	pharmacokinetic(s)
PP	per protocol
PR	partial remission
PS	[Eastern Cooperative Oncology Group] performance status
PT	preferred term
QD	Once Daily
RBC	red blood cell
SAE	serious adverse event
SAP	statistical analysis plan
SC	Subcutaneous
SMQ	Standard MedDRA Query
SOC	system organ class
SOE	Schedule of Events
sAML	secondary acute myeloid leukemia
TEAE	treatment-emergent adverse event
WBC	white blood cell
WHO	World Health Organization

4.0 OBJECTIVES

4.1 Primary Objectives

The primary objectives are:

- The primary objective of the study is to determine whether the combination of pevonedistat + venetoclax + azacitidine improves EFS compared with venetoclax + azacitidine in patients with newly diagnosed AML who are unfit for intensive chemotherapy. EFS is defined as the time from study randomization to the date of failure to achieve CR/CRi (ie, discontinuing treatment without achieving CR/CRi), relapse from CR or CRi, or death from any cause, whichever occurs first. [1]

4.2 Key Secondary Objective

The key secondary objective is:

- The key secondary objective is to determine whether the combination of pevonedistat + venetoclax + azacitidine improves OS when compared with venetoclax + azacitidine in an unfit population of patients with AML.

4.3 Other Secondary Objectives

Other secondary objectives are:

- To assess 30- and 60-day mortality rates in both treatment arms.
- To determine whether the combination of pevonedistat + venetoclax + azacitidine improves the rate of CR, composite complete remission (CCR [CR + CRi]), ORR (CR + CRi + PR), CR + partial recovery of blood cells ([CRh], and leukemia response rate (CR + CRi + PR +morphological leukemia-free state [MLFS, mCR]), compared with venetoclax + azacitidine.
- To determine whether the combination of pevonedistat + venetoclax + azacitidine improves duration of CR and CRi, compared with venetoclax + azacitidine.
- To determine whether the combination of pevonedistat + venetoclax + azacitidine shortens time to first CR, CRi, or PR when compared with venetoclax + azacitidine.
- To collect plasma concentration-time data for pevonedistat in combination with venetoclax + azacitidine to contribute to the future population PK and exposure response (safety/efficacy) analyses of pevonedistat.

4.4 Safety Objective

The safety objective is:

- The safety objective is to evaluate the safety of the combination of pevonedistat + venetoclax + azacitidine when compared with venetoclax + azacitidine in patients with AML who are unfit for induction therapy.

4.5 Exploratory Objectives

The exploratory objectives are:

- To evaluate the potential relationship between molecular characteristics of the tumor in terms of mutations, gene expression, protein abundance and protein/pathway activation status of apoptosis-related and Bcl-2 family-related effector genes/ proteins (eg, BCL2, NOXA BCL-XL, MCL1, BAX, BAK, and BH3) at baseline and efficacy and/or safety of the combination of pevonedistat + venetoclax + azacitidine versus venetoclax + azacitidine.
- To evaluate the impact of treatment on apoptosis and survival mechanisms at the RNA/protein levels within both bulk leukemia and leukemic stem/progenitor cells isolated from BMA or peripheral blood pre- and posttreatment in both treatment arms.
- To determine correlation of cytogenetic abnormalities/risk categories and molecular markers associated with poor prognosis in AML, such as FLT3 ITD, RUNX-1, IDH1, EZH2, ASXL1, TP53 with response and other clinical endpoints of interest in both treatment arms.
- To determine impact of therapy on elimination of leukemic stem cells in pevonedistat + venetoclax + azacitidine versus venetoclax + azacitidine.
- Identification of new somatic mutations posttreatment initiation and changes in activity of key signaling pathways in tumors from patients who initially respond to pevonedistat + venetoclax+ azacitidine or venetoclax + azacitidine therapy and then exhibit progressive disease (PD).
- Confirm pevonedistat target transcriptional modulation of CRL protein substrates (NQO1, SLC7A11) in peripheral blood in pevonedistat + venetoclax + azacitidine arm.
- To compare minimal residual disease (MRD) negativity rates and depth with response, EFS, relapse-free survival (RFS), OS kinetics and duration of response between study arms.
- To compare MRD negativity rates and depths in patients who achieve CR or CRi in both treatment arms.
- Exploratory endpoints such as evaluating circulating serum proteins and miRNA signatures associated with response or resistance to pevonedistat + venetoclax +

azacitidine treatment will be executed as warranted based on response, to support new emerging hypothesis or strategic need.

4.6 Study Design

This study is a multicenter, randomized, open-label, controlled phase 2 study of the triple combination with pevonedistat, venetoclax, and azacitidine (investigational arm, Arm A) versus venetoclax plus azacitidine (control arm, Arm B) in adult patients with AML who are unfit for intensive chemotherapy.

General eligibility may be assessed before the formal Screening period if it is part of standard clinical practice. However, per the Schedule of Events (SOE) (Appendix A), formal screening will occur during the screening period, which may last up to 28 days before randomization. The sponsor's project clinician (or designee) will confirm patient eligibility before randomization.

It is expected that approximately 150 patients will be enrolled in this study. At enrollment, patients will be randomized at a 1:1 ratio to receive (either pevonedistat + venetoclax + azacitidine [Arm A] or venetoclax + azacitidine [Arm B]) in 28-day treatment cycles. Patients will be stratified by age (18 to <75 years, ≥75 years) and AML subtype (de novo AML; secondary AML). Secondary AML (sAML) is defined as AML after MDS or MPN, or therapy-related AML (t-AML) following cytotoxic therapy, and/or radiotherapy for a malignant or nonmalignant disease.

Investigational Arm (Arm A):

Triple Combination (Pevonedistat + Venetoclax + Azacitidine)

- Pevonedistat 20 mg/m^2 (IV via 60-minute infusion) on Days 1, 3, and 5.
- Venetoclax (400 mg) on Days 1 through 28 in Cycle 1.

Ramp-up (Cycle 1 only): venetoclax will be administered at a dose of 100 mg on Day 1; 200 mg on Day 2; thereafter, at 400 mg on Days 3 through 28.

Venetoclax (400 mg) on Days 1 through 28 of a 28-day cycle at Cycle 2 and beyond. If, in the opinion of the investigator, venetoclax (400 mg) administered on Days 1 through 21 (of a 28-day cycle) is well tolerated, venetoclax (400 mg) dosing may be administered at full dosing frequency (400 mg given on Days 1 through 28 of 28-day cycle) in subsequent cycles.

- Azacitidine 75 mg/m^2 (IV or SC) dosing on Days 1 through 7 or Days 1 through 5, 8, and 9.

Control Arm (Arm B):

Combination (Venetoclax + Azacitidine)

- Venetoclax (400 mg) on Days 1 through 28 in Cycle 1.

Ramp-up (Cycle 1 only): venetoclax will be administered at a dose of 100 mg on Day 1; 200 mg on Day 2; thereafter, at 400 mg on Days 3 through 28.

Venetoclax (400 mg) on Days 1 through 28 of a 28-day cycle at Cycle 2 and beyond. If, in the opinion of the investigator, venetoclax (400 mg) administered on Days 1 through 21 (of a 28-day cycle) is well tolerated, venetoclax (400 mg) dosing may be administered at full dosing frequency (400 mg given on Days 1 through 28 of 28-day cycle) in subsequent cycles.

- Azacitidine 75 mg/m^2 (IV or SC) dosing on Days 1 through 7 or Days 1 through 5, 8, and 9.

Dose reductions with the study drugs, delays, or changes in the schedule may be allowed if related to safety or other unavoidable circumstances as detailed in Protocol Section 8.3.

Patients, including those who achieve CR, may receive study treatment until they experience unacceptable toxicity, relapse, or PD as defined in this study (see Protocol Section 6.3.1).

Patients in this study may also be allowed to continue study treatment (either treatment arm), even if they meet the criteria for PD based only on bone marrow blast counts if the patient is still receiving clinical benefit from the treatment. The continuation of treatment will be based on the clinical judgment of the investigator and endorsed by the sponsor's project clinician (or designee).

If the PD is a true progression of disease after CR/CRi, this would be scored as an event, despite the patient remaining on treatment. Patients who continue on study under these conditions must be reconsented before continuing study treatment. Patients may choose to discontinue treatment at any time. Patients who continue on study after implementation of Protocol Amendment 4 must be reconsented before dosing on Day 1 of the next full treatment cycle and must follow the Modified SOE.

Patients will attend the end-of-treatment (EOT) visit 30 days (+10 days) after the last dose of study drug or before the start of subsequent antineoplastic therapy if that occurs sooner. Patients will enter EFS follow-up (study visits every month to include physical examination, clinical blood tests, HRQOL assessments, and hospitalization assessment; BMA sampling to be conducted every 3 months, or upon suspected relapse from CR or CRi). Patients will enter OS follow-up (contacted every 3 months to document subsequent therapies and survival status).

Disease response assessments will be based on the Revised Recommendations of the International Working Group (IWG) for Diagnosis, Standardization of Response Criteria, Treatment Outcomes, and Reporting Standards for Therapeutic Trials in Acute Myeloid Leukemia [2]. Disease response assessments will be determined based on investigator assessments.

Bone marrow samples (biopsy and/or aspirate) will be collected at screening, during treatment, and during follow-up for blast count evaluation (to inform disease burden assessment). Bone marrow aspirates also will be used to analyze tumor cytogenetics, to analyze baseline somatic mutations and other molecular characteristics, to assess impact of therapy on depth and durability of response at predetermined time points using molecular techniques, and to identify treatment emergent mutations. Samples will be collected and analyzed from patients in both treatment arms.

Sparse sampling for the determination of pevonedistat plasma concentrations will be collected from each patient in the investigational arm receiving pevonedistat + venetoclax + azacitidine (Arm A) to contribute to a population PK analysis of pevonedistat co-administered with venetoclax and azacitidine.

AEs and ECOG performance status will be assessed; ECGs, clinical laboratory values, and vital signs measurements will be obtained, to evaluate the safety and tolerability of the study drug treatments.

Toxicity will be evaluated according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 5.0, effective 27 November 2017 [3]. Dose modification guidelines are presented in protocol Section 8.3.

5.0 ANALYSIS ENDPOINTS

5.1 Primary Endpoints

The primary endpoint is:

- EFS: EFS is defined as the time from study randomization to the date of failure to achieve CR/CRi (ie, discontinuing treatment without achieving CR/CRi), relapse from CR or CRi, or death from any cause, whichever occurs first [1].

5.2 Key Secondary Endpoint

The key secondary endpoint is:

- OS.

5.3 Other Secondary Endpoints

Other secondary endpoints are:

- Thirty-day and 60-day mortality rates.
- Disease response rates:
  - CR rate.
  - CCR (CR + CRi) rate.
  - ORR (CR + CRi + PR) rate.
  - CR + CRh (CRh is defined as <5% of blasts in the bone marrow, no evidence of disease, and partial recovery of peripheral blood counts [platelets >50,000/μL and absolute neutrophil count (ANC) >500/μL]) rate.
  - Leukemia response rate (CR + CRi + PR + MLFS [marrow CR]).
- Duration of CR and CRi.
- Time to first CR, CRi, and PR.

- Pevonedistat plasma concentration-time data.

5.4 Safety Endpoints

The safety endpoints are:

- AEs, including SAEs.
- Clinical laboratory values.
- Electrocardiograms (ECGs).
- ECOG performance status.
- Vital Signs.

5.5 Exploratory Endpoints

The exploratory endpoints are:

- Relative gene and protein expression levels of apoptosis-related and Bcl-2 family-related effectors such as BCL2, BCLXL, MCL1, BAX, and BAK in pre- and posttreatment samples of both bulk leukemia and leukemic stem/progenitor cells isolated from BMA or peripheral blood in pevonedistat + venetoclax + azacitidine versus venetoclax + azacitidine arms.
- Screening cytogenetic abnormalities/risk categories and molecular markers associated with poor prognosis in AML such as FLT3 ITD, RUNX-1, IDH1, EZH2, ASXL1, TP53, K-RAS and correlation with clinical efficacy in both treatment arms.
- Clearance of leukemic stem cells in pevonedistat + venetoclax + azacitidine versus venetoclax+ azacitidine.
- Evaluate potential mechanisms of treatment-emergent resistance, such as identification of new somatic mutations posttreatment initiation and changes in activity of key signaling pathways in tumors from patients who initially respond to pevonedistat + venetoclax + azacitidine or venetoclax + azacitidine therapy and then exhibit PD.
- Pevonedistat target transcriptional modulation of CRL protein substrates (NQO1, SLC7A11) in peripheral blood in pevonedistat + venetoclax + azacitidine arm.
- MRD negativity rates and depth in relation to response, EFS, RFS, OS kinetics and duration of response in both treatment arms.
- MRD negativity rates and depths in patients who achieve CR or CRi in both treatment arms.

6.0 DETERMINATION OF SAMPLE SIZE

The study was originally designed to have approximately 85 EFS events to provide 80% power to detect a HR of 0.58 (median EFS of 19 months in the investigational pevonedistat +

venetoclax + azacitidine arm [Arm A] versus 11 months in the venetoclax + azacitidine control arm [Arm B], assuming exponential distribution of EFS), using stratified log-rank test at one-sided 5% significance level.

Given the change being made in the pevonedistat program (noted in Section **Error! Reference source not found.** of the Protocol Amendment 4), FA for EFS will be conducted after the Protocol Amendment 4 is implemented, using the number of EFS events observed at FA.

7.0 METHODS OF ANALYSIS AND PRESENTATION

7.1 General Principles

All statistical analyses will be conducted using SAS® Version 9.2, or higher. Where appropriate, variables will be summarized descriptively by study visit. For the categorical variables, the count and proportions of each possible value will be tabulated by treatment group. The denominator for the proportion will be based on the number of subjects who provided non-missing responses to the categorical variable. For continuous variables, the number of subjects with non-missing values, mean, median, SD, minimum, and maximum values will be presented by treatment. The Kaplan-Meier survival curves and 25th, 50th (median), and 75th percentiles will be provided along with their 2-sided 90% and 95% CIs for time-to-event data.

Means and medians will be presented to 1 more decimal place than the recorded data. The standard deviations (SDs) will be presented to 2 more decimal places than the recorded data. Confidence intervals about a parameter estimate will be presented using the same number of decimal places as the parameter estimate.

P-values will be rounded to 3 decimal places prior to assessment of statistical significance if necessary.

The analyses will be performed and summarized using tables and/or figures for the corresponding analysis sets of population, wherever it is appropriate. The by-patient listings will also be provided, wherever it is appropriate.

7.1.1 Randomization and Stratification

The randomization scheme will be generated by an independent vendor. Before dosing, a randomization number will be assigned to each patient. The centralized randomization assignment will be implemented by an interactive web-based response system (IWRS).

Patients will be randomized to receive the Triple Combination Pevonedistat + Venetoclax + Azacitidine or the Combination Venetoclax + Azacitidine in a 1:1 ratio. The randomization will be stratified by age (18 to <75 years, ≥75 years) and AML subtype (de novo AML; sAML).

Randomization stratification error may occur during study conduct and will be summarized.

7.1.2 Blinding and Unblinding

This is an open-label study. Takeda's staff (or its designee) who are directly involved in the study conduct will be blinded to the treatment assignment of patients in the trial.

Following the implementation of Protocol Amendment 4, Takeda's staff (or its designee) will be unblinded.

7.1.3 Definition of Study Days

Study Day 1 is defined as the date on which a subject is administered their first dose of the medication. Other study days are defined relative to the Study Day 1 with Day 1 being Study Day 1 and Day -1 being the day prior to Study Day 1.

7.1.4 Definition of Study Visit Windows

All data will be categorized on the basis of the scheduled visit at which they are collected. These visit designators are predefined values that appear as part of the visit tab in the electronic case report form (eCRF). The analysis of PK data will be based on the actual elapsed time post dose.

7.1.5 Conventions for Missing Adverse Event Dates

Every effort will be made to avoid missing/partial dates in on-study data.

Adverse events with stop dates that are completely or partially missing will be imputed as follows:

- If the stop date has a month and year but the day is missing, the last day of the month will be imputed.
- If the stop date has a year but the day and month are missing, the 31st of December will be imputed.

After the imputation, the imputed dates will be compared against the date of death, if available. If the date is later than the date of death, the date of death will be used as the imputed date instead.

Adverse events with start dates that are completely or partially missing will be imputed as follows:

- If the start date has a month and year but the day is missing, the first day of the month will be imputed.
- If this date is earlier than the first dose date, then the first dose date will be used instead.
- If this date is later than the stop date (possibly imputed), then the stop date will be used instead.
- If the start date has a year, but the day and month are missing, the 15th of June will be imputed.
- If this date is earlier than the first dose date, then the first dose date will be used instead.
- If this date is later than the stop date (possibly imputed), then the stop date will be used instead.

If the start date of an event is completely missing, then it is imputed with the first dose date.

7.1.6 Conventions for Missing Concomitant Medication/ Subsequent Therapies Dates

Concomitant therapies with start dates that are completely or partially missing will be analyzed as follows:

- If the start date has a month and year but the day is missing, the therapy will be included in the summary table if the month and year of the start date of the event are:
- On or after the month and year of the date of the first dose of study drug

  and
- On or before the month and year of the date of the last dose of study drug plus 30 days
- If the start date has the year but the day and month are missing, the therapy will be included in the summary table if the year of the start date of the event is:
- On or after the year of the date of the first dose of study drug

  and
- On or before the year of the date of the last dose of study drug plus 30 days

If the start date of an event is completely missing, then the therapy will be included in the summary table.

Subsequent therapies with start dates that are completely or partially missing will be analyzed as follows:

- When the month and year are present but the day is missing:
- If the onset month and year are the same as the month and year of the last dose of study drug, the day of the last dose + 1 will be imputed.
- If the onset month and year are not the same as the month and year of the last dose of study drug, the first day of the month is imputed.
- When only a year is present:
  - If the onset year is the same as the year of the last dose of study drug, the date of last dose + 1 will be imputed.
  - If the onset year is not the same as the year of the last dose of study drug, the first day of the year is imputed.
- If no components of the onset date are present, the date of the last dose of study drug + 1 will be imputed.

7.1.7 Missing/Partial Dates in Screening Visit

The following rules apply to dates recorded in the Screening visits:

- If only the day component is missing, the first day of the month will be used if the year and the month are the same as those for the first dose of study drug; otherwise, the 15th will be used.
- If only a year is present, and it is the same as the year of the first dose of study drug, the 15th of January will be used unless it is later than the first dose, in which case the date of the first of January will be used, unless other data indicate that the date is earlier.

If only a year is present, and it is not the same as the year of the first dose of study drug, the 15th of June will be used, unless other data indicate that the date is earlier.

7.1.8 Definition of Baseline Values

Unless otherwise specified, for each safety parameter, the baseline value is defined as the value collected at the time closest to, but prior to, the start of study drug administration. For analysis of ECG data, the baseline value is the screening value.

7.2 Analysis Sets

7.2.1 Intent-to-Treat Population

The Intent-to-Treat (ITT) population is defined as all patients who are randomized. Patients in this population will be analyzed according to the treatment they were randomized to receive, regardless of any dosing errors.

The ITT population will be used for the primary and secondary efficacy analyses.

7.2.2 Safety Population

The safety population is defined as all patients who receive at least 1 dose of any of the study medications (pevonedistat, venetoclax, or azacitidine). Patients will be analyzed according to the actual treatment they received. Patients who received any dose of pevonedistat will be included in the pevonedistat + venetoclax + azacitidine arm (Arm A), and patients who did not receive any dose of pevonedistat and received at least 1 dose of venetoclax + azacitidine will be included in the venetoclax + azacitidine arm (Arm B), regardless of their randomized treatment.

Safety population will be used for all safety related analyses such as adverse events (AE), concomitant medication, laboratory tests, and vital signs.

7.2.3 Per-protocol (PP) Population

The PP population is a subgroup of the ITT population, consisting of all patients who do not have major protocol deviations, as determined by the study clinician.

The PP population will be used as a sensitivity analysis of the ITT population for the primary efficacy endpoint EFS.

All patients in the PP population will be analyzed according to the actual treatment received.

7.2.4 Response-evaluable Population

The response-evaluable population is defined as patients who receive at least 1 dose of study drug, have a disease assessment at Screening (baseline evaluation), and at least 1 postbaseline disease assessment.

7.2.5 Pharmacokinetic (PK) Population

The PK population is defined as all patients in the safety population and for whom at least 1 PK parameter is evaluable.

7.3 Disposition of Subjects

Patient disposition includes the number and percentage of patients for the following categories: patients randomized, patients in each of the study populations, patients discontinued from treatment, primary reason for discontinuation from treatment, patients discontinued from the study, primary reason for discontinuation from the study, and completion of study. All percentages will be based on the number of patients in the ITT population.

Patients will be considered to have completed the study if they are followed until death or until the sponsor terminates the study.

A listing will present data concerning patient disposition.

The stratification stratum at randomization is based on the disease diagnosis at screening. For the patients whose disease diagnosis changed after screening and before randomization, a listing will be provided.

7.4 Demographic and Other Baseline Characteristics

7.4.1 Demographics

Baseline demographics will be summarized for all patients in the ITT population. Baseline demographic data to be evaluated will include age at date of informed consent, sex, ethnicity, race, height, weight, body surface area (BSA), and other parameters as appropriate.

Patient enrollment by region and country will also be summarized by treatment arms.

BSA is calculated using the following formula based on the patient's height and weight collected at screening. If a weight at screening is not available, the weight at Cycle 1 Day 1 pre-dose can be used.

$$\text{BSA} = \sqrt{\frac{Ht(cm) \times Wt(kg)}{3600}}$$

No inferential statistics will be generated.

Demographic data will also be presented in a by-patient listing.

7.4.2 Inclusion/Exclusion Criteria

All inclusion/exclusion information on enrolled patients will be included in a by-patient listing. The listing will include whether all criteria were satisfied. For patients who did not satisfy the criteria, the criteria number will be listed with the deviation.

7.4.3 Baseline Disease Status

Analyses on baseline disease characteristics will be performed for the ITT population.

Baseline disease characteristics (AML: disease type of de novo or secondary, disease subtype if secondary, revised WHO classification of AML, evidence of extramedullary disease, months from initial diagnosis) and ECOG performance status will be summarized for all patients by treatment arm. Separate by-patient listings will also be presented for baseline disease characteristics and ECOG performance status.

Separate tables will summarize the numbers and percentages of patients who had prior therapy, prior radiation (including the total lifetime dose of radiation received and months from last prior radiation to first dose of pevonedistat), prior surgery (including months from last prior surgery to first dose of pevonedistat) and prior transplants for all patients in the safety population. Separate by-patient listings will also be presented for prior therapies, prior radiation, prior surgery, and prior transplants.

Months from diagnosis to the randomization date for each treatment is calculated by:

$$\frac{\text{randomization date - date of diagnosis}}{365.25/12}$$

Distribution of stratification factor also will be summarized.

A separate table will summarize the characteristics of the bone marrow aspirate samples taken at screening. This will include myeloid/erythroid ratio, myeloblast percentage, cytogenetic results, cell maturing status, and presence of Auer rods. Baseline bone marrow aspirate data also will be presented in by-patient listings.

A separate table will summarize the results of the bone marrow biopsy samples taken at screening. This will include myeloblast percentage. Bone marrow biopsy data and sample collection also will be presented in by patient listings.

A listing will be generated for patients who receive hydroxycarbamide (hydroxyurea) at enrollment, which includes screening WBC and screening bone marrow aspirate myeloblasts.

7.5 Medical History and Concurrent Medical Conditions

General medical history and prior medications will be listed for the ITT population.

7.6 Medication History and Concomitant Medications

Concomitant medications will be coded by Preferred Term using the World Health Organization (WHO) Drug Dictionary. The number and percentage of patients taking concomitant

medications from the first dose through the end of the on-treatment period will be tabulated by Anatomical Therapeutic Chemical (ATC) classification pharmacological subgroup and WHO drug generic term for each treatment arm in the Safety population. A by-patient listing will also be presented for concomitant medications.

Concomitant procedures will not be coded but will be presented in a data listing for the Safety population.

7.7 Study Drug Exposure and Compliance

7.7.1 Extent of Exposure

Pevonedistat

An overall summary of drug exposure for pevonedistat will be presented, including the number of cycles, the mean number of doses per cycle, and the distribution of the number of cycles (numbers and percentages of patients who are treated for at least 1 cycle, 2 cycles, 3 cycles, …), for the treatment arm of pevonedistat + venetoclax + azacitidine in the safety population.

Patients will be considered to have been treated for a cycle if they receive at least one dose of pevonedistat during the 28 days of that cycle.

The mean number of doses per cycle will be calculated for each patient and then summarized for the treatment arm of pevonedistat + venetoclax + azacitidine in the safety population.

Dosing intensity will be summarized for the treatment arm of pevonedistat + venetoclax + azacitidine in the safety population. Percent Dosing Intensity will be calculated using the following equations for Daily Expected Dose (mg), Daily Prepared Dose (mg), and Daily Dose Received (mg):

$$\text{Daily Expected Dose} = \text{Dose Level Assigned at Study Entry } (\text{mg/m}^2) * \text{Body Surface Area } (\text{m}^2)$$

$$\text{Daily Prepared Dose} = \text{Scheduled Dose Level } (\text{mg/m}^2) * \text{Body Surface Area } (\text{m}^2)$$

$$\text{Daily Dose Received} = \text{Daily Prepared Dose} * \left(\frac{\text{Volume of IV bag actually infused (mL)}}{\text{Prepared Volume}}\right)$$

Daily Expected Dose and Daily Prepared Dose may differ if there are dose decreases. The scheduled dose level will be collected on the electronic case report form (eCRF) for each dosing day. Daily Expected Dose and Daily Prepared Dose will be calculated on the BSA measured at baseline unless the patient experiences a >5% change in body weight from the weight used for the most recent BSA calculation. If the patient experiences a >5% change in body weight from the weight used for the most recent BSA calculation, body surface area (BSA) will be calculated on Cycle 1, Day 1, and at Day 1 of subsequent cycles and will be used for the calculation of Daily Expected Dose and Daily Prepared Dose at the corresponding visits.

Total Dose Received, Total Dose Expected, and Dosing Intensity for pevonedistat (MLN4924) will be based on the following formulas:

$$\text{Total Dose Received} = \text{Sum of Daily Dose Received across all days that MLN4924 was administered}$$

$$\text{Total Dose Expected} = \text{Daily Expected Dose} * 3 \text{ doses per cycle} * \text{number of treated cycles}$$

$$\text{Percent Dosing Intensity} = \frac{\text{Total Dose Received}}{\text{Total Dose Expected}} * 100$$

If there are dose increases, the Dosing Intensity may exceed 100%. The number of patients with ≥100% intensity, 80% - <100%, 50 - <80, and <50% intensity will be summarized for the treatment arm of pevonedistat + venetoclax + azacitidine.

Azacitidine

For azacitidine dosing, the percentage of all doses that were administered IV or SC will be summarized by treatment arm. The extent of exposure will be summarized by treatment arm in a similar manner as pevonedistat.

Daily Expected Dose, Daily Prepared Dose for Aza IV, Daily Dose Received for Aza IV, Daily Dose Received for Aza SC, Total Dose Received, Total Dose Expected, and Dosing Intensity for azacitidine will be based on the following formulas:

$$\text{Daily Expected Dose} = 75 \text{ mg/m}^2 * \text{BSA}$$

$$\text{Daily Prepared Dose (Aza IV)} = \text{Scheduled Dose Level (mg/m}^2\text{)} * \text{Body Surface Area (m}^2\text{)}$$

$$\text{Daily Dose Received (Aza IV)} = \text{Daily Prepared Dose} * \left(\frac{\text{Volume of IV bag actually infused (mL)}}{\text{Prepared Volume}}\right)$$

$$\text{Daily Dose Received (Aza SC)} = \text{Daily Dose Received}$$

$$\text{Total Dose Received} = \text{Sum of Actual Dose across all days of dosing}$$

$$\text{Total Dose Expected} = \text{Sum of "Daily Expected Dose} * 7 \text{ doses per cycle" across all treated cycles}$$

$$\text{Percent Dosing Intensity} = \frac{\text{Total Dose Received}}{\text{Total Dose Expected}} * 100$$

Dosing intensity for azacitidine will be summarized by treatment arm in a similar manner to pevonedistat dosing intensity.

Dosing data will also be presented in by-patient listings.

Venetoclax

For venetoclax dosing, the extent of exposure will be summarized by treatment arm in a similar manner as pevonedistat, including the number of cycles, the mean number of doses per cycle, and the distribution of the number of cycles (numbers and percentages of patients who are treated for at least 1 cycle, 2 cycles, 3 cycles, …), in the safety population.

Patients will be considered to have been treated for a cycle if they receive at least one dose of venetoclax during the 28 days of that cycle.

Dosing intensity for venetoclax will be summarized by treatment arm in a similar manner to pevonedistat dosing intensity. Percent Dosing Intensity will be calculated using the following formulas:

Total Dose Received = Sum of actual dose across all days of dosing

Total Dose Expected = Sum of planned venetoclax dose across all treated cycles

Percent Dosing Intensity = (Total Dose Received/Total Dose Expected)*100

The planned venetoclax dosing regimens are as below:

Venetoclax dosing regimens targeting 400 mg Once Daily (QD):

1. Ramp-up (Cycle 1 Only): venetoclax will be administered at a dose of 100 mg on Day 1; 200 mg on Day 2; thereafter, at 400 mg on Days 3 through 28.
2. No Ramp: Venetoclax (400 mg) on Days 1 through 28 of a 28-day cycle at Cycle 2 and beyond: If, in the opinion of the investigator, venetoclax (400 mg) administered on Days 1 through 21 (of a 28-day cycle) is well tolerated, venetoclax (400 mg) dosing may be administered at full dosing frequency (400 mg given on Days 1 through 28 of 28-day cycle) in subsequent cycles.

Dosing data will also be presented in by-patient listings.

7.7.2 Treatment Compliance and Modifications

The actions on study drugs will be summarized by treatment arm in the safety population. Data will be summarized for Cycle 1 only as well as all cycles. A patient will count only once for each type of action.

7.7.3 Duration of Follow-up

The duration of follow-up is defined as time from randomization to the date of death or last known visit. If a subject dies, the duration will equal the date of death minus the date of study start + 1, with a censor variable = 1 (censored for follow-up). If a subject is alive, the duration will equal the date when the subject was last known to be alive minus the date of study start + 1, with a censor variable = 0 (event for follow-up).

7.8 Efficacy Analysis

All available efficacy data will be included in data listings and tabulations. Data that are potentially spurious or erroneous will be examined according to standard data management operating procedures. In general, missing data will be treated as missing, and no data imputation will be applied, unless otherwise specified.

All primary efficacy evaluations for the primary and key secondary efficacy endpoints will be conducted using ITT population. In addition, sensitivity analyses may be performed using the PP population or response-evaluable population when appropriate. The analysis of other secondary

efficacy endpoints will be performed on the ITT population, unless specified otherwise. Analyses based on other subsets of patients will be specified when needed.

7.8.1 Primary Efficacy Endpoint

The primary endpoint of the study is EFS. The analysis of EFS will use the investigator assessment. EFS is defined as the time from study randomization to the date of failure to achieve CR or CRi (ie, discontinuing treatment without achieving CR/CRi), relapse from CR/CRi, or death from any cause, whichever occurs first. For patients who have achieved CR/CRi, if the relapse is not observed by the time of the analysis, patients will be censored at the date of last disease assessment. If patients fail to achieve CR or CRi, the date of treatment failure will be set on the day of randomization. Data for patients without any disease assessments performed after randomization will be censored at the date of randomization (except those who died before any assessment could be performed).

The stratified log-rank test statistic will be used to compare the treatment groups with respect to EFS at the 1-sided $\alpha = 5\%$ significance level. An unadjusted stratified Cox proportional hazard regression model with treatment as a factor will be used to estimate the hazard ratio (HR) and its 2-sided 90% CIs for the treatment effect. The stratification factors include the randomization strata of age (18 to <75 years, ≥75 years) and AML subtype (de novo AML; sAML). The K-M survival curves and K-M medians (if estimable), along with their 2-sided 90% CIs, will also be provided for each treatment group. Two-sided 95% CIs for HR and median EFS will also be computed.

The details regarding the handling of missing assessments and censoring for the EFS analysis are based on the FDA rules and presented in Table 7.a.

Table 7.a Handling of Missing Assessments and Censoring for EFS Primary Analysis Based on the FDA Rules

Situation	Date of Event or Censoring	Outcome
No post baseline disease assessment, and no death	Date of Randomization	Event
Failure to achieve CR or CRi	Date of randomization	Event
Relapse from CR/CRi	Date of relapse from CR/CRi	Event
No documented EFS event	Date of last adequate disease assessment[b]	Censored
Lost to follow-up, withdraw consent before any documented EFS event	Date of last adequate disease assessment[b]	Censored
Relapse from CR/CRi or death after CR/CRi happened after more than 1 missing disease assessments visit	Date of last adequate disease assessment[b]	Censored
Alternate antineoplastic therapy started prior to EFS event (excluding stem cell transplantation)	Date of last adequate assessment prior to starting alternate antineoplastic therapy	Censored
Death before first disease assessment	Date of death	Event
Death between adequate disease assessment visits	Date of death	Event

a Adequate disease assessment is defined as there is sufficient data to evaluate a patient's disease status.

One IA was initially planned but following decisions and changes being made within the pevonedistat program after read-out from the Pevonedistat-3001 study, the IA is removed and no event size re-estimation will be conducted. Instead FA will be conducted, the timing of which will no longer be based on EFS events but instead it will be based on sponsor discretion. An updated analysis for safety data is planned at study closure.

Final Analysis

EFS will be tested at the full one-sided alpha of 5% at FA.

The null and alternative hypotheses for EFS are:

H_0: EFS in Triple Combination Arm = EFS in Control Arm

H_a: EFS in Triple Combination Arm > EFS in Control Arm

The stratified log-rank test statistic will be used at FA to compare EFS between the treatment groups. An unadjusted stratified Cox regression model including treatment as a covariate will be used to estimate the hazard ratio and its 2-sided 90% CIs and 2-sided 95% CIs for the treatment effect. The stratification factors include the randomization strata of age (18 to <75 years, ≥75 years) and AML subtype (de novo AML; sAML). The Kaplan Meier (K-M) survival curves and K-M medians (if estimable), along with their 2-sided 90% CIs and 2-sided 95% CIs, will also be provided for each treatment arm.

In addition, a stratified Cox regression model will be used to further evaluate the treatment effects on EFS after adjusting for some prognostic factors. Besides treatment, the following prognostic factors will be included in the model simultaneously: region (North America vs ex North America), baseline ECOG score (0-1 vs 2-3), baseline peripheral WBC (<15,000 per µL vs >= 15,000 per µL), baseline platelet (<100,000 vs >=100,000).

For patients with EFS events, the reasons leading to the determination of EFS will be tabulated. For patients without EFS events, the main reason for censoring will also be tabulated.

Sensitivity Analysis

Sensitivity analysis will be performed for EFS assessed by investigator using different censoring mechanisms; for example, not censoring for patients who discontinue treatment and go on alternative antineoplastic therapy. The alterations of the handling of missing assessments and censoring based on EMA rules for sensitivity analyses are presented in Table 7.b. Sensitivity analyses for EFS will be performed for each alteration and the combined alterations.

Table 7.b Handling of Missing Assessments and Censoring for EFS Sensitivity Analysis Based on the EMA Rules

Situation	Date of Event or Censoring	Outcome
Alternate antineoplastic therapy started prior to EFS event	Date of documented EFS event	Event
Relapse from CR/CRi or death after CR/CRi happened after more than 1 missing disease assessments visit	Date of documented EFS event	Event

Additional sensitivity analyses for EFS will include:

- EFS assessed by investigator in the PP population.

7.8.2 Key Secondary Efficacy Endpoint

OS is the key secondary efficacy endpoint. OS is defined as the time from the date of randomization to the date of death due to any cause. Patients without documented death at the time of the analysis will be censored at the date that the patient was last known to be alive.

At final analysis, OS will be tested. The null and alternative hypotheses for OS are:

H_0: OS in Triple Combination Arm = OS in Control Arm

H_a: OS in Triple Combination Arm > OS in Control Arm

The 1-sided stratified log-rank test at the $\alpha = 5\%$ significance level will be used to compare the treatment groups with respect to OS and calculate the p-value. In addition, a stratified unadjusted Cox model including treatment as a covariate will be used to estimate the HR and its 2-sided 90% CIs for the treatment effect. The stratification factors include the randomization strata of age (18 to <75 years, ≥75 years) and AML subtype (de novo AML; sAML). The K-M survival curves and K-M medians (if estimable), along with their 2-sided 90% CIs, will also be provided for each treatment group. Two-sided 95% CIs for HR and median OS will also be computed.

In addition, a stratified Cox regression model will be used to further evaluate the treatment effects on OS after adjusting for some prognostic factors. Besides treatment, the following prognostic factors will be included in the model simultaneously: region (North America vs ex North America), baseline ECOG score (0-1 vs 2-3), baseline peripheral WBC (<15,000 per µL vs >= 15,000 per µL) , baseline platelet (<100,000 vs >=100,000).

7.8.3 Secondary Efficacy Endpoint(s)

Other secondary efficacy parameters are: 30- and 60-day mortality rates; disease response rates: CR rate, CCR (CR + CRi) rate, ORR (CR + CRi + PR) rate, CR + CRh rate, leukemia response rate (CR + CRi + PR + MLFS[mCR]); duration of CR and CRi; time to first CR, CRi, or PR.

Patients who receive myeloid growth factors will not be included in assessment of neutrophil response within 2 weeks of growth factor administration.

Disease response-related endpoints will be analyzed using investigator assessments.

30- and 60-Day Mortality Rates

The 30- and 60-day mortality rates are defined as the proportion of patients who survive at most 30 and 60 days, respectively, from the first dose of study drug, which will be summarized by treatment arm in a table. The relative risk with its 2-sided 90% and 95% CIs will be calculated. The absolute rate difference will also be provided with its 90% and 95% CIs calculated using the asymptotic method.

Disease Response Rates: CR Rate, CCR (CR + CRi) Rate, ORR (CR + CRi + PR) Rate, CR + CRh Rate, Leukemia Response Rate (CR + CRi + PR + MLFS[mCR|)

The disease response rates are defined as the proportion of patients who achieve the corresponding response in the corresponding group of patients. The number and percentage of patients for each definition of response will be summarized by treatment group. Disease response-related endpoints will be analyzed using investigator assessments. The key analysis will be based on the ITT population, with response non-evaluable patients treated as non-responders. Sensitivity analysis will be performed using the response-evaluable population.

The number and percentage of patients for each definition of response will be summarized by treatment group. Stratified Cochran-Mantel-Haenszel (CMH) chi-square test will be used to compare the 2 treatment arms. The CMH chi-square test p-value, the relative risk with its 2-sided 90% and 95% CIs will be calculated. The absolute rate difference will be provided with its 90% and 95% CIs using the asymptotic method.

Duration of CR and CRi: Duration of CR and CRi, is defined as the time from the date of first documentation of a CR or CRi, to the date of first documentation of PD or relapse from CR. Responders without documentation of PD or relapse from CR will be censored at the date of their last response assessment that is SD or better. Analysis will be based on the patients achieved CR or CRi responses.

Duration of CR and CRi will be summarized descriptively using the KM method based on the responders. Kaplan Meier (K-M) survival curves and K-M medians (if estimable) will be provided for each treatment arm.

Time to First CR, CRi and PR

Analysis of time to first CR, CRi, and PR will be based on the response-evaluable population.

Time to first CR, CRi, and PR is defined as time from randomization to the first documented CR or CRi or PR, whichever occurs first. The analysis will be performed using the K-M estimate, with the presentation of medians and associated 90% and 95% confidence intervals.

7.8.4 Additional Efficacy Endpoint(s)

Not applicable.

7.9 Pharmacokinetic/Pharmacodynamic Analysis

7.9.1 Pharmacokinetic Analysis

PK parameters will be summarized using descriptive statistics. Individual pevonedistat concentration-time data will be presented in listings. The plan for the population PK analysis may be defined separately and the results reported separately.

7.9.2 Pharmacodynamic Analysis

Not applicable.

7.10 Other Outcomes

Not applicable.

7.11 Safety Analysis

All available safety data will be included in data listings and tabulations. Data that are potentially spurious or erroneous will be examined according to standard data management operating procedures.

Safety population will be used for all safety analyses. All analyses will be performed by treatment arm for the safety population.

Safety will be evaluated by the incidence of AEs, severity and type of AEs, and by changes from baseline in the patient's vital signs, weight, ECOG performance score, ECG results, and clinical laboratory results using the safety population. Exposure to study drug and reasons for discontinuation will be tabulated.

7.11.1 Adverse Events

7.11.1.1 Adverse Events

AEs will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent is defined as any AE that occurs after administration of the first dose of study treatment and through 30 days after the last dose of any study drug.

AEs will be tabulated by system organ class (SOC), high level term (HLT), and preferred term (PT) by treatment arm. Summary tabulations include the following categories:

- Treatment-emergent AEs
- Drug-related treatment-emergent AEs
- Treatment-emergent Grade 3, 4 and 5 AEs (presented by grade and overall)
- Treatment-emergent drug-related Grade 3, 4 and 5 AEs (presented by grade and overall)
- Treatment-emergent AEs resulting in study drug discontinuation

- Treatment-emergent SAEs
- Treatment-emergent drug-related SAEs
- Non-serious treatment-emergent AEs (>5% in any arm)

Patients with the same AE more than once will have that event counted only once within each body system, once within each High Level Term, and once within each Preferred Term.

Treatment-emergent AEs will be tabulated by SOC, HLT, PT, and highest intensity. Most commonly reported (at least 5% in any arm) treatment-emergent AEs will be presented by SOC and preferred term. All adverse events will also be reported in by-patient listings.

Adverse events with start dates that are completely or partially missing will be analyzed as follows:

- If the start date has month and year but day is missing, the event will be considered treatment emergent if both the month and year of the start date of the event are on or after the month and year of the date of the first dose of study drug and on or before the month and year of the date of the last dose of study drug plus 30 days.
- If the start date has year, but day and month are missing, the event will be considered treatment emergent if the year of the start date of the event is on or after the year of the date of the first dose of study drug and on or before the year of the date of the last dose of study drug plus 30 days. If the start date of an event is completely missing, then the event is assumed to be treatment emergent.

7.11.1.2 Serious Adverse Events

The number and percentage of patients experiencing at least one treatment emergent serious AE (SAE) will be summarized by MedDRA SOC, HLT, and PT by treatment arm. Similar summary will be generated for treatment emergent drug-related SAEs.

A by-patient listing of the SAEs will be presented by treatment arm (the patient listing will contain all SAEs regardless of treatment emergent AE status).

An additional listing of treatment emergent C1D1 grade 2 or higher SAEs will also be generated by treatment arm.

7.11.1.3 Deaths

A by-subject listing of all deaths (on-study or during follow-up) will be presented by treatment arm.

On-study death is defined as the death that occurs between the first dose of study drug and 30 days after the last dose of study drug.

7.11.1.4 Adverse Events Resulting in Discontinuation of Study Drug

The number and percentage of patients experiencing at least one adverse event resulting in discontinuation of study drug will be summarized by MedDRA SOC, HLT, and PT.

A by-patient listing of treatment emergent AEs resulting in discontinuation of study drug will be presented.

7.11.1.5 TEAEs of Clinical Interest

The following TEAEs of clinical interest will be presented by listing and be summarized in a table for incident rate:

- Haemorrhages (SMQ broad and narrow):
- By-patient line listing for patients with ANY GRADE TEAE of Haemorrhages (defined by SMQ Haemorrhages) concurrently occurred within 5 days of Thrombocytopenia (PT) or Platelet Count Decreased (PT) or post-baseline lab of platelet count decreased will be provided.
- Liver Function Test Elevations (PTs including Acute hepatic failure, Blood alkaline phosphatase, Blood alkaline phosphatase abnormal, Blood alkaline phosphatase increased, Hyperbilirubinaemia, Hepatic function abnormal, and PTs subsumed under HLT Liver function analyses)
- Asthenia (HLT: Asthenic Conditions)
- Musculoskeletal and Connective Tissue Disorders (SOC)
- Acute Renal Failure (SMQ broad and narrow)
- Cardiac Failure (SMQ broad and narrow)
- Cardia Arrhythmia (SMQ broad and narrow)
- Drug Related Hepatic Disorders – (Comprehensive search SMQ broad and narrow)
- Haemodynamic Oedema, Effusions and Fluid Overload (SMQ broad and narrow)
- Haematopoietic Cytopenias (SMQ broad and narrow)

  A listing of treatment emergent events retrieved by this SMQ haematopoietic cytopenias will be generated by sub-SMQs listed below and by treatment arm. The sub-SMQs are:

  – Haematopoetic cytopenias affecting more than one type of blood cell
  – Haematopoetic erythropenia
  – Haematopoetic leukopenia
  – Haematopoetic thrombocytopenia
- Anaemia of Chronic Disease (PT) and Anaemia of Malignant Disease (PT)

- Injection Site Reactions: (PTs subsumed by HLT: Injection site reactions or PT Injection site abscess or PT Injection site cellulitis or PT Injection site infection or PT Injection site joint infection)
- Dehydration (SMQ broad and narrow)
- Hypersensitivity (SMQ broad and narrow)
- Infections:

  By-patient line listing for patients with ANY GRADE TEAE of Infections (defined by SOC Infections and Infestations. or HLGT Respiratory Tract Infections, or HLT Lower Respiratory Tract Inflammatory and Immunologic Conditions) concurrently occurred within 5 days of Febrile neutropenia (defined by PT Febrile neutropenia) will be generated. The listing will include: subject ID, Treatment group, Febrile neutropenia (reported term and PT, Start date/End date, Days from first dose/Days from last dose, Seriousness), Infections (reported term and PT, Start date/End date; Days from first dose/Days from last dose; Seriousness).

  By-patient line listing for patients with ANY GRADE TEAE of Infections (defined by SOC Infections and Infestations. or HLGT Respiratory Tract Infections, or HLT Lower Respiratory Tract Inflammatory and Immunologic Conditions) concurrently occurred within 5 days of Neutropenia (defined by PT Neutropenia, PT Neutrophil Count Decreased, PT White Cell Count Decreased) will be generated. The listing will include: subject ID, Treatment group, Neutropenia (reported term and PT, Start date/End date, Days from first dose/Days from last dose, Seriousness), Infections (reported term and PT, Start date/End date; Days from first dose/Days from last dose; Seriousness).

  A summary table of patients with concurrent infections and infestation TEAE (defined by SOC Infections and Infestations. or HLGT Respiratory Tract Infections, or HLT Lower Respiratory Tract Inflammatory and Immunologic Conditions) within 5 days of febrile neutropenia or neutropenia will also be generated.

The following additional tables are also planned:

- Patients with TEAEs coded to PTs subsumed by Haemorrhages SMQ will be summarized respectively for occurrences of thrombocytopenia (PT), platelet count decreased (PT), and lab platelet toxicity grade of at least 2.
- Incidence of TEAEs of Febrile Neutropenia (PT), Neutropenia (PT), and Concurrent Infections and Infestation (SOC)
- Incidence of TEAEs of Thrombocytopenia (PT)/Platelet Count Decreased (PT) and Concurrent Hemorrhage (SMQ)

7.11.1.6 Dose Modifications due to LFT Abnormalities

A listing of patients that required dose modification of due to LFT abnormalities, defined by TEAEs coded to the following HLTs and PTs:

- Acute hepatic failure (PT)
- Hyperbilirubinemia (PT)
- Blood alkaline phosphatase (PT)
- Hepatic function abnormal (PT)
- Blood alkaline phosphatase abnormal (PT)
- Liver function analyses (HLT)
- Blood alkaline phosphatase increased (PT)

during study to display trend over time (Week 1-4, Week 5-8, Week 9-12, and Week 13+) for pevonedistat in the triple combination arm and for azacitidine and venetoclax by treatment arm.

7.11.1.7 Dose Modifications due to Renal Abnormalities

A listing of patients that required dose modification due to renal abnormalities (Acute renal failure SMQ) during study to display trend over time (Week 1-4, Week 5-8, Week 9-12, and Week 13+) for pevonedistat in the triple combination arm and for azacitidine and venetoclax by treatment arm.

7.11.1.8 Dose Modifications due to Myelosuppression

A listing of patient that required dose modification due to myelosuppression [defined by the terms listed below plus 2 additional PTs of Thrombocytopenia and Platelet count decreased)] during study to display trend over time (Week 1-4, Week 5-8, Week 9-12, and Week 13+) for pevonedistat in the triple combination arm and for azacitidine by treatment arm.

- Anaemia
  - Anaemia of chronic disease
  - Haemoglobin decreased
  - Anaemia of malignant disease
  - Mean cell haemoglobin decreased
  - Anaemia
  - Haematocrit decreased
  - Red blood cell count decreased
  - Neutropenia
  - Agranulocytosis

- Neutropenia
  - Granulocyte count decreased
  - Neutropenic infection
  - Band neutrophil count decreased
  - Neutropenic sepsis
  - Band neutrophil percentage decreased
  - Neutrophil count abnormal
  - Febrile neutropenia
  - Neutrophil count decreased
  - Idiopathic neutropenia
  - Neutrophil percentage abnormal
  - Leukopenia
  - Neutrophil percentage decreased

7.11.1.9 Overall Summary

The number and percentage of patients who experience any of the following groups will be summarized by treatment arm:

1. Any treatment emergent adverse event (including separate summaries of maximum toxicity grade experienced (Grade 1 to Grade 5))
2. Drug-related treatment emergent adverse event (including separate summaries of maximum toxicity grade experienced (Grade 1 to Grade 5))
3. Serious treatment emergent adverse event
4. Drug related serious treatment emergent adverse event
5. Treatment emergent adverse events resulting in study drug discontinuation
6. Treatment emergent adverse events that required dose modification
7. On-study deaths

The summary tables will also be provided for overall TEAE summary by age (18-75, >75), including on-study deaths, Grade 3 or higher TEAEs, drug related adverse events, serious adverse events, drug related serious adverse events, adverse events leading to treatment discontinuations.

7.11.2 Clinical Laboratory Evaluations

For the purposes of summarization in both the tables and listings, all laboratory values will be converted to standardized units. If a lab value is reported using a non-numeric qualifier (eg, less than (<) a certain value, or greater than (>) a certain value), the given numeric value will be used in the summary statistics, ignoring the non-numeric qualifier.

If a patient has repeated laboratory values for a given time point, the value from the last evaluation will be used.

Laboratory test results will be summarized according to the scheduled sample collection time point. Change from baseline will also be presented. Unscheduled laboratory test results will be listed and included in laboratory shift tables.

Shift tables of the change in NCI CTC from baseline to the post baseline worst CTC grade will be generated for relevant measurements. Summary tables will be generated to display the actual values and percent changes from baselines for selected labs. Graphical displays will be used to show changes in laboratory measures over time for patients:

- Box graphs and line graphs of individual tests over time by treatment arm. .
- Scatter plots of baseline versus worst post-baseline values for all patients. Separate plotting characters will be used for each combination of treatment arm. These will be generated for only selected labs in Table 7.c.

Table 7.c Selected Labs

Panel	Test	CTCAE Shift Table	Box Graphs	Scatter Plots	Summary Tables
Chemistry	Albumin	X	X		
	ALT	X	X		X
	AST	X	X		X
	Alkaline Phosphatase	X	X		
	Carbon Dioxide		X		X
	Direct Bilirubin		X		
	Total Bilirubin	X	X		X
	Blood urea nitrogen		X	X	
	Corrected Calcium	X	X		
	Chloride		X	X	
	Creatinine	X	X		
	Creatinine Clearance		X	X	X
	Glucose	X	X		
	Lactate dehydrogenase (LDH)		X	X	
	Magnesium	X	X		
	Phosphate	X	X		X
	Potassium	X	X		X
	Sodium	X	X		
	Urate	X	X		
Hematology	Platelets	X	X		X
	Hemoglobin	X	X		
	Leukocytes	X	X		
	Neutrophils (ANC)	X	X		X
	Monocytes		X		
Additional	Reticulocyte		X		X
	Ferritin		X		X

For patients with neutrophil lab results reported as segmented neutrophils and neutrophil bands, ANC will be calculated as:

ANC=total leukocyte count × total percentage of neutrophils (segmented neutrophils + band neutrophils)

Example:

If total leukocyte count = 4.3 x 10^3; segmented neutrophils = 48%; band neutrophils = 2% Then: 4300 × (0.48 + 0.02) = 4300 × 0.5 = ANC of 2150

Creatinine clearance will be derived using one of the Cockcroft-Gault and CKD-epi formulas as follows:

Cockcroft-Gault equation:

For males:

$$\text{Creatinine Clearance (mL/min)} = \frac{(140 - \text{age[years]}) \times \text{weight [kg]}}{0.81 \times (\text{serum creatinine } [\mu\text{mol/L}])}$$

OR

$$\text{Creatinine Clearance (mL/min)} = \frac{(140 - \text{age[years]}) \times \text{weight [kg]}}{72 \times (\text{serum creatinine [mg/dL]})}$$

For females:

$$\text{Creatinine Clearance (mL/min)} = \frac{0.85 \times (140 - \text{age[years]}) \times \text{weight [kg]}}{0.81 \times (\text{serum creatinine } [\mu\text{mol/L}])}$$

OR

$$\text{Creatinine Clearance (mL/min)} = \frac{0.85 \times (140 - \text{age[years]}) \times \text{weight [kg]}}{72 \times (\text{serum creatinine [mg/dL]})}$$

A cap value of 125 will be set to creatinine clearance (calculated from Cockcroft-Gault equation) higher than 125.

CKD-EPI equation (http://nephron.com/epi_equation):

For males:

$$\text{GFR (mL/min/1.73 m}^2) = 141 \text{ x } \min(\text{Scr}/0.9, 1)^{-0.411} \text{ x } \max(\text{Scr}/0.9, 1)^{-1.209} \text{ x } 0.993^{\text{Age}},$$

where Scr = serum creatinine (mg/dL).

For black males:

$$\text{GFR(mL/min /1.73 m}^2) = 141 \text{ x } \min(\text{Scr}/0.9, 1)^{-0.411} \text{ x } \max(\text{Scr}/0.9, 1)^{-1.209} \text{ x } 0.993^{\text{Age}} \text{ x } 1.159,$$

where Scr = serum creatinine (mg/dL).

For females:

$$\text{GFR (mL/min/1.73 m}^2) = 141 \text{ x } \min(\text{Scr}/0.7, 1)^{-0.329} \text{ x } \max(\text{Scr}/0.7, 1)^{-1.209} \text{ x } 0.993^{\text{Age}} \text{ x } 1.018,$$

where Scr = serum creatinine (mg/dL).

For black females:

$$GFR\,(mL/min/1.73\,m^2) = 141 \times \min(Scr/0.7,\ 1)^{-0.329} \times \max(Scr/0.7,\ 1)^{-1.209} \times 0.993^{Age} \times 1.018 \times 1.159$$

,

where Scr = serum creatinine (mg/dL). All chemistry and hematology lab data will also be presented in by-patient listings.

The percentage of marrow progenitor cells in peripheral blood will be presented in by-patient listings, including leukemic blasts, myeloblasts, promyelocytes, myelocytes, metamyelocytes, and uncharacterized blasts.

In addition, the urinalysis parameters will be presented in by-patient listings. These include turbidity and color, pH, specific gravity, protein, ketones, bilirubin, occult blood, nitrite, urobilinogen, glucose, erythrocytes, leukocyte esterase, and leukocytes.

Events that potentially met the biochemical criteria for Hy's law (eg, patients with any elevated aminotransferase of >3x ULN and alkaline phosphatase <2x ULN, in association with an increase in bilirubin >2x ULN) will also be provided for overall and by cycles and by treatment arm. Incidences of the following will be provided:

- >3x-, >5x-, >10x-, and >20x ULN elevations of AST and/or ALT;
- Any elevations of bilirubin: elevated total bilirubin to >2x ULN;
- Any elevations of alkaline phosphatase >1.5x ULN;
- Elevation of aminotransferase (>3x ULN) accompanied by elevated bilirubin (>1.5x ULN, >2x ULN); and
- Potential Hy's law cases. The Sponsor qualifies these as "potential" cases, since a bona fide case definition requires that no other cause nor other drug has been shown to be causative than the test article. In some advanced cases with more cholestasis, the alkaline phosphatase may be >2x ULN.

7.11.3 Vital Signs

Boxplots over time for temperature, DBP, SBP, and heart rate during Cycle 1 will be generated. Vital sign data will also be presented in a by-patient listing by treatment arm.

Summary table of weight and percent change from baseline in weight over time will be provided.

7.11.4 12-Lead ECGs

The number and percent of patients experiencing abnormal ECG results will be summarized for each time point by treatment arm and azacitidine route.

QTcF and QTcB will be derived using the following formulas.

$$QTcF = \frac{QT_{uncorrected}}{\left(\frac{60}{Ventricular\ Rate}\right)^{1/3}} \qquad QTcB = \frac{QT_{uncorrected}}{\sqrt{\frac{60}{Ventricular\ Rate}}}$$

ECG findings will also be presented in by-patient listings by treatment arm.

7.11.5 Other Observations Related to Safety

Eastern Cooperative Oncology Group performance status will be listed. Shifts from baseline to the worst postbaseline score will be tabulated by treatment arm.

7.12 Changes in the Statistical Analysis Plan

Reference materials for this statistical plan include Clinical Study Protocol Pevonedistat-2002 (Protocol Amendment 4 dated 21 January 2022).

8.0 REFERENCES

1. Dohner H, Estey E, Grimwade D, Amadori S, Appelbaum FR, Buchner T, et al. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. Blood 2017;129(4):424-47.
2. Cheson BD, Bennett JM, Kopecky KJ, Buchner T, Willman CL, Estey EH. 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. Journal of Clinical Oncology 2003;21(24):4642-9.
3. Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. U.S. Department of Health and Human Services, National Institutes of Health, National Cancer Institute. November 2017.
4. DiNardo CD, Pratz KW, Letai A, Jonas BA, Wei AH, Thirman M, et al. Safety and preliminary efficacy of venetoclax with decitabine or azacitidine in elderly patients with previously untreated acute myeloid leukaemia: a non-randomised, open-label, phase 1b study. Lancet Oncol 2018;19(2):216-28.
5. Cui L, Hung HM, Wang SJ. Modification of sample size in group sequential clinical trials. Biometrics 1999;55(3):853-7.
6. Liu Y, Hu M. Testing multiple primary endpoints in clinical trials with sample size adaptation. Pharmaceutical Statistics 2016;15(1):37-45.
7. Fenaux P, Mufti GJ, Hellstrom-Lindberg E, Santini V, Finelli C, Giagounidis A, et al. Efficacy of azacitidine compared with that of conventional care regimens in the treatment of higher-risk myelodysplastic syndromes: a randomised, open-label, phase III study. Lancet Oncology 2009;10(3):223-32.
8. Silverman LR, McKenzie DR, Peterson BL, Holland JF, Backstrom JT, Beach CL, et al. Further analysis of trials with azacitidine in patients with myelodysplastic syndrome: studies 8421, 8921, and 9221 by the Cancer and Leukemia Group B. Journal of Clinical Oncology 2006;24(24):3895-903.
9. Fayers PM, Aaronson NK, Bjordal K, et al. The EORTC QLQ-C30 Scoring Manual (3rd Edition). Brussels: European Organisation for Research and Treatment of Cancer; 2001.
10. Silverman LR, McKenzie DR, Peterson BL, Holland JF, Backstrom JT, Beach CL, et al. Further analysis of trials with azacitidine in patients with myelodysplastic syndrome: studies 8421, 8921, and 9221 by the Cancer and Leukemia Group B. Journal of Clinical Oncology 2006; 24(24):3895-903.
11. K. K. Gordon Lan, & Wittes, J. The B-Value: A Tool for Monitoring Data. Biometrics 1988; 44(2): 579-585.

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